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Editor

Hypertrophic Cardiomyopathy

Second Edition

Foreword by Bernard Gersh and Historical Context by Eugene Braunwald

Springer

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Foreword

Hypertrophic cardiomyopathy (HCM) is a relatively new disease or group of diseases that seem to be a magnet for controversy in many aspects. It is an important clinical entity and together with bicuspid aortic valve is one of the two commonest monogenetic inherited cardiac diseases. What is so controversial also contributes to its fascination in that the disease entity is characterized by heterogeneity in regard to the clinical presentation, natural history, response to therapy, and the underlying genetic substrate.

This excellent book is a valuable contribution to the literature, and its appearance is particularly opportune given the publication of the recent ACCF/AHA guidelines in 2011—on which the editor of this textbook, Dr. Srihari S. Naidu, and I served together—and the expected ESC Guidelines in 2014. Such guidelines are a testament to the fact that we have reached a point in which there is much that we agree upon; but in addition, a reasonable body of evidence has also helped us to define our areas of disagreement, and all of these are well covered in this excellent book edited by Dr. Naidu with contributions from recognized experts in the field.

The list of contents emphasizes that this book encompasses the entire scope of hypertrophic cardiomyopathy and the issues that continue to stimulate vibrant and spirited discussion among those interested in this condition. It adds a level of detail as well as practical information that cannot be fully realized within national guidelines on the subject, and the chapter by Dr. Eugene Braunwald, whose seminal work in the 1960s taught us so much about this entity, is a classic and unique insight into a period of discovery and a wonderful contribution to this book.

What this book also emphasizes is that we are dealing with a very complex clinical syndrome, which serves to underscore the need for centers of excellence. Such centers need to have adequate patient volumes and the availability of experts in many different fields including clinical adult and pediatric cardiologists, up-to-date cardiac imaging expertise, interventional cardiologists and cardiac surgeons with expertise in surgical myectomy and alcohol septal ablation, electrophysiologists, geneticists, and genetic counselors. All centers of excellence need to provide unimpeded access to all forms of therapy and particularly the invasive modalities, whether this be on-site or by a seamless mechanism of referral. In this regard, the chapter on constructing a center of excellence is a novel addition and will, I suspect, be particularly well received.

This is a dynamic field and ripe for further clinical and basic investigation and collaboration between centers nationally and internationally. I would emphasize the latter because despite the relative frequency of this disease entity, the majority of centers still see a limited number of patients, and the ability to collaborate across regions and countries will ensure the development of the databases we need for the future. In an era of large global trials in many areas of cardiovascular disease, hypertrophic cardiomyopathy is somewhat of an outlier in that it has not lent itself to many randomized trials. Drugs needed for the pharmacological treatment of symptomatic hypertrophic cardiomyopathy (beta-blockers, calcium blockers, and disopyramide) are approximately 50 years old, and these have been evaluated in only a few small randomized trials.

In regard to the preferred method of septal reduction therapy in particular with surgical myectomy or alcohol septal ablation, we have no randomized trials, and none are likely to be performed in the future given the sample size and duration of follow-up required and the

already existing knowledge in regard to early outcomes. Guidelines and other statements have therefore had to rely upon a reasonable consensus. In this respect, the recent ACCF/AHA guidelines have concluded that in good surgical candidates, myectomy in experienced hands is the "gold standard." In poor or suboptimal surgical candidates, alcohol septal ablation is an excellent alternative. In patients who are deemed appropriate surgical candidates but who wish to decline surgery, alcohol septal ablation is reasonable but only after a full, detailed, informed, and balanced discussion between physician and patient. In all cases, it is essential that patients understand the pros and cons of both procedures. Indeed, the preferred method of septal reduction therapy has been the impetus for considerable and vigorous debate and remains a changing landscape.

It is intriguing to speculate upon the changes we might find in the second or third editions of this book. Part of the fascination of hypertrophic cardiomyopathy is that its knowledge base continues to unfold, and I suspect that some answers to the current research agenda proposed by the guidelines will be forthcoming in the near future. This research agenda does not lack for questions. From a genetic standpoint, we know little about the causes of hypertrophic cardiomyopathy both in patients who are mutation positive and mutation negative. Hopefully, the rapid technical innovations in genetics will likely bear fruit in this area in the near future. The link between the genotype and the phenotype needs further clarification in particular, as does the management and evaluation of genotype-positive/phenotype-negative patients. Whether genotyping will be a useful tool for the prognosis and risk stratification of sudden cardiac death and other sequelae such as heart failure remains to be determined. Although the role of genotyping for prognosis in current clinical practice is extremely limited with the exception of genetic counseling, it is likely that as geneticists are able to delve into the secrets of the hypertrophic genotype in more detail, genotyping as a prognostic tool may very well become a reality.

Ongoing studies using MRI will likely in the next few years clarify the clinical significance of myocardial fibrosis and the attributed risk of sudden cardiac death among other manifestations of the disease. Moreover, the entire area of risk stratification for prognosis including for sudden cardiac death and ICD implantation needs to be refined, and large collaborative studies are needed. There is also a need for new medical therapies, and this will depend upon an enhanced understanding of the basic physiology and energetics of the hypertrophied heart. Finally, as already alluded to, there is a particular need for comparative assessments of septal reduction strategies with longer-term follow-up, particularly after alcohol septal ablation.

So after 50 years of discovery and clinical investigations, the natural history of hypertrophic cardiomyopathy has been clarified; in regard to the pathophysiology of the role of obstruction, this is now well understood, but other mechanisms at play in this disease need further study. The use of molecular genetics in regard to genetic counseling should be a routine clinical tool in hypertrophic cardiomyopathy centers, but one gains the impression that we are just now seeing the tip of the genetic iceberg and that much more interesting information will emanate in the next few years. Finally, we do have a number of effective diagnostic, pharmaceutical, and invasive therapeutic approaches that need comparative studies. "We now know much more about what we do not know."

Dr. Naidu and his colleagues should be congratulated on this excellent and timely book. Hypertrophic cardiomyopathy has risen on the radar screen within national guidelines, clinical practice, and the mainstream media. I have no doubt that this book will be welcomed as a vital resource for both individual clinicians and centers of excellence interested in this fascinating disease and that we will see many future editions of this book, which will be considered as one of the definitive texts in the field.

Rochester, MN, USA Bernard J. Gersh, MD, ChB, DPhil, FRCP, MACC

Foreword to 2nd Edition

The first edition of this superb book provided a comprehensive and detailed overview of this complex and fascinating disease or group of diseases. The contents spanned a wide spectrum ranging from the history of discovery beginning in the 1950s and 1960s to many aspects of the heterogeneity of this disease which underscored the need for centers of excellence.

A new edition of this book is indeed welcome and further establishes this book as one of the definitive texts in the field. Since the initial edition, the 2014 ESC Guidelines have been published in addition to a marked growth in the establishments of centers of excellence and an increasing awareness of the relative frequency of this disease at a community level in addition to the encouraging results of modern therapeutic approaches.

There have been many new additions to the literature which have been incorporated into updates of all existing chapters. In addition, there are additional chapters and discussion on the management of associated hypertension, coronary heart disease, congenital heart disease, pulmonary pathology, sleep-disordered breathing, and, of interest in the era of TAVR, sections devoted to concomitant structural heart disease. Moreover Willebrand disease, epiphenomena such as von Willebrand factor and gastrointestinal bleeding in addition to a chapter on managing the high-risk patient and, of great importance in the current era, sections on training and credentialing have been added. Other associated and important modifiers of the disease include nutrition and obesity, and after 50 years of a lack of pharmacologic development, the discussion on the new pharmacotherapeutic agents is of great interest. Another new addition is the questions and answers posttest for each chapter as a means of solidifying new concepts.

I thought that the first edition was a really important addition to the literature. Dr. Naidu and his colleagues are to be congratulated for their efforts in taking this superb book to a new level.

Rochester, MN, USA — Bernard J. Gersh, MD, ChB, DPhil

Preface

Writing a textbook is no easy task. Indeed, it is oftentimes described as a labor of love, something that your passion must push forward lest you lose steam halfway through. Now at the culmination of what started almost 2 years ago, I will tell you that this is true. The desire to simply finish what has been started is not nearly enough; an author has to really want a book to be not only completed but also worthy of the time, effort, and inspiration that designed it. So what kept me going? I have often wondered how I came to this point in my career, where I care so deeply about a single disease that I would want to become instrumental in its course. It is, I think, an interesting story and one that I will now share with you. In doing so, perhaps you will understand a little bit of why I created this book and the void I was hoping to fill.

I first heard the term *hypertrophic cardiomyopathy* (HCM) in 1994 as part of my second-year cardiovascular pathophysiology course at Brown University Medical School. What was clear to me within just a few short weeks was that this was a remarkable disease. Not only was the physiology impossibly intricate, but the diverse symptomatology, differential age at presentation from childhood to the elderly, and genetic and social aspects, as well as the diagnostic and therapeutic challenges made this disease uniquely appealing. To be clear, at the time, there was little in terms of treatment and only a relatively rudimentary understanding of diagnosis, physiology, and genetics. But that was part of what fascinated me—the feeling that despite years of progress, we remained in some ways at the beginning.

My next memory of HCM is from 1998 during internal medicine residency at Cornell Medical Center/New York Presbyterian Hospital in Manhattan. A senior resident was presenting a case during morning conference, and it turned out to be one of HCM. As he went around the room, I remember being able to articulate the underlying etiology of dynamic outflow tract obstruction, something I was quite proud of. He went on to describe the potential management options. At the time, dual-chamber pacing to reduce outflow tract obstruction was a leading concept having first been reported formally in 1992. In addition, he described a novel percutaneous approach to eliminating obstruction, alcohol septal ablation, which in early studies had been shown to mimic results of surgical septal myectomy. A few things stood out in my mind at this time. First, it appeared that HCM was extremely rare, this being the first case that we had seen during my 2 years of residency. Second, it seemed that neither surgical myectomy nor alcohol septal ablation was being performed with any regularity. And third, the disease was still fascinating to me—something I wanted to learn more about.

My own inroads into the management of HCM started in fellowship training at the University of Pennsylvania. Believe it or not, I went there initially to become a heart failure and transplant specialist. My interest in hemodynamics, physiology, and heart failure in particular was paramount up until the point that I stepped into the cardiac catheterization laboratory. As it turns out, I like to use my hands and soon realized that the hemodynamic and heart failure concepts I so loved were right there at the cath table. So it was that in 2000, I saw my first alcohol septal ablation performed by one of my mentors, Dr. John Hirshfeld. Here was a patient suffering from severe heart failure, unable to walk one block on a flat level without significant dyspnea despite high-dose medications and unable to climb a flight of stairs without fear of passing out. The procedure went smoothly, and 3 days later, the patient was transformed. His heart failure was vastly improved. It was surreal, and I have never forgotten.

Four years later, I graduated fellowship and took my first job as a faculty interventionalist back at my residency program, Cornell. My goals were to be an academic interventional cardiologist focusing on drug-eluting stents while becoming as good a clinician as I could. As it were, though, most academic institutions like their faculty to develop niches—areas of expertise that they could call their own, master, and develop. So it was that a patient presented to the emergency room with severe hypertrophic cardiomyopathy refractory to multiple and high-dose medications. Moreover, this patient had already undergone surgical myectomy 4 years prior, but the area of maximal septal-valve contact was clearly missed. His gradients were almost 300 mmHg with provocation, 100 mmHg resting, and the patient described ongoing severe symptoms that only worsened after surgery. This was my first alcohol septal ablation patient. Ten years later, I count him as not only a patient but a longtime friend, someone whose life has vastly improved due to my efforts.

Over the next few years, I became first the local and then the regional HCM expert. I read all the relevant original articles and all the reviews and became intimately involved in every aspect of the disease from presentation to diagnosis and management. After moving to Winthrop University Hospital in 2006 as director of the Cardiac Catheterization Laboratory, I created the HCM Treatment Center. What started as a handful of patients has now grown to almost 500. Over time, the Center has grown to include all aspects of diagnosis including cardiac MRI and genetics, electrophysiology, family screening, original research, randomized controlled trials, pediatrics, surgery, and alcohol septal ablation. We are now reaching into the community to raise awareness in high schools and impact statewide legislation. With all this, our national presence has grown with presentations at national meetings, live proctoring courses (Fig. 1), numerous grand rounds, as well as a biannual patient-centered regional conference.

So where does this book come in? No one reads books anymore, I was once told—and to some extent, they are correct. But HCM is different, I think. In 2009, I was asked to serve on the

Fig. 1 (**a**) Dr. Naidu with select faculty and participants from the first annual alcohol septal ablation live proctoring course in 2014. (**b**) Dr. Naidu addresses the audience. (**c**) Dr. Naidu and co-director of the live course, Dr. George Hanzel, perform an alcohol septal ablation. (**d**) Dr. Michael Fifer (*right*) teaches from the viewing area

first official American College of Cardiology (ACC)/American Heart Association (AHA) guideline on the diagnosis and management of HCM—I was to be the official representative of the Society for Cardiovascular Angiography and Interventions (SCAI). Although chosen to represent an interventional society, I brought all my insights as a medical director of a busy HCM program contributing as much as possible on all aspects. This was a transformative process for me. Working alongside luminaries such as Guideline Chair Dr. Bernard Gersh, I realized that those on the committee were part of a larger mission to (a) make sure our combined wisdom makes it to paper, (b) help physicians realize that HCM management is difficult and time-consuming and should thus be done alongside an HCM Center of Excellence, and (c) make sure the recommendations we are writing are practical enough to be followed. Two years later, I was very proud of the group's efforts and culminating document. But something was missing.

It struck me at that point that there was no vehicle other than these newly created guidelines to explain why we do what we do for patients with this disease. We explained what to do and made dozens of formal recommendations, but the "why" and the "how" were limited—necessarily so as most were consensus driven. That's when I realized that books are still necessary for rare diseases. This is the way we put down in words what our experience has taught us. This is the way we can teach others. This is how we can grow the understanding, appeal, and impact of appropriately treating these patients and their families. This is where the details come. A book could be a blueprint not only for treating patients in a comprehensive yet practical way but also for creating and sustaining a center of excellence—and in doing so sustaining the optimal yet dynamic management of a rare disease.

This textbook is constructed purposefully to do this. After the foreword and this preface, we travel back in time to rediscover HCM, dive into the pathology, and tease out the nuances of diagnosis from echocardiography to cardiac MRI. As a treat for the reader, Dr. Eugene Braunwald provides his firsthand account of encountering HCM. We discuss management including medications, pacemakers and defibrillators, and invasive septal reduction therapy—both surgical myectomy and alcohol septal ablation. Chapters on genetics, family screening, lifestyle concerns, and athletic screening are added given the ongoing controversies and differences of opinion on many of these. Advanced management including imaging, heart failure, and transplantation are also discussed in detail.

The chapters are meant to be practical, with each one starting off with key points of knowledge and ending with clinical pearls—the tiny morsels of information that only the experts have known about. The practical approach continues with dedicated chapters on creating a center of excellence and on case-based reviews and discussions. This last chapter takes you through the management of actual patients, showing over decades the nuances to diagnosis and management and the sometimes abrupt changes in the course of their diseases that necessitate correspondingly abrupt modifications in treatment. Through it all, the reader not only understands the dogma of HCM care as depicted in the guidelines but also the stuff between the cracks—the knowledge that not only separates the student from the teacher but the teacher from the master.

I would be remiss if I did not credit several individuals for making sure that HCM—the disease—was not "lost" after its discovery over 50 years ago and then for rapidly raising awareness and helping develop treatment options over the past two decades. Perhaps the two most influential would be Dr. Eugene Braunwald and Dr. Barry Maron. While the former helped describe the first cases and delineate the underlying pathophysiology, the latter took the disease in—like it was part of his family—and shepherded its rise and acceptance as well as the growth of other physicians with similar passion. As a result, there are now many HCM experts throughout the world with unique expertise that ranges from pathophysiology to medical therapy, genetics to imaging, alcohol septal ablation to surgery, and electrophysiology to transplantation. And patient-centered groups have also arisen right alongside providing that much-needed patient voice and drive for advocacy. Together, we form a very strong community tied by our deep passion for this disease and the patients and families that are affected by it—in essence, we are each other's extended family.

This book would not have been possible without several people who have inspired and supported me over the years. To my parents and sister, who quietly told me I could do anything and always stood by me even when I was my own worst enemy; to Vartan Gregorian, whose leadership style I think rubbed off on me; to John Hirshfeld, Howard Herrmann, Robert Wilensky, Daniel Kolansky, and Mariell Jessup, who inspired me to reach higher, focus, and be impactful in everything I do; to Kevin Marzo and Michael Niederman, who took a chance on me and let me fly; to Garry Schwall, who supported my interest in HCM right from the beginning; to Nicole Goldman, who keeps me on track with my patients; to Nina Naidu, who told me not just that I could do this but that I should; and to my son, Kiran Naidu, who makes me happy every single moment of my life and lets me take the time to enjoy it. This book is for all of you. And I thank you.

Mineola, NY, USA Srihari S. Naidu, MD, FACC, FAHA, FSCAI

Preface to 2nd Edition

I must admit, 4 years pass by in the blink of an eye. With the first edition's release in late 2014, *Hypertrophic Cardiomyopathy* was instantly well received, surpassing 10,000 purchases per year between downloads and hard copy sales. We have credited this mostly to its fortuitous timing, wherein this genetic disorder had finally begun to emerge as a "common, uncommon" disease, with its nuances and complexity increasingly acknowledged as demanding more detailed study. This recognition among physicians and patients alike has been something to behold, prompting the development of regional centers of excellence at rapid pace and improving both awareness and outcomes throughout the world. Together, this growth has fueled a desire to learn as much about the disease as possible, sharing experience from experts around the world—which is where the textbook came in.

Yet, it remained difficult for us to know when a second edition would be warranted. By 2017, however, it became clear that enough had evolved in terms of our knowledge base that a new edition would not only be reasonable, but is indeed necessary. Key areas that needed updating included risk stratification for sudden cardiac death, choice of septal reduction therapy and the effect of procedure volume on outcomes, newer defibrillators including a subcutaneous version, advances in our understanding of the genetic basis of disease, cardiac imaging including novel cardiac magnetic resonance techniques, medications in various stages of development, and technical modifications to both alcohol septal ablation and surgical myectomy, including an apical approach of the latter. All these have been updated in this new edition, giving careful attention to where the field has come and appears to be going.

Even more exciting, this new edition has expanded into areas previously not discussed yet quite important for any busy practice. There are now chapters on sleep apnea and pulmonary hypertension, refractory systemic hypertension with or without obstructive physiology, epiphenomena such as von Willebrand disease, managing diet and obesity, taking care of the high-risk patient in the critical care unit, incorporating new percutaneous procedures such as transcatheter aortic valve replacement (TAVR), mitral valve repair (MitraClip) and left atrial appendage closure (LAAO), and managing epicardial or microvascular coronary artery disease. These additional topics, among others, add much-needed color to the management of this complex disease and allow programs to be truly comprehensive.

From a structural standpoint, figures and tables have been updated and reformatted in-house, and questions with one paragraph answers in board-style format have been added to each chapter to engage different learning styles. Key points and clinical pearls remain as bookends to each chapter and have been expanded where needed. Taken together, the new edition is comprehensive and thoughtful in its approach to guiding patients and clinicians across a broad range of specialties through the optimal care of these patients.

Four years has also brought about a change to our HCM program at my home institution, changes that perhaps serve as a template for others. In late 2016, the patient base moved to Westchester Medical Center with the goal (and dedicated resources) to create a comprehensive, one-stop-shop, world-class program. As one of the few hospitals with advanced heart failure and transplantation, a dedicated children's hospital with cardiac surgery, complex electrophysiology, geneticists and genetic counselors, and the ability to perform both surgical myectomy and alcohol septal ablation consistently, the program has grown to see over 300

patients in its first year, combining with the previous center's experience to total over 1000 patients and families over 15 years. Two offices, one in Long Island and one in Westchester, allow for expanded reach, each with their own HCM coordinator to handle patient calls and throughput. By the end of the first year here, a nurse practitioner was added, and cardiology fellows started rotating through for educational purposes. Clinical trials, observational research, center-specific and multi-institutional publications, editorials, and national education continue, including the alcohol septal ablation live proctoring course in Detroit, now celebrating its 5th anniversary, and presentations at most of the major cardiology meetings. Importantly, this has been a team effort—with all members contributing and enhancing their expertise over time—creating a comprehensive certified center of excellence accredited by the HCM Association.

I mention this transition not necessarily to self-promote but to show what can be done and should be done throughout the country and the world to help get HCM patients the care they deserve, if appropriate resources are allocated and blueprints provided in this book are carried through. Accordingly, the chapter on creating a center of excellence has been expanded, and we encourage all centers to go through this process of self-reflection and resource procurement to get what they need to develop a strong program and continue to iterate toward certification.

I'd like to thank the many individuals who helped with this second edition, either directly or indirectly. From the authors of the individual chapters, to the members of our HCM team, to my family and friends, this edition is a culmination of all the support and all the hard work you have put into it. Thanks for your dedication to HCM as a field, to the care of your patients as individuals, and to me personally as a friend and colleague. And, finally, to all the readers of this book, thank you for allowing us to participate indirectly in the care of your patients.

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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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Natural History of Hypertrophic Cardiomyopathy

2

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Key Points

- Patients with HCM typically develop left ventricular hypertrophy during adolescence or early adulthood with degree of hypertrophy plateauing after the initial period of thickening.
- Development of myocardial fibrosis, as demonstrated by late gadolinium enhancement on cardiac magnetic resonance, is found in 42–73% of patients and is likely to play a major role in the development of systolic dysfunction (end-stage HCM).
- Most HCM patients develop few or no symptoms with 76–91% having NYHA class I–II symptoms when first evaluated.
- Overall mortality rates in HCM cohorts are higher than in the general population; however, HCM-related mortality remains relatively low (≈0.5%/year in most recent publications).
- Atrial fibrillation develops in ≈20% of patients and is an important cause of stroke and exacerbation of symptoms. It is also associated with increased mortality rates.
- Advanced heart failure symptoms (NYHA class III–IV) develop in 9–24% of patients and are associated with significantly worse outcomes.
- Left ventricular outflow tract obstruction is found in 30% of patients at rest and another 40% after provocation (e.g., Valsalva maneuver, exercise). It is associated with higher mortality and greater risk of progression to advanced heart failure, especially if present at rest.
- Systolic dysfunction (i.e., end-stage HCM) develops in 3.5–5% of patients and portends an especially poor prognosis with 30% dying and another 30% undergoing heart transplant within ≈3 years.

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Introduction

The first cases described in any new syndrome are frequently the most severe and carry the worst prognosis. With increased awareness, improved diagnostic techniques, and implementation of screening programs, milder cases are uncovered, and the true natural history of the disease turns out to be more favorable. Hypertrophic cardiomyopathy (HCM) is a typical example of such progression in our understanding of a medical condition. From the early description by Teare of autopsies in sudden cardiac death (SCD) cases of young individuals [1] to the latest large cohorts including thousands of patients, our understanding of the prognosis in HCM has changed dramatically. It has long been appreciated that while some patients may develop severe disease and suffer from significant morbidity and mortality, many will have few symptoms if any and enjoy a lifespan that does not fall from that of their peers. Furthermore, with an estimated prevalence of 1:500 [2–6], most HCM patients are likely to remain undiagnosed. It is reasonable to assume that many of these are mild cases that fly under the "medical radar" and are likely to have a good prognosis.

At the same time, contemporary cohorts are influenced by the fact that they include patients receiving contemporary treatment. Pharmacological therapy, septal reduction interventions, and cardiac implantable electronic devices (CIED)

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have all been demonstrated to significantly reduce morbidity and mortality. It therefore should be appreciated that the insights regarding disease progression gained from these large cohorts do not reflect the natural history of disease but that of patients receiving modern therapy.

Disease Progression and Penetrance

Cardiac hypertrophy in patients with HCM may develop at any age. While the most severe cases present immediately after birth [7], some patients may develop a clinical phenotype only in their fifth or sixth decade of life. Typically, however, hypertrophy develops during adolescence and early adulthood and plateaus after a period of wall thickening.

Thinning of the myocardial wall may develop later in life as demonstrated by one study including patients with a maximal wall thickness >30 mm and a mean age of 33 [8]. In these patients, wall thickness decreased by a mean of 0.6 mm/year over 8 years of follow-up and was accompanied by increase in left ventricular and atrial size. Progression to systolic dysfunction (left ventricular ejection fraction, LVEF <50%), however, was noted only in 7% of patients with significant wall thinning (>5 mm decrease). Development of myocardial fibrosis is likely to play an important role in this process. Studies examining the extent of late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR), an accepted surrogate for myocardial fibrosis [9], have associated it with development of systolic dysfunction [10, 11]. Although LGE is relatively common in patients with HCM (Fig. 2.1), identified in 42–73% of cases [12], in the majority its extent is only mild to moderate (<10% of myocardial mass in 70% of patients and <20% in 86%) [11].

Disease penetrance in HCM is known to be incomplete. In one Dutch study, out of 446 relatives of patients with HCM (mean age 39 ± 18, range 1–86) that were found to carry the familial mutation, only 24% were phenotype positive [13]. Among those who were followed (n = 238), penetrance increased from 32% to 44% at last follow-up, demonstrating late-onset disease development. Despite this data, the exact penetrance and age of disease onset remain speculative. Large studies following genotype-positive patients from childhood to late adulthood are required in order to accurately answer these questions.

Prognosis and Outcomes

HCM is a highly complex disease that can present with a variety of symptoms developing as a result of multiple pathophysiological processes (see Chap. 7). The most common symptoms are exertional shortness of breath, chest pain, dizziness, fatigue, and palpitations, but the most feared outcomes are syncope, stroke, and SCD. Most patients, however, develop few if any symptoms. NYHA class I or II, for instance, was noted in 76–91% of patients during first evaluation with younger patients less likely to suffer from significant symptoms [14–16]. Women comprise only 30–40% of HCM cohorts but seem to be more symptomatic and may have worse prognosis than men [17–19]. It is not clear, however, whether this is due to older age at presentation, bias leading to increased diagnosis of men, or hormonal and environmental influences.

Mortality

HCM-related deaths include SCD, death due to heart failure (HF) or transplant-related complications, stroke-related death, and death complicating an interventional procedure (e.g., myectomy, alcohol septal ablation). In one single-center study published in 2006 including 956 HCM patients of all ages (mean- 42), the overall mortality over a median of 69 months of follow-up was 12% [20]. Most of the mortality (70%) was HCM-related out of which 62% were SCDs, 27% HF-related, and the remainder stroke or procedure-related. The annual rate of the combined endpoint of SCD, resuscitated cardiac arrest, and appropriate implantable cardioverter-defibrillator (ICD) interventions was 1%.

More contemporary data can be gleaned from a recent series of publications originating from two large referral centers in North America analyzing outcomes of their large HCM cohorts by age of presentation (<30, 30–59 & ≥60) [14–16]. Although no direct comparison between the age groups was performed, tentative conclusions may be reached. According to the published data, while the annual overall mortality rises as expected with increasing age, the HCM-related mortality seems to decline slightly (Table 2.1). The result is that the standardized mortality ratio of HCM patients in comparison with their non-HCM peers falls from 5.8 in the youngest group to 1.5 in the oldest. In other words, older HCM patients are less likely to die of HCM probably because of competing comorbidities and because patients surviving to older age have a milder disease. While their lifespan remains shorter than that of their non-HCM peers, this difference diminishes with age. Another interesting observation pertains to the differing causes of HCM-related death. While in the youngest patients HCM-related mortality is mainly due to SCD, stroke becomes a major cause of death in the elderly. Whether stroke should still be regarded as HCM-related in this population is a matter of debate. Finally, appropriate ICD therapies, resuscitated cardiac arrests, and heart transplantations may be viewed as deaths prevented by contemporary management. In the youngest group, the annual rate of these events was 1.8%, declining to 0.8% in the middle aged group and close to 0 in the oldest. Combining

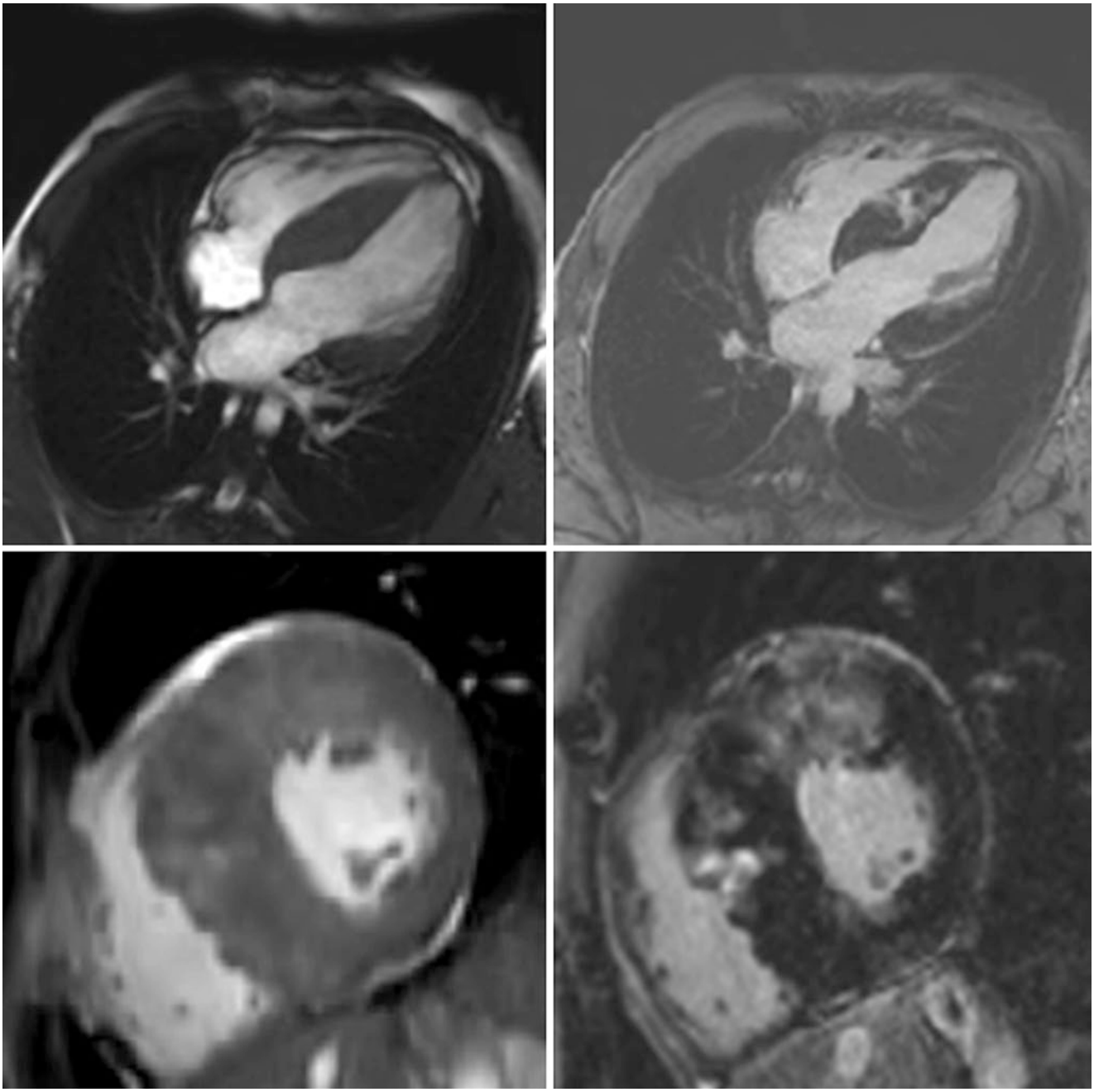

Fig. 2.1 Late gadolinium enhancement. Late gadolinium enhancement on cardiac MRI in a patient with septal hypertrophy extending to the anterior wall

the preventable and actual mortality may provide an estimate of the expected HCM-related mortality in an untreated HCM population (Table 2.1). This estimate is likely to be exaggerated, however, due to the limitation of appropriate ICD therapies as a surrogate endpoint for SCD [21].

In pediatric patients, prognosis is highly dependent on age of presentation. Patients diagnosed with isolated HCM during their first year of life are much more likely to die or undergo heart transplant than those diagnosed at an older age (19% vs. 0.5% after 1 year of follow-up and 21% vs. 3% after 2 years) [22]. Those who did survive to 1 year, however, had mortality rates similar to those diagnosed at an older age [23].After the first years of life, mortality drops to close to zero with a second peak occurring during adolescence [23]. Patients presenting with mixed cardiomyopathies (including characteristics of restrictive or dilated cardiomyopathy) and those with hypertrophy secondary to malformation syndromes or inborn errors of metabolism have a much worse prognosis [22].

Table 2.1 Mortality in patients with hypertrophic cardiomyopathy by age of presentation

Age group	<30	30–59	≥60
Cohort size, n	474	1000	428
Age, mean (range)	20 (7–29)	45 (30–59)	70 (61–91)
Annual overall mortality, %	0.66	1.16	NA
Annual actual HCM-related mortality, %	0.54	0.53	0.48[a]
Annual preventable HCM-related mortality[b], %	1.8	0.79	0.16[a]
Annual actual + preventable HCM-related mortality[c], %	2.3	1.3	0.64
Standardized mortality ratio[d]	5.8	1.7	1.5
Causes of HCM-related death[e]			
Sudden cardiac death, %	67	42.5	17
Heart failure, %	28	42.5	17
Stroke-related, %	0	5	50
Procedure-related, %	5	10	17

Data derived from three publications, including analysis of data from two large referral centers in the USA [14–16]. Direct comparison of data between the three age groups was not performed

[a]Estimate calculated from published data.

[b]A combined endpoint of appropriate ICD therapies, resuscitated cardiac arrest, and heart transplant

[c]This may be viewed as the mortality rate of untreated patients with hypertrophic cardiomyopathy. See text for details

[d]Compared with expected mortality in age- and gender-matched US population

[e]Percentage out of all HCM-related deaths

Atrial Fibrillation and Stroke

Atrial fibrillation (AF) is more common in HCM than in the general population [24], affecting approximately 20% of patients [25–29]. Its 5- and 10-year cumulative incidence in patients with HCM without known AF at presentation were calculated as 16% and 33%, respectively [26]. The annual incidence of AF in such patients was 3.1% in one meta-analysis [25] but was 7% when CIEDs (mainly ICDs) implanted for other indications were used for monitoring [30]. Although CIEDs are expected to be much more sensitive for detection of AF than other methods, patients with such devices are likely to have more severe disease than patients without. Therefore, the incidence of AF in all HCM patients is probably lower than that detected in the group with CIEDs but higher than detected on routine follow-up without an implantable device. The main risk factors for the development of AF include age, female gender, left atrial size, and NYHA class [26].

The importance of AF in patients with HCM is threefold:

1. *Exacerbation of symptoms*: AF has been demonstrated to cause new symptoms or exacerbations of previous symptoms in 84% of patients [24]. Most patients (60%) suffer from shortness of breath or chest pain; however, heart failure or syncope also develops in a substantial minority (18% and 22%, respectively). As methods for detection of silent AF were not implemented in this study, it is likely that its impact on development of symptoms is smaller, especially in patients with milder disease.
2. *Increased risk of stroke*: As in patients without HCM, patients with AF are at higher risk of stroke than those in sinus rhythm (risk ratio of 10 [27] and hazard ratio of 8 [31] in different studies). The annual incidence of thromboembolism in patients with HCM and AF has been estimated at 2.5–3.75% [25, 27]. The CHA_2DS_2-VASc risk score is thought to be less accurate in patients with HCM, who are younger and have relatively few risk factors, and is not recommended for risk stratification in this population [31–33].

   The annual incidence of stroke in the general HCM population (with and without AF) was 0.8% in one study and highly dependent on age (it was 1.9% in patients >60) [27]. Two other studies reported a generally similar incidence of 11.5% after 11 years of follow-up [34] and a calculated 5- and 10-year cumulative incidences of 2.9% and 6.4%, respectively [31].
3. *Association with mortality*: Most studies demonstrate that AF is a marker of increased overall mortality [26, 28, 29] and cardiovascular mortality [26, 28]. This association is likely the result of both direct impact of AF (e.g., stroke, HF) and the fact that it is more likely to occur in older and sicker patients.

Advanced Heart Failure and End-Stage HCM

Shortness of breath is the most common symptom in patients with HCM and may be the result of several mechanisms. Left ventricular outflow tract obstruction (LVOTO), mitral regurgitation due to systolic anterior motion (SAM) of the anterior leaflet, diastolic dysfunction, and systolic dysfunction (in end-stage HCM) are all well-described mechanisms in this context. AF, as noted above, is an important factor in exacerbation of symptoms and is more common in patients with HF (found in 48–64% of patients with NYHA class III–IV) [35, 36].

Advanced HF symptoms (NYHA class III–IV) develop in 9–24% of patients [14–16, 36] and are more likely to develop in women [36]. In one study including 293 HCM patients, 17% of whom developed advanced symptoms, the predominant pathophysiology was diastolic dysfunction which was responsible for symptoms in 48% of cases [36]. Systolic dysfunction was the cause in 30% and LVOTO in 22%. During a median of 6 years of follow-up 20% of the patients with advanced symptoms died and 16% underwent heart transplant.

End-stage HCM is defined as systolic dysfunction with LVEF<50% in the absence of alternative causes (e.g., ischemic heart disease). It develops in 3.5–5% of patients [10, 35, 36] ranging in age from 14 to 74 years (mean 45) with an incidence

of 1.12/100 patient/years [35]. Prognosis is much poorer than in other HCM patients. In the largest publication describing this group of patients ($n = 44$), 18% died of HF, and 11% died suddenly during a median follow-up of 3.3 years [35]. Another 30% underwent heart transplant. The annual incidence of adverse events (death, transplant, or appropriate ICD therapy) was 11%. Interestingly, the time from diagnosis to the development of advanced symptoms and end-stage disease is typically prolonged (>10 years); however, once these develop progression to death or transplant is rapid (2–3 years) [35, 36]. This is in contrast to patients with advanced symptoms due to other mechanisms, in whom progression to NYHA class III–IV occurs sooner after diagnosis but with a more protracted course and slower deterioration thereafter [36].

The pathophysiology underlying the development of end-stage disease is poorly understood although it has been associated with more extensive LGE [10, 11, 35]. In one study focusing on this issue, all patients with end-stage HCM had LGE with a median burden of 29% of LV mass [10]. To put this into perspective, 42–73% of HCM patients are found to have LGE on CMR, but the mean extent of LGE out of LV mass in these patients is much lower (3.2–15.5%) [12, 37].

A paucity of data is available on patients with HCM undergoing heart transplantation. The majority of these patients have end-stage HCM; however, patients with preserved systolic function without LVOTO (that therefore cannot be managed by septal reduction procedures) comprise 5–48% of those referred to transplant [38, 39]. In the largest study describing outcomes of transplanted HCM patients, the 1-,5-, and 10-year survival rates post-transplant were 85%, 75%, and 61%, respectively [40]. Two smaller studies demonstrated 1- and 5-year survival rates of 90–100% and 84–94%, respectively [38, 41]. These survival rates were comparable to those of non-ischemic cardiomyopathy patients undergoing transplant but higher than in those with ischemic cardiomyopathy [38, 40, 41].

Outcomes in Hypertrophic Cardiomyopathy Subgroups

Patients with HCM may develop several different morphological patterns of hypertrophy (Fig. 2.2) although the mechanisms

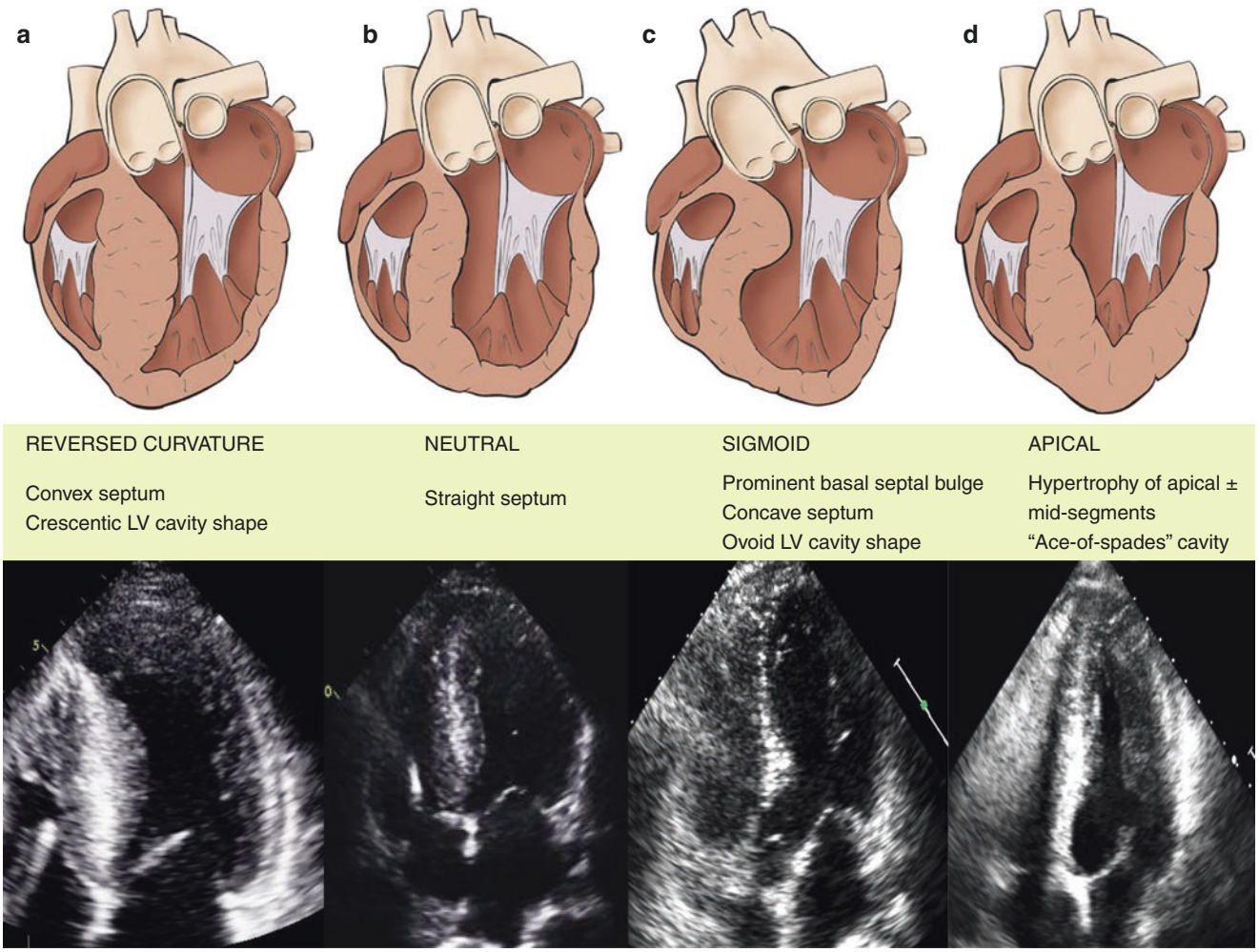

Fig. 2.2 Spectrum of morphologic subtypes in hypertrophic cardiomyopathy

leading to the development of any specific pattern remain unknown. Further diversity in phenotypic expression may be seen in the presence or absence of LVOT or mid-ventricular obstruction (Fig. 2.3). The impact of these characteristics on prognosis is discussed here. The influence of age and gender has been discussed in previous sections and that of genetic findings in Chap. 10.

Left Ventricular Outflow Tract Obstruction and Mid-Ventricular Obstruction

LVOTO is defined as an LVOT gradient ≥30 mmHg and is found in about 40% of HCM patients at rest and another 30% after provocation (e.g., Valsalva maneuver, exercise) [42]. It is caused by SAM and septal-leaflet contact leading to

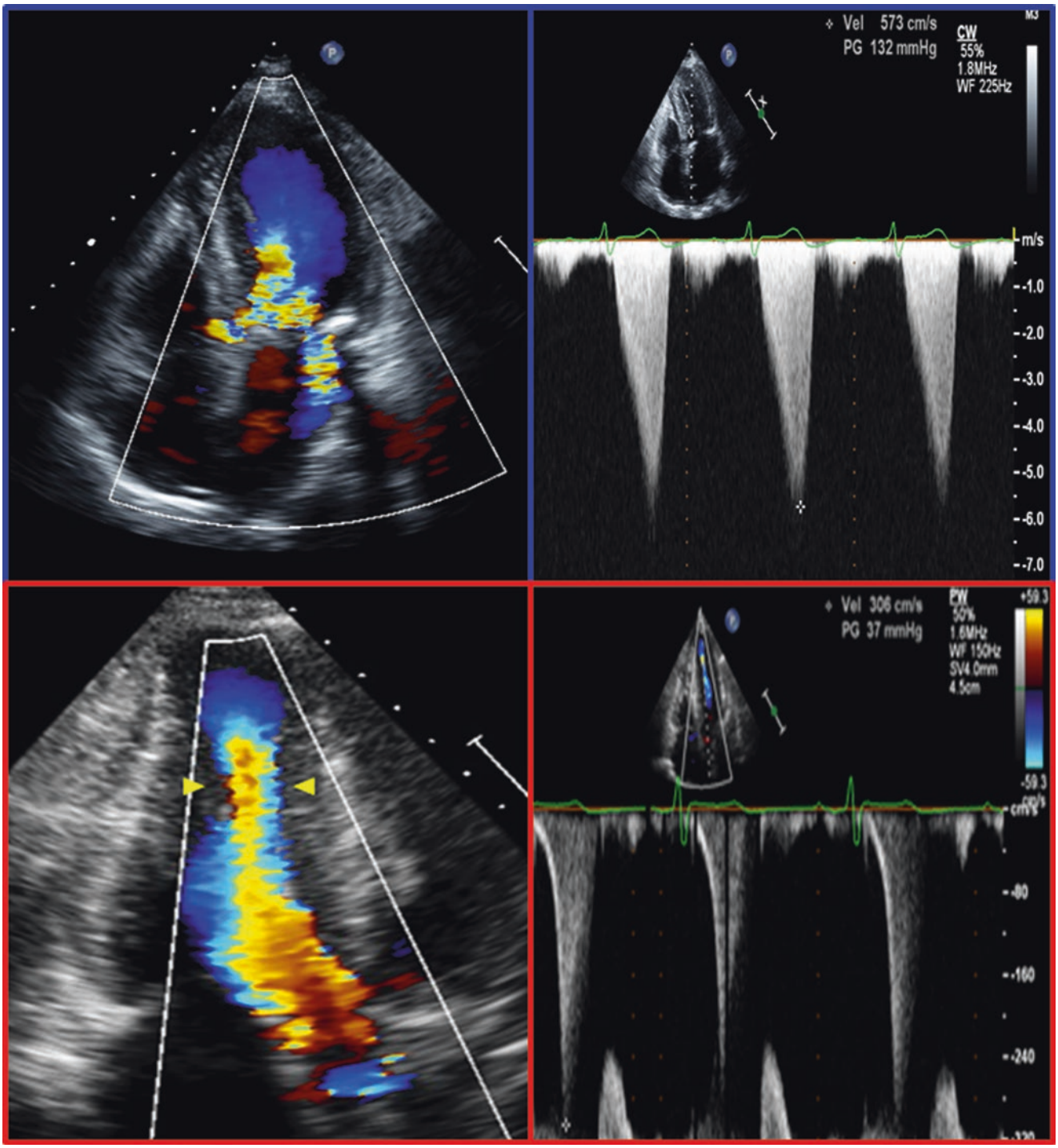

Fig. 2.3 Obstructive HCM. Upper panels: color Doppler and continuous wave Doppler demonstrating left ventricular outflow tract obstruction and posteriorly directed mitral regurgitation. Lower panels: color Doppler and pulse wave Doppler demonstrating mid-ventricular obstruction

obstruction of the outflow of blood from the left ventricle (Fig. 2.3). Basal septal hypertrophy, elongated mitral leaflets, and apically displaced papillary muscles all contribute to the development of this phenomenon.

LVOTO has been associated with increased risk of all-cause mortality, HCM-related mortality, and SCD in several large studies [43–45]. This association, however, may be dependent on severity of symptoms. In patients with mild or no symptoms (NYHA class I–II), HCM-related mortality is low irrespective of LVOTO status [46]. Similarly, in patients who develop advanced symptoms LVOTO loses its predictive power [45]. As may be expected, LVOTO is also a strong predictor of development of AF [45] and progression to advanced HF. Patients in NYHA class I–II and LVOTO at rest progress to NYHA class III–IV at an annual rate of 7.4%, compared to 3.2% and 1.6% in patients with provocable-only (i.e., latent) obstruction or no LVOTO, respectively [46].

Mid-ventricular obstruction (MVO) is defined as mid-ventricular gradients ≥30 mmHg and occurs in 8–10% of HCM cases [47, 48]. It is the result of direct contact of the hypertrophied septum with the free wall (Fig. 2.3) [49]. Hypertrophied papillary muscles and, infrequently, direct insertion of the papillary muscle into the mitral leaflet may also contribute to the development of mid-ventricular gradients.

In the largest study focusing on this HCM subgroup, patients with MVO were more likely to be symptomatic (only 28% were in NYHA I) [47]. They also had an increased risk of HCM-related death and SCD when compared with other HCM patients. When compared with patients with LVOTO, HCM-related death rates were similar, but arrhythmic events (SCD or life-threatening arrhythmias) were more frequent in the MVO group, potentially related to the secondary development of apical aneurysms. Nevertheless, the validity of MVO as a marker of adverse outcomes awaits studies on larger cohorts.

Apical HCM

The prevalence of ApHCM varies greatly from 1% to 41% and seems to be higher in East Asian (13–41%) [50–55] than in Western (1–17%) [50, 52, 56–59] cohorts. Some of this variance may be attributed to definitions of ApHCM with inclusions of only "pure" forms (defined as hypertrophy confined to segments distal to the papillary muscles) in some publications. In others, "predominantly" ApHCM cases, responsible for 15–46% of apical cases, were included and may have increased the prevalence of this subtype [53–56]. Yet discrepancy is seen even in publications directly comparing Japanese and Western cohorts. In 1992 such a comparison between cohorts in Kochi, Japan, and London, UK, demonstrated no significant difference in prevalence of ApHCM (13% vs. 11%, respectively) [50]. A decade later comparison between a Japanese cohort from the same center and a cohort from Minneapolis, USA, reached different conclusions (15% vs. 3%, respectively) [52]. It is therefore likely that technical issues and lack of strictly defined criteria are also partly responsible for the large variance in prevalence between studies.

When taking into account the limited amount of hypertrophy in most ApHCM patients and the rarity of LVOTO in this subgroup, an improved prognosis compared with other forms of HCM could be expected. Indeed, Eriksson et al. have demonstrated an overall mortality rate similar to that in the general population (10.5% over a mean follow-up period of 13.6 years) and an annual cardiovascular mortality rate of merely 0.1% [56]. Similar good prognosis has also been reported by others [55], but in cohorts including older patients, higher mortality than in the general population has been noted [60]. Other adverse events in ApHCM patients, including AF, transient ischemic attacks, stroke, HF, nonfatal ventricular arrhythmias and myocardial infarctions (MI) occurred in 25% of patients over 15 years [56]. MIs in this group are of specific interest as they usually occur in the apical region and in the absence of significant coronary artery disease [56].

Apical aneurysms (Fig. 2.4) may develop either in patients with ApHCM or with mid-ventricular hypertrophy ("hourglass morphology") and are found in 4.8% of all HCM patients [61] and 18% of those with ApHCM [62]. Patients with aneurysms were demonstrated to have low annual all-cause and HCM-related mortality (3.4% and 0.8%, respectively) similar to that seen in HCM patients without aneurysms. A trend toward higher risk of thromboembolism (1.1%/year vs. 0.5%/year, $p = 0.06$) was noted, potentially due to formation of thrombi within the aneurysm itself. Indeed, in another 14% of patients, the aneurysm was found to harbor thrombi in the absence of thromboembolic events. Finally, the risk of arrhythmic events was fivefold greater (4.7%/year vs. 0.9%/year, $p < 0.001$) driven mainly by appropriate ICD therapies. It is important to note, however, that this large apparent relative risk may have been confounded by a very high rate of ICD implantation in patients with aneurysms (60%) due to the higher perceived risk of SCD in this population. Based on this limited amount of data, HCM patients with apical aneurysms seem to have worse prognosis than those without, but the significance of aneurysms as independent predictors of outcome remains to be validated.

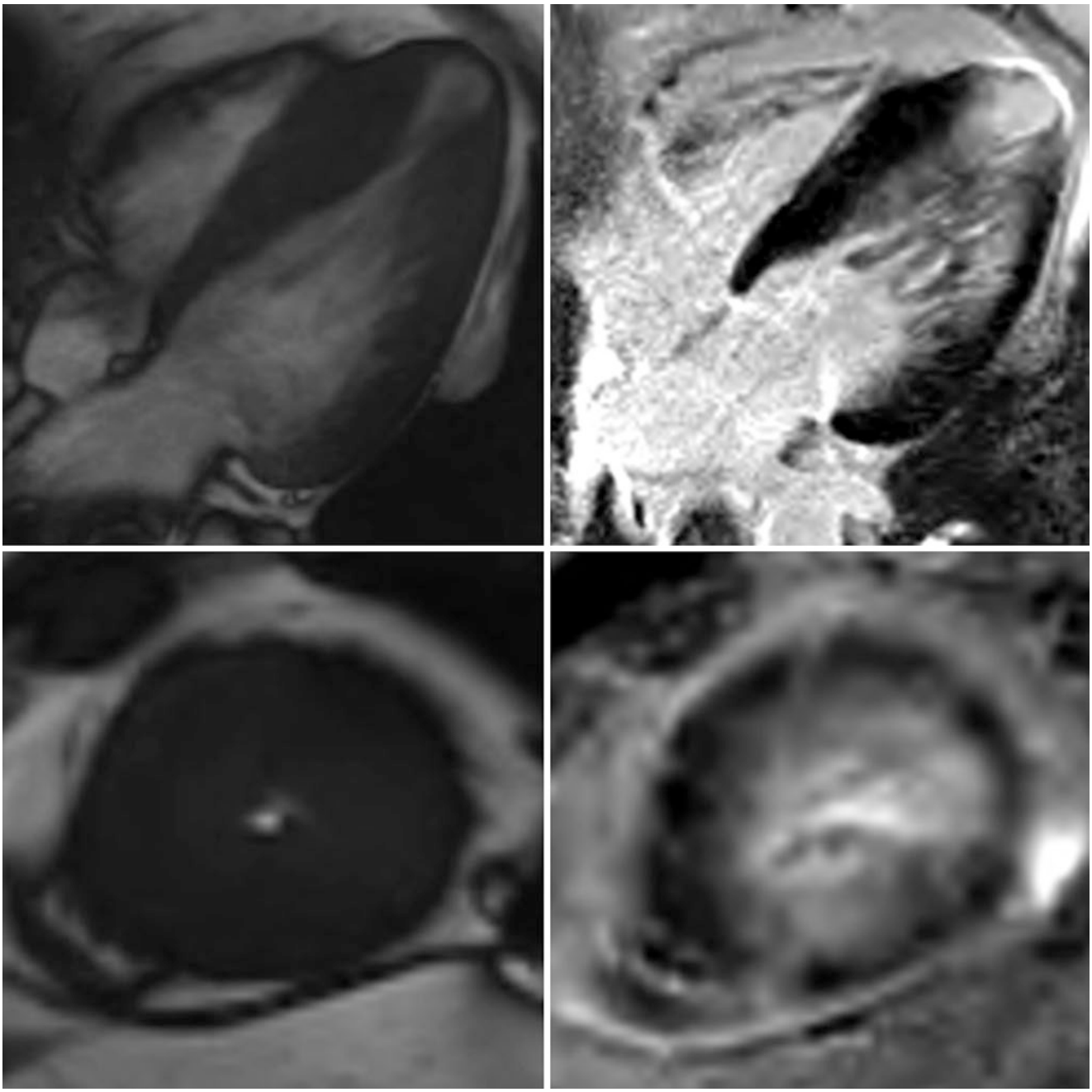

Fig. 2.4 Apical HCM. Cardiac MRI images of a patient with apical HCM. Note apical aneurysm with transmural late gadolinium enhancement of the aneurysm's rim

Future Directions

Although our knowledge of the natural history of HCM has expanded greatly since it was first described, many uncertainties remain. One central question that remains only partially answered is "what are my chances of developing disease?" Unfortunately, data regarding disease penetrance and the exact age range of disease development is still limited. Answering this question will require a large cohort of genotype-positive patients identified through family screening and followed for decades. Information regarding prognosis of subgroups of HCM (e.g., patients with end-stage disease) is also limited because of the relatively small cohorts studied up to date. Present and future international collaboration will hopefully aid in acquiring such data by analyzing larger cohorts. Finally, most of our knowledge is derived from cohorts including mainly patients of European descent, with more limited data on Asian and especially African patients. Future studies will hopefully provide information that will enable filling this gap.

Clinical Pearls

- The use of current knowledge regarding the relatively favorable natural history of HCM may be used to mitigate some of the fears which may naturally arise with the diagnosis of an inherited cardiac condition.
- Asymptomatic older patients diagnosed incidentally may be especially reassured that disease progression becomes less likely with increasing age and that their prognosis is generally favorable.
- At the same time, the risk associated with HCM should not be downplayed, as routine follow-up and life style changes may prevent the occurrence of serious adverse outcomes (e.g., stroke, SCD).
- The fact that phenotypic expression is highly variable should be emphasized. Relatives of patients with minor symptoms are less likely to comply with screening recommendations if they are under the impression that serious adverse outcomes are unlikely. Conversely, relatives of patients with severe outcomes should know this does not necessarily reflect on their own prognosis.
- In patients who develop end-stage disease close monitoring may be recommended, even if asymptomatic, as rapid deterioration is relatively common.

Posttest

1. What is true regarding HCM disease penetrance and progression?
   A. Left ventricular wall thickness continues to progress throughout lifetime in most patients.
   B. A patient who has not developed signs of HCM by the age of 30 is almost certainly going to remain phenotype negative and can be discharged from follow-up.
   C. Most patients who survive to their sixth decade will develop end-stage HCM.
   D. Almost all patients who carry the familial mutation will develop at least some signs of the disease during their lifetime.
   E. Most patients who develop signs of HCM do so during adolescence or early adulthood.

   Answer: E. Although most HCM patients first develop signs of the disease during adolescence or early adulthood, some will do so only later in life. No recommendation regarding the exact age after which follow-up can be discontinued is available, but development of HCM after the age of 30 is certainly possible. Wall thickness usually plateaus after the initial spurt and does not continue to progress with aging in most cases. End-stage HCM develops in <5% of patients. The exact disease penetrance in HCM is unknown, but it is highly unlikely to approach 100%.

2. What is false regarding mortality in patients with HCM?
   A. The annual incidence of sudden cardiac death in contemporary HCM cohorts is <1%.
   B. In infants diagnosed with HCM, HCM-related mortality is exceedingly low during childhood.
   C. Sudden cardiac death remains a leading cause of death, especially in young HCM patients.
   D. HCM patients have a higher mortality rate than in the general population, but this is attenuated with age.
   E. Contemporary therapies (e.g., ICD implantation, heart transplantation) have contributed to the declining mortality rates in HCM patients.

   Answer: B. The prognosis of patients diagnosed during their first year of life is relatively poor with a 19% risk of death or transplant within 1 year of diagnosis. In the overall HCM population, however, mortality rates have declined over the past few decades, partially due to the advent of contemporary therapies and partially due to inclusion of milder cases in HCM cohorts. Current annual SCD rates are below 1% although it remains an important cause of death, especially in the young. The standardized mortality rate in older HCM patients approaches that in the general population.

3. What is true regarding myocardial fibrosis as demonstrated by late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR)?
   A. It develops in <20% of patients with HCM.
   B. In about half of the cases, it is extensive (>20% of myocardial mass).
   C. It is associated with lower incidence of sudden cardiac death.
   D. Only a minority of HCM patients with LGE on CMR will develop end-stage HCM.
   E. LGE is not regarded as a good surrogate for myocardial fibrosis in HCM patients.

   Answer: D. Although myocardial fibrosis probably plays a significant role in the development of systolic dysfunction, most patients with LGE will not develop end-stage HCM. LGE is found in 40–70% of HCM patients and in most cases is mild to moderate (<20% of myocardial mass). It has been associated with increased risk of sudden death (see Chap. 14) and is regarded as a good surrogate for myocardial fibrosis.

4. What is true regarding atrial fibrillation in HCM?
   A. The prevalence of AF in HCM is similar to that in the general population.
   B. Because HCM patients with AF are usually younger and have less comorbidities than patients without HCM who have AF, anticoagulation is not necessary in the majority of cases.
   C. AF has been associated with increased mortality in the general population but not in patients with HCM.
   D. Stroke rates in HCM patients with AF do not increase with age.
   E. Female gender is a risk factor for the development of AF in patients with HCM.

   Answer: E. Age, female gender, left atrial size, and higher NYHA class are all important risk factors for AF in HCM. The prevalence of AF in patients with HCM is around 20%, much higher than in the general population. The CHA_2DS_2-VASc score is not regarded as an accurate method for estimating stroke risk in HCM and anticoagulation is recommend for all patients who do not have a contraindication.

5. What is false regarding an HCM patient who develops shortness of breath?
   A. NYHA class III–IV symptoms develop in the minority of patients.
   B. Atrial fibrillation is an important cause for the development of new symptoms in HCM patients.
   C. The majority of HCM patients with NYHA class III–IV symptoms have LVOTO.
   D. NYHA class III–IV symptoms are a bad prognostic sign.
   E. Coronary artery disease should be ruled out in older patients who develop new symptoms.

   Answer: C. Advanced shortness of breath (NYHA class III–IV) is most commonly attributed to diastolic dysfunction and only in the minority of cases to LVOTO (in 22% according to one study). That being said, septal reduction therapy may alleviate both obstruction and diastolic dysfunction in symptomatic patients. In a patient with new onset shortness of breath, AF and CAD should be ruled out as these are important causes for symptoms. Patients with advanced symptoms have worse prognosis with a 6-year risk of death or heart transplant of 36% according to one study. Luckily, less than 25% of patients develop advanced symptoms with the youngest patients least likely to do so.

6. What is false regarding a patient who is found to have a left ventricular ejection fraction <50% in the absence of coronary artery disease?
   A. His prognosis is significantly worse than an HCM patient without systolic dysfunction.
   B. Such a finding is uncovered in ≈ 20% of HCM patients.
   C. Myocardial fibrosis is thought to play an important role in the development of systolic dysfunction in this patient.
   D. Once systolic dysfunction is diagnosed, clinical deterioration is relatively rapid.
   E. If cardiac transplant is indicated, the survival post-transplant is better than in patients with ischemic heart disease.

   Answer: B. End-stage HCM, defined as LVEF <50% in the absence of non-HCM-related causes, occurs in <5% of patients. Data on this subgroup of patients is limited, but their risk of death or transplant is considerable (59% over 3.3 years of follow-up according to one publication). Although the time from HCM diagnosis to the development of systolic dysfunction is typically prolonged (> 10 years) once systolic dysfunction is detected deterioration is relatively rapid. On the positive side, survival post-transplant is comparable to that of other nonischemic cardiomyopathy patients and better than in patents with ischemic heart disease. Myocardial fibrosis is thought to play a major role in development of systolic dysfunction in HCM, and its burden is much higher in end-stage cases.

7. What is true regarding a patient with an LVOT gradient of 20 mmHg at rest and 60 mmHg postexercise?
   A. Advanced symptoms (NYHA class III–IV) are more likely to occur in this patient than in a patient without LVOT gradients even after provocation.
   B. The fact that he has no gradient at rest suggests SAM is not part of the mechanism leading to LVOTO.
   C. Such findings occur in <15% of HCM patients.
   D. Patients with LVOTO are at increased risk of SCD but not overall mortality.
   E. AF is unlikely to develop in this patient.

   Answer: A. LVOTO, defined as an LVOT gradient ≥30 mmHg at rest or after provocation, is a risk marker for development of advanced symptoms, mortality (including SCD, HCM-related, and overall mortality), and AF. LVOTO only after provocation occurs in ≈ 1/3 of patients. The mechanism of LVOTO in these patients is the same as in patients with significant gradients at rest.

8. What is true regarding a patient with hypertrophy isolated to segments distal to the papillary muscles?
   A. Such morphology is rare in Asian HCM patients.
   B. The thickened apex protects this patient from the development of an apical aneurysm.

C. The finding of an apical scar in this patient invariably suggests coronary artery disease.
D. The absence of basal septal hypertrophy suggests advanced fibrosis and wall thinning of these segments.
E. This patient's prognosis is favorable when compared with a patient with "reverse curvature" morphology.

Answer: E. Apical HCM is associated with less morbidity and mortality than other types of HCM. These patients may develop, however, apical aneurysms in the absence of CAD. The reason for development of hypertrophy limited to the apical segments is unknown and is not due to "burnt out" basal segments. Most studies demonstrate it is more common in Asians.

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Pathology and Pathophysiology

3

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Abbreviations

HCM Hypertrophic cardiomyopathy
MRI Magnetic resonance imaging

Key Points

- Diagnosis of HCM is dependent on pathologic findings in the heart along with family history.
- HCM must be distinguished from physiologic enlargement of the heart in athletes.
- Conditions that may result in myofiber disarray other than HCM include other causes of ventricular hypertrophy, aortic stenosis, and chronic hypertension.
- Risk factors of sudden death include sustained ventricular or supraventricular tachycardia, recurrent syncope in the young, non-sustained ventricular tachycardia, bradycardia, and massive myocardial thickening >3 cm.

Introduction

In 1958 Teare's first report of asymmetric hypertrophy of the heart in a 14-year-old boy was described as a "localized and diffuse hypertrophy of the interventricular septum in close proximity to the mitral valve with a coarse texture" and microscopically had "bizarre arrangement of bundles of muscle fibers running in diverse directions." He thought it represented a tumor of the heart. In the 1960s investigators from Bethesda, London, and Toronto defined the clinical, hemodynamic, and pathologic features of hypertrophic cardiomyopathy (HCM), and these investigators emphasized the obstructive nature of the disease [1]. The original definition by the World Health Organization (WHO) of cardiomyopathy in 1980 was "heart muscle disease of unknown etiology." Diseases that involved the myocardium but were of a known cause were considered separately and termed specific heart muscle diseases. The report of the 1995 WHO/International Society and Federation of Cardiology Task Force defined cardiomyopathy as "disease of the myocardium associated with cardiac dysfunction." They classified these into dilated cardiomyopathy, HCM, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and unclassified cardiomyopathies. Since then, much progress has been made in our understanding of the etiology and pathogenesis of heart muscle disease such that the distinction between cardiomyopathy and specific heart muscle disease has become much clearer.

The first modern pathologic description as stated above was provided by Teare [2], and the most important early clinical report was given by Braunwald et al. in 1964 [3]. Using the term asymmetry of the heart in young adults, Teare hypothesized that the condition was likely to be a hamartoma that resulted in outflow tract obstruction. Further pathological characterization of the condition, later referred to as "idiopathic subaortic hypertrophic stenosis," followed [4]. It was gradually accepted that HCM was a result of generalized ventricular dysfunction and that significant outflow tract obstruction occurred in only 50–70% of patients [5]. The importance of myofiber disarray and its quantification by morphometric techniques occurred in the late 1970s [1, 6, 7]. Although an autosomal dominant mode of inheritance was described as early as 1960 [8, 9], the genetic basis for many of the inherited forms of the disease was established only in 1990, more than 30 years after the initial morphological description [10].

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Epidemiology

HCM is a common genetic cardiovascular disease with a global distribution; epidemiological studies from several parts of the world report a similar prevalence of LV hypertrophy, the quintessential phenotype of HCM, to be 0.2% in the general population, which is equivalent to at least 600,000 affected individuals in the USA (120,000 in the UK) [11–13]. In a previous published analysis of 1866 sudden death in young athletes in the USA, HCM was the major underlying cardiovascular disorder in confirmed cardiovascular events (Fig. 3.1) [14]. The variability in this range is probably due to study methodology, as the lower prevalence is based on patients presenting with symptomatic disease and the higher prevalence is based on echocardiographic screening. The disease may occur at any age, although most patients are in their 30s or 40s at the time of diagnosis. In an older clinical study of 600 patients, the mean age was 45 (range 7–79 years), and 66% of patients were men [15]. Males were affected one and one-half times as frequently as females in a different multicenter study [16]. The disease is either under-recognized or clinical diagnosis is delayed, more frequently in women and in African-Americans. The mean age at presentation is approximately 45 years, with a bimodal distribution that peaks in early and later adulthood. The infantile form of the syndrome is probably a heterogeneous entity distinct from the adult disease. However, hereditary forms of the disease have been identified with expression of typical HCM in infancy. Clinically, elderly patients are more likely hypertensive, with greater basal septal bulging and anterior septal hypertrophy of the left ventricle [17].

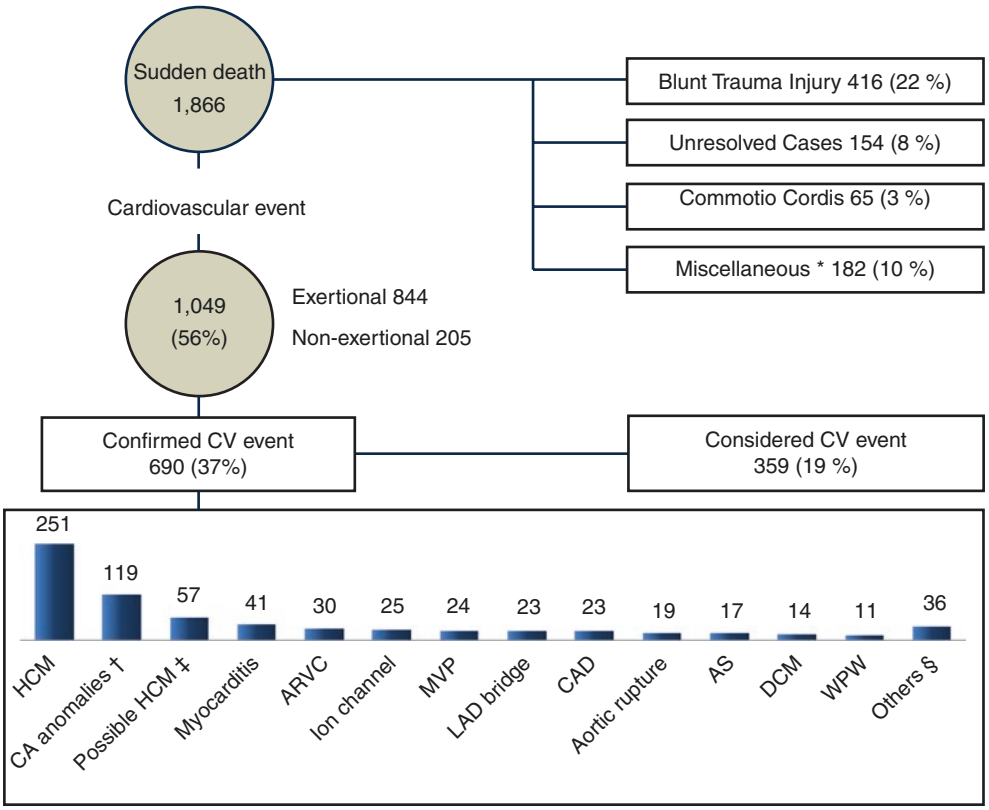

Fig. 3.1 Distribution of sudden death (SD) attributed to underlying cardiovascular disease in young competitive athletes in the USA (1980–2006). Hypertrophic cardiomyopathy (HCM) is the most common primary cardiovascular disease leading to SD in this cohort. *Heat stroke (n = 46), drugs (n = 34), pulmonary disease (n = 35), suicide (n = 22), lightning (n = 12), drowning (n = 10 and 3 during the swimming segment of triathlon events), cerebral aneurysm (n = 9), rhabdomyolysis (n = 8), epilepsy (n = 2), and miscellaneous (n = 4). †Of wrong sinus origin coursing between aorta and pulmonary trunk; most commonly, anomalous left main coronary artery from right (anterior) sinus of Valsalva (n = 65) and anomalous right coronary artery from the left sinus (n = 16). ‡Regarded as possible (not definitive) evidence for hypertrophic cardiomyopathy at autopsy with mildly increased left ventricular wall thickness (18 ± 4 mm) and heart weight (447 ± 76 g). §Congenital heart disease (n = 8), myocardial infarction (n = 6), Kawasaki disease or related conditions (n = 5), sickle-cell trait (n = 5), sarcoidosis (n = 4), stroke (n = 3), cardiac tumor (n = 1), conduction system disease (n = 2), miscellaneous (n = 2). ARVC arrhythmogenic right ventricular cardiomyopathy, AS aortic stenosis, CA coronary artery, CAD coronary artery disease, CV cardiovascular, DCM dilated cardiomyopathy, LAD left anterior descending coronary artery, MVP mitral valve prolapse syndrome, WPW Wolff-Parkinson-White syndrome. (Modified and reproduced from Maron et al. [14])

Gross Pathology (Figs. 3.2, 3.3, 3.4, 3.5, 3.6, and 3.7)

HCM is indeed unique because it may present at any age from infancy to old age [18]. Clinically HCM requires a hypertrophied non-dilated left ventricle without evidence of any other cardiac or systemic disease (e.g., systemic hypertension) that could produce the extent of hypertrophy observed. In the vast majority of adults dying from HCM, there is cardiomegaly typically in the range of twice the normal heart weight. The mean heart weight is above 600 g in most autopsy series, and several reports describe heart weights of over 1000 g [19–21]; however sudden death in HCM may occur in the absence of left ventricular hypertrophy (Fig. 3.2). The heart weight should be evaluated in conjunction with body weight, especially in sudden death in young individuals, where marked cardiomegaly may not have yet developed [22]. The latter cases, although rare, have been documented on the basis of family studies and histological findings of myofiber disarray, in which there is loss of the normal parallel configuration of cardiomyocytes [23].

In early stages of the disease, the left ventricular cavity is small, and there is usually left atrial dilatation resulting from decreased left ventricular compliance. In children, there may be relatively rapid accumulation of myocardial mass, with 250% increases in ventricular thickness occurring over 3–6 years [24]. The gross features of apical HCM differ from other types (Fig. 3.4). The heart weight may be only mildly increased, and the apex of the ventricular septum demonstrates scarring and myofiber disarray which may be grossly visible and involve the right ventricle and left ventricular septum.

In later stages of disease, there may be gradual dilatation of the left ventricle, and areas of hypertrophy may be partly replaced by grossly discernible fibrous tissue. The replacement of hypertrophied areas by scarring may transform previously hypertrophied areas of ventricular wall to normal or even thin ones [25], and transmural scars may be present in the absence of epicardial coronary occlusions [7].

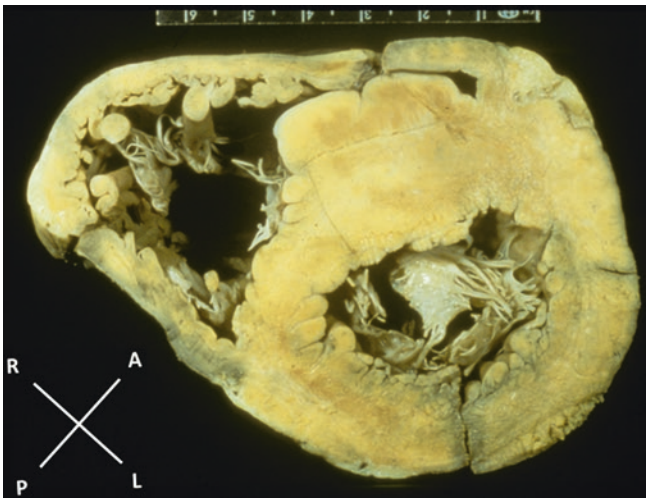

Fig. 3.3 Hypertrophic cardiomyopathy, asymmetric hypertrophy. The anterior portion of the septum is thickened, which is the most common area in the septum to demonstrate hypertrophy. (Modified and reproduced from Virmani et al. [79])

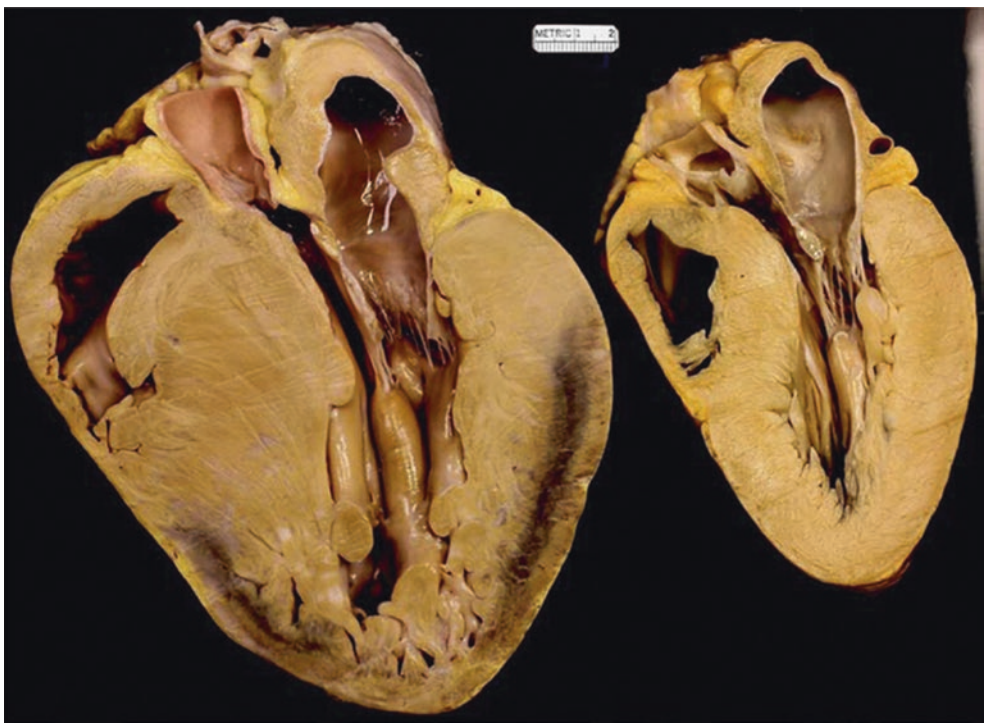

Fig. 3.2 The hearts of two 15-year-old male patients with hypertrophic cardiomyopathy, each of whom died suddenly. The heart on the left weighed 1415 g, and the ventricular septum was much thicker than the left ventricular free wall. The heart on the right weighed 425 g, and the thicknesses of the ventricular septum and left ventricular free wall were similar. (Modified and reproduced from Roberts W.C., et al. Am J Cardiol 2009;103:431–4 and Maron BJ, et al. Am J Cardiol 2008;101:544–47)

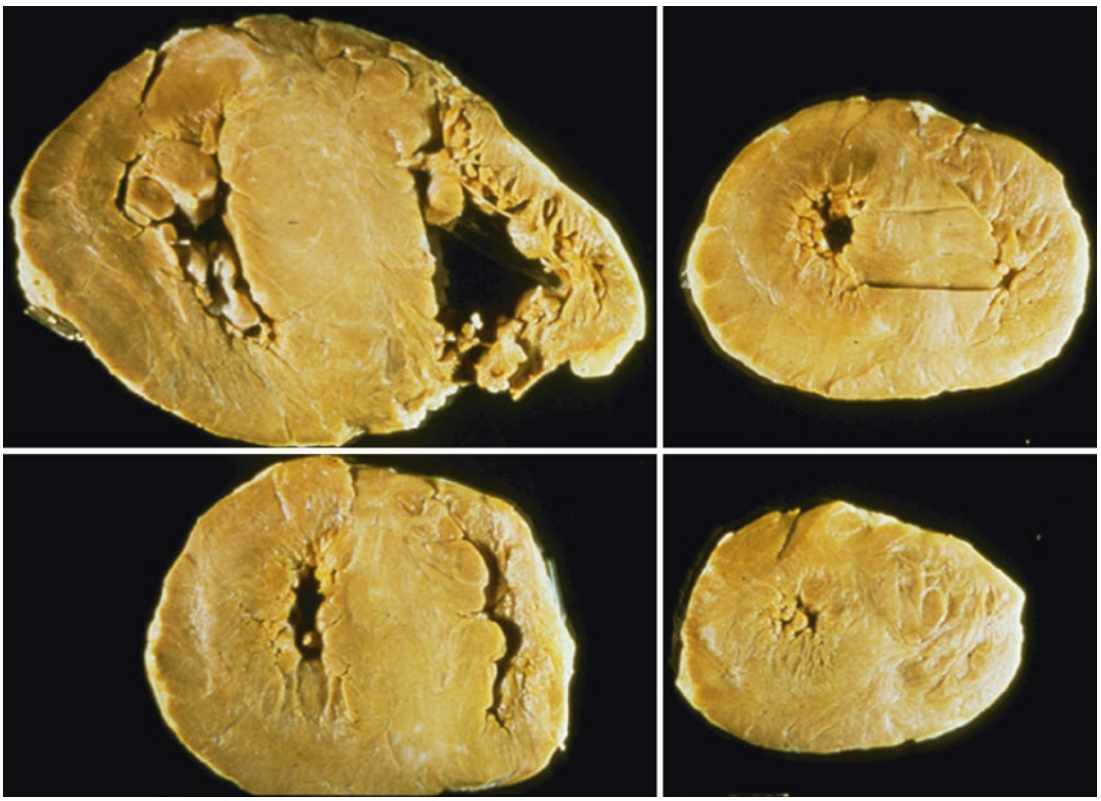

Fig. 3.4 Apical hypertrophic cardiomyopathy. The predominant area of septal hypertrophy was toward the apex. (Modified and reproduced from Burke and Virmani [80])

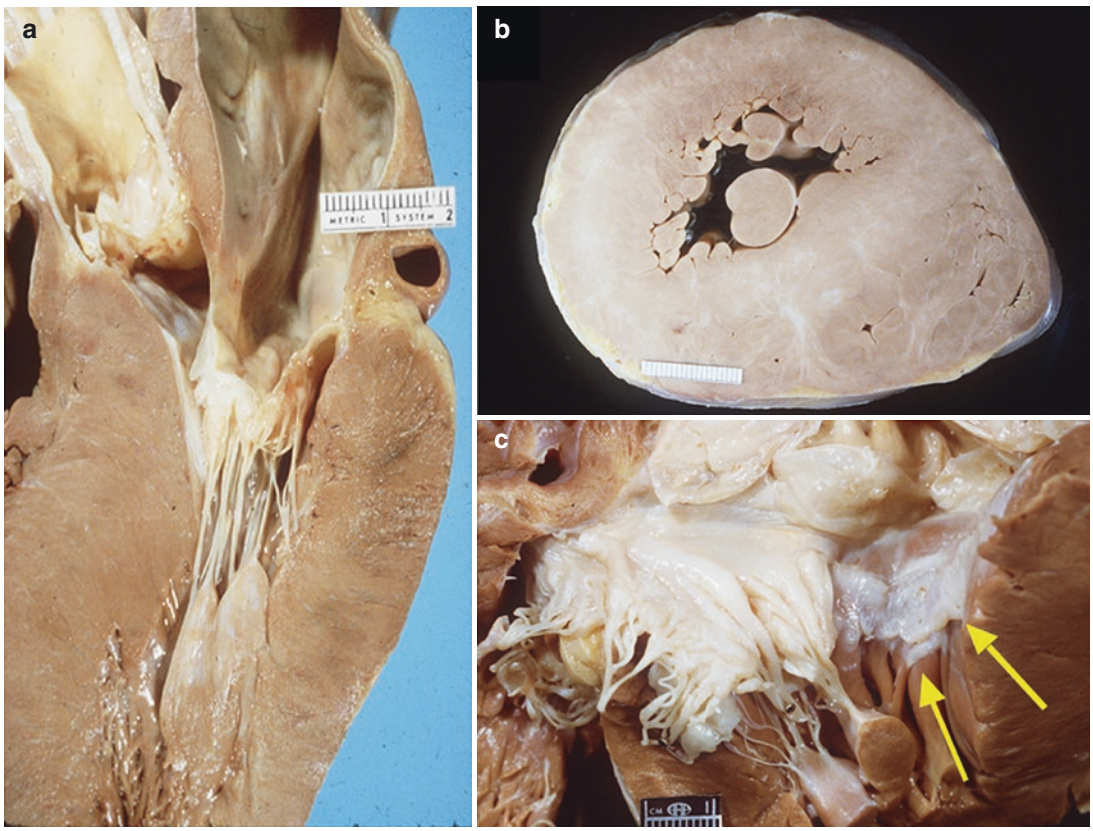

Fig. 3.5 Hypertrophic cardiomyopathy, left ventricular outflow tract plaque. (**a**, **b**) Hypertrophic cardiomyopathy with left ventricular outflow tract plaque. (**c**) A higher magnification of the outflow tract, with the anterior leaflet of the mitral valve lifted back, shows a discrete outflow tract plaque

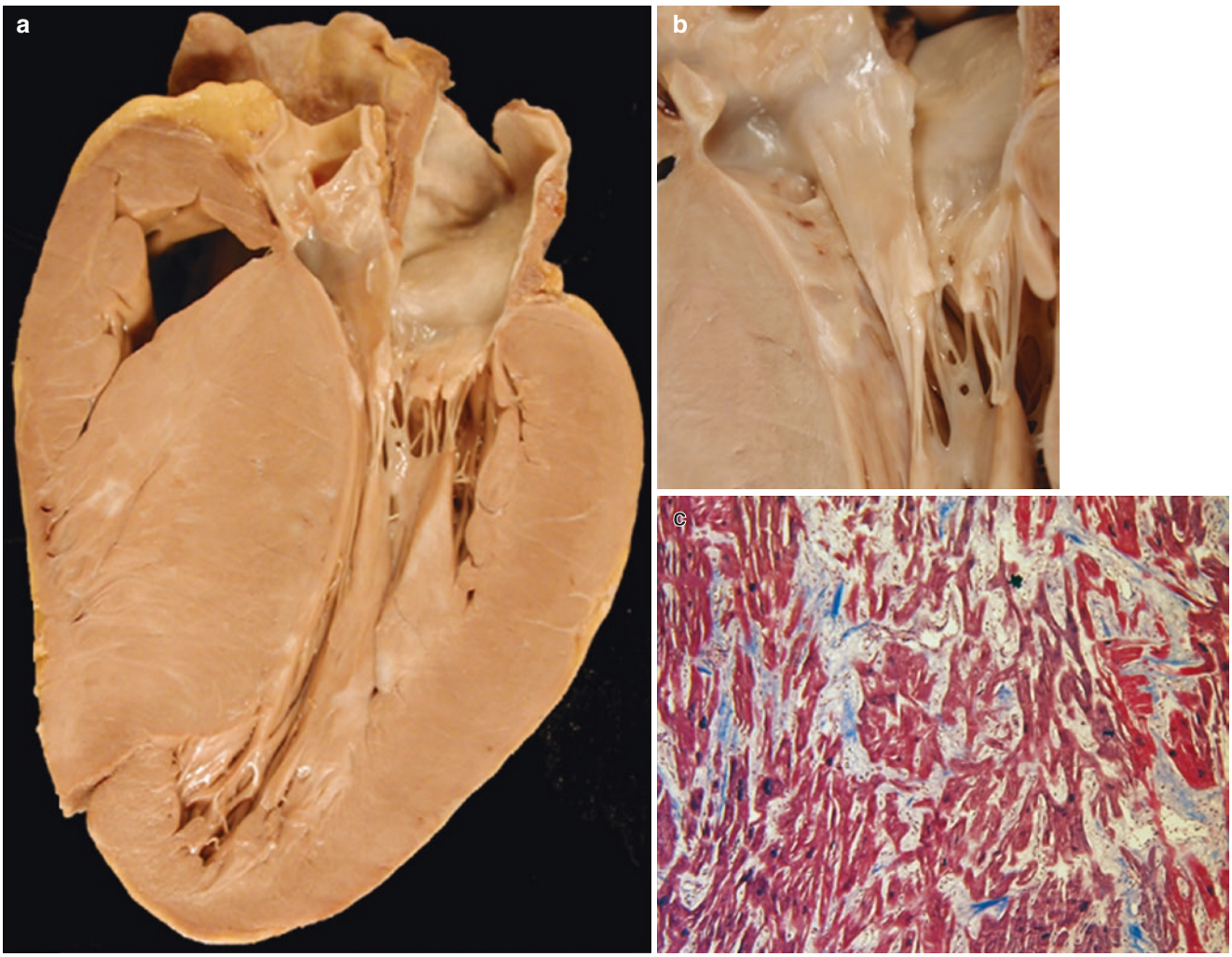

Fig. 3.6 Hypertrophic cardiomyopathy. (**a**) Long-axis echocardiographic view of the right and posterior half of the heart demonstrates asymmetric hypertrophy. (**b**) A higher magnification of the outflow tract, with the anterior leaflet of the mitral valve lifted back, shows a discrete outflow tract plaque. (**c**) Masson trichrome stain demonstrating fibrosis in the area of myofiber disarray (blue-stained interstitial collagen)

Occasionally, there may be diffuse gross myocardial scarring in late stages of disease. The evolution of morphologic features must be considered if autopsy findings are compared to cardiac imaging performed years prior to death.

Recently Melacine et al. reported their finding in HCM patient ($n = 293$) who developed progressive severe heart failure [$n = 50$ (17%)], and among those with heart failure, atrial fibrillation was observed in 64%. Therefore the actual number with atrial fibrillation is relatively small proportion (11%) of the total population studied. Of these patients, 12 HCM hearts were available for pathologic examination, and 5 had atrial fibrillation and thrombi in the left atrial appendage including 3 who had history of embolization (Fig. 3.7) [26].

The site of hypertrophy has been classified on the basis of echocardiographic criteria into four types [15]: in type I, only the anterior ventricular septum is thickened (Fig. 3.3); in type II, the entire septum is thick, with a normal free wall; in type III, there is involvement of the free wall as well as the ventricular septum; and in type IV, the least common the anterior septum is normal, and the hypertrophy is found in other locations of the septum or free wall. In the past, M-mode echocardiography was the main method for confirming the presence of HCM. However, increasingly high-resolution cardiovascular MRI has assumed an important role in the clinical diagnosis of HCM, especially in individuals with hypertrophy of the anterolateral free wall, apex, or posterior septum [18]. By pathologic examination the location of the hypertrophy can be easily established. In patients with HCM, the left ventricular wall thickness ranges widely from mild (13–15 mm) to massive (>50 mm). In 73% of hearts, asymmetric hypertrophy is accompanied by the presence of a left ventricular outflow tract plaque, which correlates clinically with subaortic stenosis and systolic anterior motion of the anterior leaflet of the mitral valve (Figs. 3.5 and 3.6) [19]. Mitral valve thickening and elongation, with increased mass of the valve, is frequently observed.

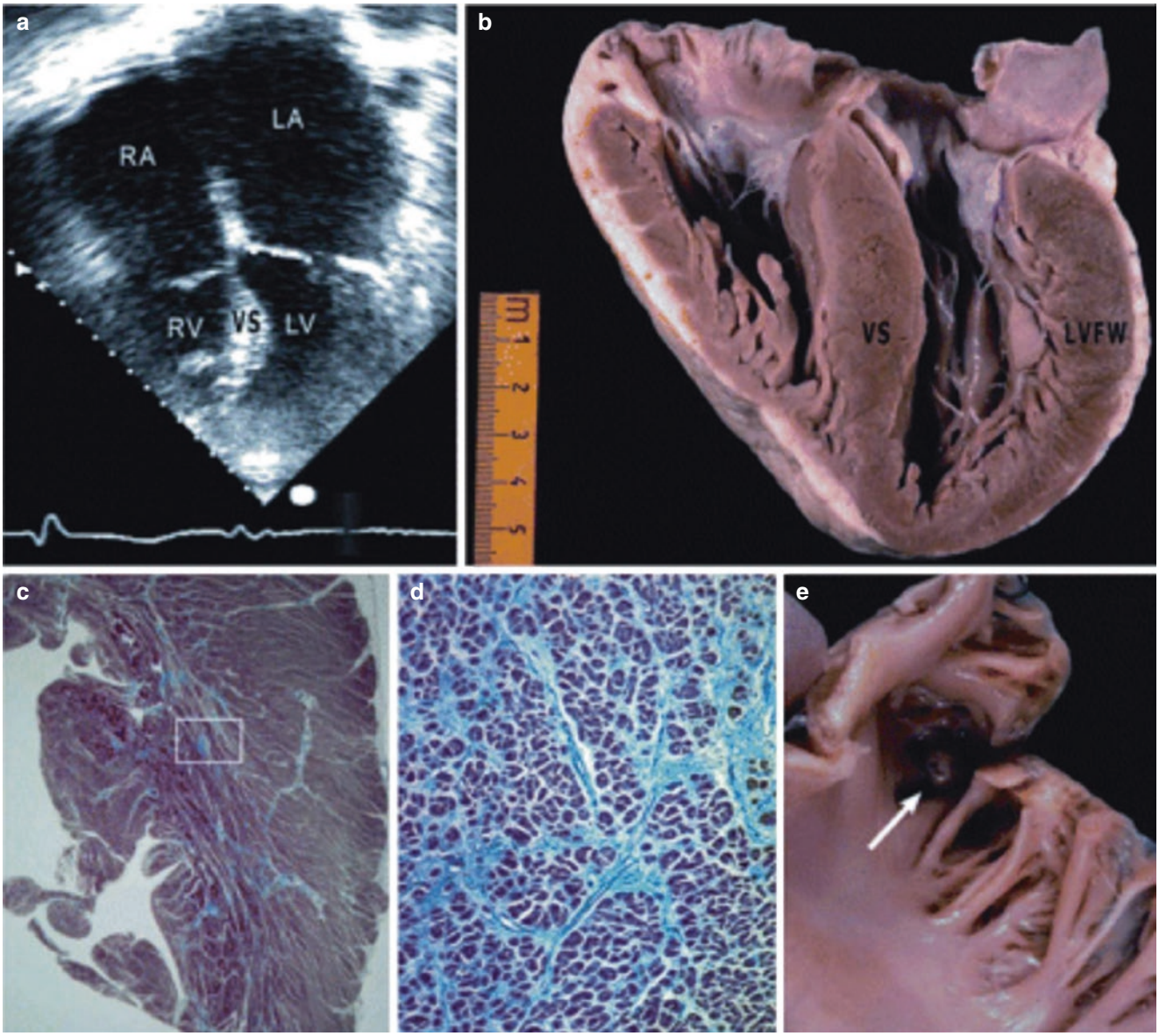

Fig. 3.7 Nonobstructive hypertrophic cardiomyopathy with preserved systolic function and atrial fibrillation. A 60-year-old male patient with a β-myosin heavy-chain mutation. (**a**) Four-chamber view at end-diastole showing severe dilatation of both atria [transverse dimension of left atrium (LA), 90 mm], normal-sized left ventricle (LV) and right ventricle (RV), and mild LV hypertrophy (ventricular septum, VS; 18 mm) as well as preserved systolic function. (**b**) Heart removed at transplantation. (**c**) Histological section of left ventricular free wall (LVFW) showing the absence of replacement fibrosis. Trichrome stain ×3. (**d**) High-power view of area in box in (**c**) showing increased interstitial fibrosis. Trichrome stain ×40. (**e**) Thrombus within LA appendage (arrow). RA right atrium. (Modified and reproduced from Melacini et al. [26])

Apical Hypertrophic Cardiomyopathy

Apical HCM is characterized by hypertrophy of the myocardium, predominantly in the left ventricular apex (Fig. 3.4) [27–29]. This relatively rare variant of HCM, first described in Japan, constitutes 13–25% of all cases of HCM in Japan; however, it is much less often observed in non-Japanese populations. Despite a relatively good prognosis for apical HCM, long-term observations have occasionally included sudden cardiac death, severe arrhythmias, and apical infarctions with apical aneurysms. In the USA, the apical form of the disease is rare, accounting for only 1% of cases pathologically, although this may underestimate the true clinical prevalence given the more benign prognosis.

Endocardial and Valvular Pathology (Figs. 3.5 and 3.6)

As stated above left ventricular outflow tract plaque is observed in up to 73% of hearts [19]. In contrast to congenital subaortic stenosis, the area of endocardial fibrosis is limited to that opposite the anterior leaflet of the mitral valve. The frequency of a left ventricular outflow tract plaque is 95% in patients

with documented subaortic stenosis by catheterization and less than 50% in patients without subaortic stenosis [19]. The area of stenosis may be surgically removed to relieve outflow tract obstruction. Currently, percutaneous ethanol injection into the ventricular septum is performed in lieu of surgical correction (see below) in a significant portion of patients, and the plaque location is oftentimes utilized as an echocardiographically visible guide for targeted alcohol infusion.

Microscopic Pathologic Features (Table 3.1 and Fig. 3.8)

The characteristic histological features in HCM are the presence of marked myofiber disarray (also called myocyte disarray, myocardial disarray (Fig. 3.8) [30], and myocyte disorganization [31]). Myocyte hypertrophy, interstitial fibrosis, and intramural coronary abnormalities (thickening with severe narrowing) have all been described. Myocytes show hypertrophy with increase in transverse diameter, and the myocyte nuclei appear hyperchromatic and hypertrophied and assume bizarre shapes. The histologic manifestations of myocyte disarray include oblique alignment of myocytes, producing a whorled, tangled, or pinwheel configuration [32, 33]. In addition, the shape of myocytes is abnormal, with branching fibers common, and lateral attachments are increased. Some earlier studies have suggested that at least 5% of the ventricular septal myocytes should show disarray, a diagnostic sensitivity of 86%, and a specificity of 90% [6]. The histological boundaries of myofiber disarray are not circumscribed, and the evaluation may be somewhat subjective. It must be kept in mind, in addition, that the evaluation of myofiber disarray is only possible if cross sections (short-axis cuts) are taken for microscopic evaluation. It has been reported that cellular disarray is widely varied but occupies on an average 33% and is more extensive in the young patients who die of their disease [34, 35].

Conditions that may result in myofiber disarray other than HCM include other causes of ventricular hypertrophy, including aortic stenosis and chronic hypertension [36]. However, the degree of myofiber disarray in these conditions is generally minimal and less than 5%. Normal hearts may demonstrate myofiber disarray at the junction of the free walls and septum. The myocyte disarray of HCM is characterized by a greater enlargement of myocyte size in the affected region (usually in the middle third of the ventricular septum) than in the subendocardial areas in the same section of myocardium. Myofiber disarray is usually accompanied by increase in fibroblasts and collagen, the former predominating in early stages and the latter in later stages of the disease [37–39].

Table 3.1 Autopsy pathologic features, hypertrophic cardiomyopathy

Feature	Frequency[a]
Gross	
Cardiomegaly	95%
Asymmetric hypertrophy	90%
Subendocardial scars	80%
Left ventricular outflow tract plaque	60%
Mitral valve prolapse	3%
Transmural scars	2%
Apical septal hypertrophy	1%[b]
Histologic	
Myofiber disarray >5% of ventricular septum	85%
Intramural coronary artery thickening	83%
Interstitial fibrosis	95%

Modified and reproduced from Virmani et al. [79]
[a]These are approximate and may vary by definitions used and phase of illness
[b]Up to 25% in Japanese

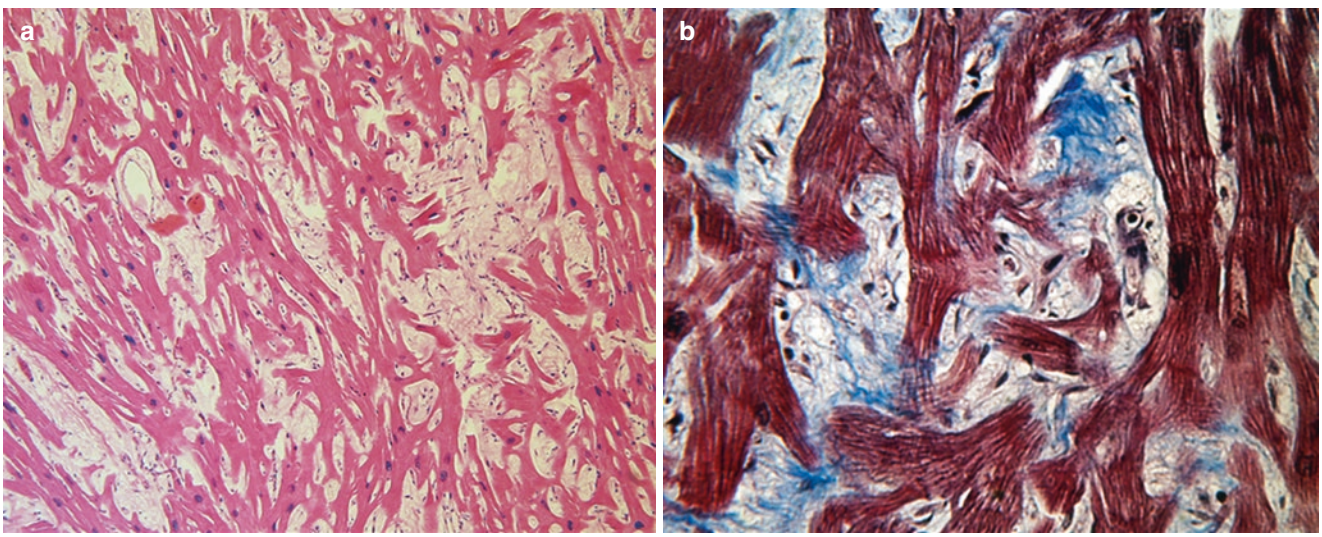

Fig. 3.8 Fibromuscular disarray in hypertrophic cardiomyopathy. (**a**) Hematoxylin-eosin-stained section demonstrating hypertrophied myocytes with abnormal branching forms. (**b**) Masson trichrome stain demonstrating fibrosis in the area of myofiber disarray (blue-stained interstitial collagen)

Abnormal patterns of desmin immunoreactivity have been described in areas of myofiber disarray. These include a decrease or loss of labeling of intercalated discs and Z bands, longitudinal arrangement of desmin intermediate filaments, and focal intense, granular staining of myocytes [40]. Ultrastructurally, malalignment of sarcomeric myosin filaments has been described in patients with HCM with known genetic mutations [41].

Fibrosis (Fig. 3.9)

The ventricular septum in HCM may also demonstrate interstitial and replacement fibrosis, as well as foci of lymphocytic inflammation. The fibrosis is often most marked in areas of myofiber disarray. In patients with longstanding disease, there may be diffuse scarring throughout the ventricles and the free wall. In such cases, the distinction between HCM and idiopathic restrictive cardiomyopathy may be difficult. It has been suggested that many cases of restrictive cardiomyopathy are, in fact, forms of HCM [42]. In the dilated phase of HCM, extensive scarring may be present but is predominantly found in the ventricular septum and the right ventricle and has been attributed to intramyocardial small vessel disease [43].

Recent clinicopathologic studies indicate that the expanding myocardial fibrosis area may involve more than one-third of the left ventricular myocardium and preferentially involved the left ventricular apex and the mid wall in end-stage HCM, in patients undergoing transplantation [44]. It is well known that contrast-enhanced cardiac magnetic resonance imaging (MRI) represents the area of myocardial fibrosis in HCM [45]. Several studies have reported that the amount of fibrotic area as assessed by cardiac MRI predicts prognosis, including sustained arrhythmias, worsening of heart failure, progressive dilation, and SCD, in patients with HCM [46, 47].

Coronary Artery Abnormalities (Fig. 3.10)

Another important microscopic feature of HCM is intramural coronary abnormalities. Intramural coronary artery thickening is present in the ventricular septum in 83% of HCM [48], and the location correlates fairly well with areas of myofiber disarray. Intramural coronary artery thickening is

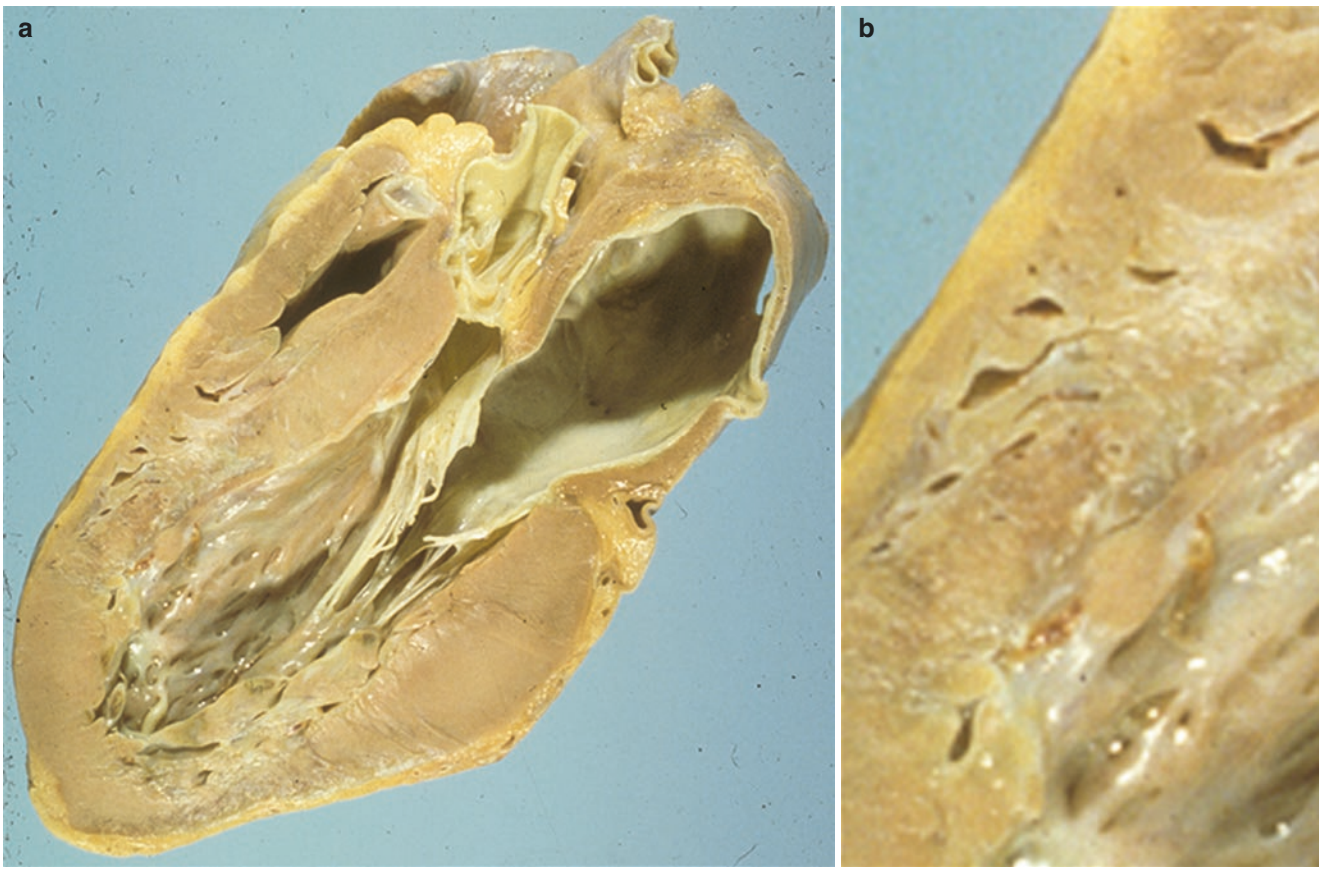

Fig. 3.9 Hypertrophic cardiomyopathy, ventricular scarring. (**a**) The thinned scarred septum located in the apical half of the left ventricle. (**b**) A higher magnification demonstrates grossly visible myocardial scars. (**c**) Histologic section of the ventricular septum showing scarring (*blue*) and intramyocardial coronary artery thickening (Masson trichrome stain). (Modified and reproduced from Virmani et al. [79])

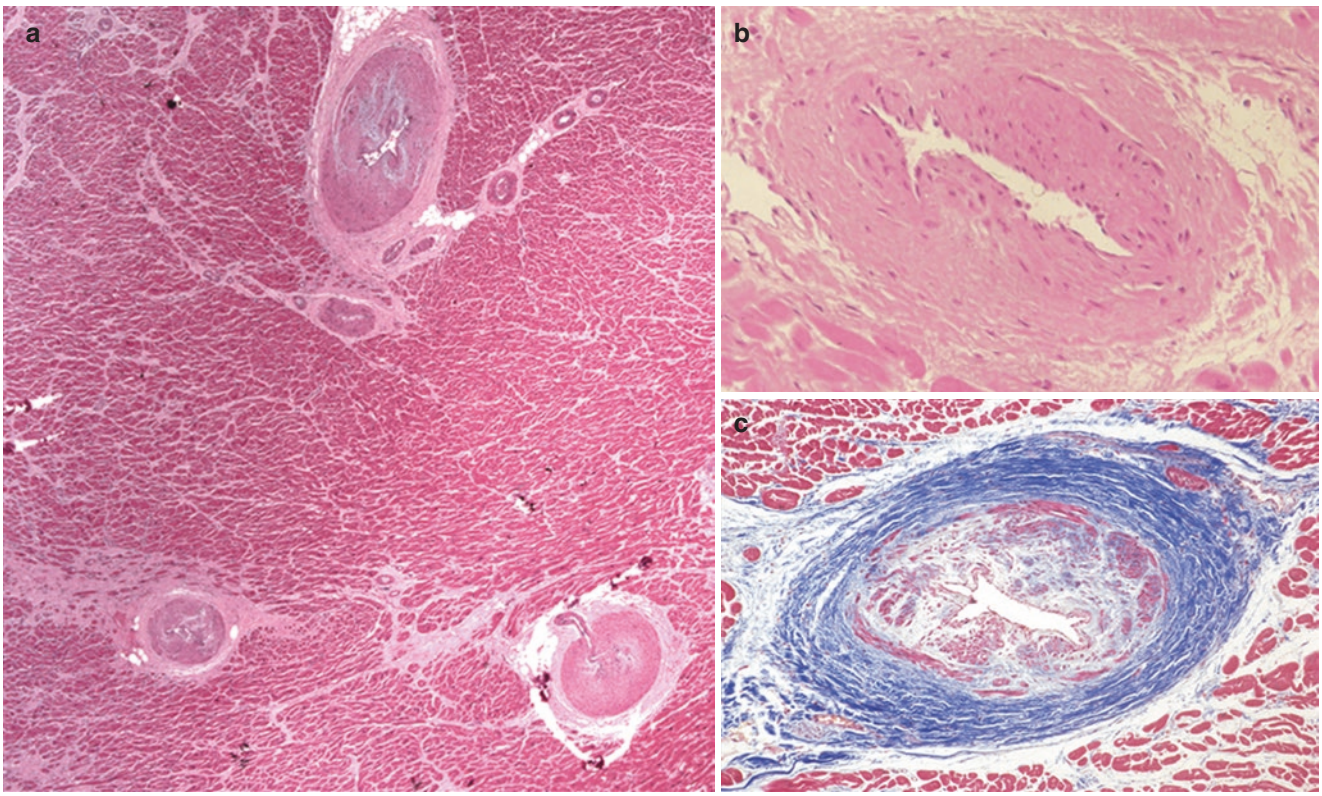

Fig. 3.10 Intramural coronary artery thickening. Intramural coronary artery thickening demonstrated in multiple intramural arteries (**a**). H&E (**b**) and Masson trichrome stain (**c**) showing adventitial scarring with thickening and dysplastic media. (Modified and reproduced from Burke and Virmani [80])

more common in hearts with fibrosis than those without significant fibrosis [48–50]. The vessels are dysplastic without a well-developed internal elastic lamina, and smooth muscle cells are in disarray.

Epicardial coronary arteries are usually normal in HCM. It is debated whether the interstitial and replacement fibrosis are secondary to ischemic insults or are an intrinsic part of the disease. It seems likely, although difficult to prove with certainty, that the majority of fibrosis is not related to ischemia. Also, the presence of a myocardial bridge over a portion of the left anterior descending artery (tunnel) has been associated with an increased risk of sudden death, especially in children [51].

HCM patients have been associated with many different complications (Table 3.2), one of them is thinning of the apex of left ventricle which appears as an aneurysm and can occur secondary to healed infarction in the presence or absence of coronary artery disease (Fig. 3.11).

We have studied 64 hearts from 51 men and 13 women dying with HCM. These patients were divided into four groups: [1] those dying suddenly during exertion (mean age 26 years), [2] those dying at rest (mean age 38 years), [3] those dying from their disease but not suddenly (mean age 34 years), and [4] those dying of other causes (mean age 51 years) (incidental). Those dying during exercise were significantly younger than the other groups (mean age, 26 years vs. 43 years, $P = 0.0009$). The mean heart weight was also significantly greater in the incidental group (696 g) than the other groups (range of means 496–622 g, $p = 0.02$).

Table 3.2 Complications of hypertrophic cardiomyopathy

Death: Sudden and non-sudden
Atrial dilatation: Atrial fibrillation
Mitral valve disease: Mitral regurgitation
Fibrous thickening (anatomic systolic anterior motion)
Insertion, papillary muscle, into leaflet
Rupture of chordae tendineae
Prolapse
Annular calcification
Infective endocarditis
Papillary muscle calcification
Myocardial infarction: Left ventricular dilation
Left ventricular apical diverticulum
Pulmonary hypertension
Aneurysm pulmonary arteries
Ossific nodules, lungs
Heart block and bundle branch block

Modified and reproduced from Roberts W.C., et al. Am J Cardiol 2009;103:431–4

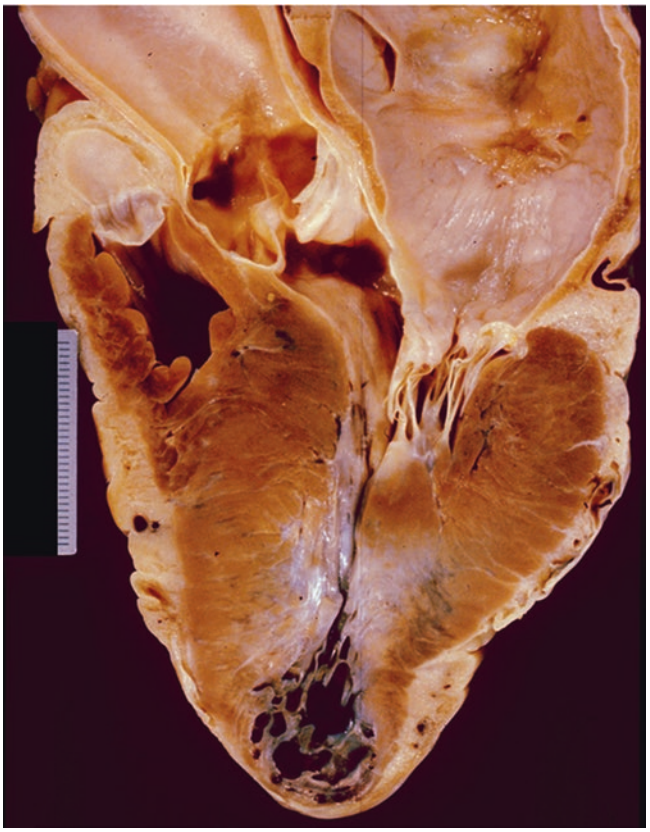

Fig. 3.11 Hypertrophic cardiomyopathy. Long-axis echocardiographic view of the right and posterior half of the heart from a patient with hypertrophic cardiomyopathy. There is marked left atrial dilatation; the patient had long-standing atrial fibrillation. The thinning of the apical left ventricle was secondary to healed infarction secondary to coronary artery disease. (Modified and reproduced from Virmani et al. [79])

Asymmetric hypertrophy with an outflow tract plaque was observed more frequently in the exercise group than in the incidental group or those dying of the disease at rest. The degree of intramural coronary artery thickening was also greatest in the exertion group, as compared with non-exertional deaths and incidental cases. These results suggest that there are morphological differences in hearts from patients with HCM dying during exertion and that there is a higher frequency of left ventricular outflow tract obstruction and intramural coronary artery thickening. Litovsky et al. reported on 55 cases of HCM and showed that asymmetric septal hypertrophy was more prevalent in younger than older subjects. Sudden death was more prevalent in the younger patients and had endocardial outflow tract plaque more often than elderly patients. Also, myofiber disarray was greater, and intramural coronary artery thickening was more frequent in younger patients compared with elderly patients [50]. The largest experience comes from the laboratory of William C. Roberts with examination of over 200 hearts at autopsy (Tables 3.3 and 3.4). He has described marked diversity in the anatomic findings, and of the ten morphologic characteristics studied, not a single heart showed all ten features.

Table 3.3 Cardiac findings in hypertrophic cardiomyopathy divided by the presence or absence of cardiac operation

	Cardiac operation		
Characteristic	0 (n = 153)	+ (n = 77)	Total (n = 230)
Dilated atria	98%	100%	99%
Increased heart weight	95%	96%	96%
Non-dilated left ventricle	82%	75%	80%
Thickened anterior mitral leaflet	66%	94%	75%
Mural plaque, LV outflow tract	60%	93%	71%
VS larger than left ventricle	71%	63%	68%
Transmural scarring, VS and/or LV wall	42%	43%	42%
Disorganization, cardiac myocytes	95%	95%	95%
Intramural coronary disease	83%	83%	83%
Interstitial fibrosis, VS and LV wall	90%	90%	90%

Modified and reproduced from Roberts W.C., et al. Am J Cardiol 2009;103:431–4
LV left ventricular, *VS* ventricular septum

Table 3.4 Gross cardiac findings by 3 age groups in 153 patients with hypertrophic cardiomyopathy without cardiac operations

	Age group (yrs)		
Characteristic	≤10 (n = 15)	11–70 (n = 124)	>70 (n = 14)
Dilated atria	95%	100%	100%
Increased heart weight	80%	98%	86%
Non-dilated left ventricle	73%	81%	93%
Thickened anterior mitral leaflet	27%	66%	100%
Mural plaque, LV outflow tract	27%	78%	100%
VS larger than left ventricle	73%	71%	79%
Transmural scarring, VS and/or LV wall	0%	45%	50%

Modified and reproduced from Roberts W.C., et al. Am J Cardiol 2009;103:431–4
LV left ventricular, *VS* ventricular septum

Histologic Findings of Myomectomy Specimens

Patients with >50 mmHg subaortic gradient are often treated surgically with myomectomy and/or myotomy for the relief of outflow tract obstruction. In a study of 89 myomectomy specimens from patients with HCM, myofiber disarray was present in 58%, generally in the deepest portion of the specimen. In contrast, myofiber disarray is present in a smaller proportion of endomyocardial biopsies, secondary to sampling error [52]. Other histologic features of HCM that may be seen in myomectomy specimens include intramural artery thickening and endocardial fibrous plaque [52].

Pathophysiology

The pathophysiology of HCM is complex and consists of multiple interrelated abnormalities, including left ventricular outflow tract obstruction, diastolic dysfunction, mitral regurgitation, myocardial ischemia, and arrhythmia [53, 54]. HCM may be suspected because of a dynamic heart murmur. It is clinically important to distinguish between the obstructive and nonobstructive forms of HCM because the management strategies are largely dependent on the presence or absence of symptoms caused by obstruction. The symptoms of HCM are those of pulmonary congestion which include dyspnea, fatigue, orthopnea, and paroxysmal nocturnal dyspnea. Impaired consciousness, chest pain, and sudden cardiac death have all been reported [12]. Because of the known familial nature of the illness, up to 25% of cases are identified incidentally because of an afflicted family member. It is important to distinguish between the normal adaptations of the heart to routine physiologic training. It has been shown that measurements of the left ventricle dimensions and wall thickness remain within normal limits; however, a small proportion of highly trained athletes develop substantial ventricular hypertrophy [21]. Table 3.5 shows the criteria used for differentiating the diagnosis of HCM from athlete's heart with physiologic left ventricular hypertrophy [21].

The hemodynamic derangements in HCM are caused by a small left ventricular cavity that restricts ventricular filling during diastole. The ejection fraction, in the initial phases of the illness, is normal or increased. There are many causes of diastolic dysfunction which includes abnormal chamber geometry and volume, myocyte hypertrophy, myocyte and myofibrillar disarray, and myocardial ischemia. Collagen turnover is increased, with collagen type 1 synthesis prevailing over degradation; there is also evidence for abnormal inhibition of matrix metalloproteinases (MMP-1 and MMP-2). Subaortic pressure gradient is present in a little over half of patients and is often variable and labile [55, 56].

Echocardiographically, the hallmarks of HCM include left ventricular hypertrophy, a small ventricular cavity, systolic anterior motion of the anterior leaflet of the mitral valve, and a characteristic ground-glass appearance of the myocardium. Asymmetric hypertrophy is typical, occurring in 80–98% of cases [15]. The distribution of left ventricular hypertrophy is heterogeneous, encompassing extensive and diffuse wall thickening to mild and segmental thickening. The anterior ventricular septum is thickened in 96% of patients and in 83% is the predominant area of hypertrophy [15]. True mitral valve prolapse is observed in 3% of patients and is not considered an increased incidence over the general population. A greater extent of left ventricular hypertrophy is associated with younger age and more marked mitral valve systolic anterior motion and outflow obstruction but shows no relation to symptoms or gender [15].

In addition to echocardiography, MRI should also be considered for routine family screening especially if echocardiography is equivocal. Today high-resolution MRI is considered superior to echocardiography especially for the characterization of phenotype, for example, the presence and extent of left ventricular hypertrophy in the anterolateral free wall [57, 58], apex [58], or posterior septum [58], and the identification of high risk apical aneurysms, along with the determination of subaortic obstruction, e.g., elongated or enlarged mitral valve [59] or accessory and displaced papillary muscles [60].

Sudden cardiac death (SCD) is not an uncommon complication of HCM and is often precipitated by exercise. The frequency of sudden death in HCM is up to 1% per year in adults with 2–4% per year in children and adolescents [21]. Even though, for the last three decades, several studies reported differences in the rate of SCD between patients with outflow obstructive HCM (HOCM) and nonobstructive HCM (NOCM), a recent meta-analysis showed that annualized incidence of SCD was only slightly higher in obstructive HCM (1.43%) than nonobstructive HCM (1.14%) patients, indicating that the well-recognized complication of SCD is higher in HOCM; however SCD in NOCM is not negligible [61]. In a series of athletes younger than age 30 years dying suddenly, HCM is among the most common findings at autopsy [62] in the USA [14], whereas in the Italian series, arrhythmogenic right ventricular cardiomyopathy is the most common cause of sudden death [63].

Table 3.5 Criteria for differential diagnosis of left ventricular (LV) hypertrophy in hypertrophic cardiomyopathy (HCM) and athlete's heart

	HCM	Athlete's heart
Distribution of hypertrophy	Mostly asymmetric	Substantially symmetric
Maximum LV wall thickness	≥16 mm[a]	<16 mm
LV cavity dimension	Normal or reduced (≤45 mm)	Normal or increased (≥55 mm)
LV filling and relaxation (by Doppler and TDI)	Usually abnormal	Normal
Regression of hypertrophy with detraining	Absent (or marginal)	Present
Marked ECG abnormalities[b]	Common	Uncommon
Familial evidence of HCM	Usually present	Absent

Modified and reproduced from Pelliccia A, et al. Eur J Cardiovasc Prev Rehabil 2006;13:876–85

ECG electrocardiogram, *TDI* tissue Doppler imaging

[a]LV wall thickness may also be <16 mm in a subset of HCM patients

[b]Most commonly deep Q waves, deeply inverted T waves, markedly increased R and/or S wave amplitudes in precordial leads

Those features that most reliably identify high-risk patients include age younger than 35 years and a family history of HCM with sudden death, African-American athletes, genetic abnormalities associated with increased prevalence of sudden death, sustained ventricular or supraventricular tachycardia, recurrent syncope in the young, non-sustained ventricular tachycardia, bradycardia, and massive myocardial thickening >3 cm (Table 3.6). A seminal paper has been published that showed that the presence of two or more of these risk factors was associated with a higher annual risk of 3–6%, while the presence of any single risk factor correlated with an annual risk of approximately 1% [21, 64].

The clinical course of patients with HCM is highly variable. Overall, there is approximately 2–3% mortality per year in adults and a somewhat higher rate of mortality in children [65, 66]. In 10% of patients or more, there is a progression to dilated cardiomyopathy. Hearts from patients dying with the dilated form of HCM may show diffuse scarring with myofiber disarray and an absence of asymmetric hypertrophy or even thinning of the ventricular septum. According to Dr. Barry Maron, extensive ventricular scarring with dilatation of the left ventricular cavity is observed in 2% of patients. It is believed that the scarring may be related to the presence of intramyocardial coronary artery thickening. HCM also appears to predispose to infective endocarditis. A few patients (2%) may develop severe mitral or aortic regurgitation, or both, requiring valve replacement secondary to infective endocarditis [67]. Vegetations usually developed on the anterior mitral valve leaflet but can also involve the outflow tract endocardium at the point of mitral-septal contact or may involve the aortic valve. Therefore it has traditionally been recommended that patients with HCM, particularly patients with outflow obstruction, receive prophylactic antibiotic therapy before dental or high-risk surgical procedures that predispose to infective endocarditis [68, 69]. Formal guidelines, however, do not consider prophylaxis mandatory in HCM, with or without obstructive physiology [70].

Table 3.6 Risk factors for sudden death

Secondary prevention
Cardiac arrest or sustained ventricular tachycardia
Conventional primary prevention risk markers
Family history of sudden death due to hypertrophic cardiomyopathy
Unexplained recent syncope
Multiple repetitive non-sustained ventricular tachycardia (on ambulatory ECG)
Hypotensive or attenuated blood pressure response to exercise
Massive left ventricular hypertrophy (thickness, ≥30 mm[a])
Extensive and diffuse late gadolinium enhancement
Potential high-risk subsets for primary prevention
End-stage phase (ejection fraction <50%)
Left ventricular apical aneurysm and scarring
Potential arbitrators for primary prevention[b]
Substantial left ventricular outflow gradient at rest
Multiple sarcomere mutations
Modifiable
Intense competitive sports
Coronary artery disease

Modified and reproduced from Maron BJ and Maron MS. [18]
ECG electrocardiogram
[a]Or the equivalent in children according to body size
[b]To arbitrate decision-making about implantable defibrillators in patients for whom risk level remains ambiguous after assessment by the conventional risk factor algorithm

Treatment for HCM includes medical therapy, possibly cardiac pacing and, in patients with outflow tract obstruction, surgical myectomy or percutaneous alcohol septal ablation. Atrioventricular synchronous pacing with appropriate placement of the lead in the right ventricular apex has been reported to reduce left ventricular outflow obstruction and symptoms in patients with hypertrophic obstructive cardiomyopathy [71]. However, treatment with pacing is controversial, and some authorities do not support its use in patients with obstructive HCM, and some even consider that it may worsen the prognosis [72], due to the long-term negative remodeling that may occur with chronic pacing.

A low perioperative mortality rate and a high late survival rate (72% at 15 years follow-up) have been reported after surgical myectomy [73]. Surgical septal myectomy was first performed in the early 1960s which involved removal of 5–10 grams of myocardial tissue from the basal ventricular septum (Fig. 3.12). Surgical septal myectomy or alcohol septal ablation should be considered in all patients with outflow tract gradients greater than 50 mmHg (at rest or with physiological provocation) and symptoms refractory to medical therapy [53, 74]. These procedures result in a significant reduction in mitral regurgitation and long-term symptomatic improvement. Notably, operative mortality for myectomy at high-volume surgical centers is now low, reduced to less than 1% [75]. According to the 2011 American College of Cardiology and the American Heart Association guidelines for the diagnosis and treatment of HCM, surgical myectomy remains the "first option" and is the "gold standard" for obstructive HCM. Alternatives to surgical myectomy include a modified Konno procedure, with aortic valve replacement and left ventricular outflow reconstruction [76]. Nonsurgical septal reduction using selective coronary alcohol injection (percutaneous alcohol septal ablation) to induce localized septal infarcts has been popularized and described almost simultaneously by two research groups, one in Germany and the other at the Royal Brompton Hospital, London, and multiple studies have shown reduced symptoms and outflow gradient, as well as long-term mortality, using this technique that mirror that seen with myectomy, in appropriately selected patients [77]. The more recent 2014 European Society of Cardiology guidelines place surgical myectomy and alcohol septal ablation as comparable therapies in appropriate patients.

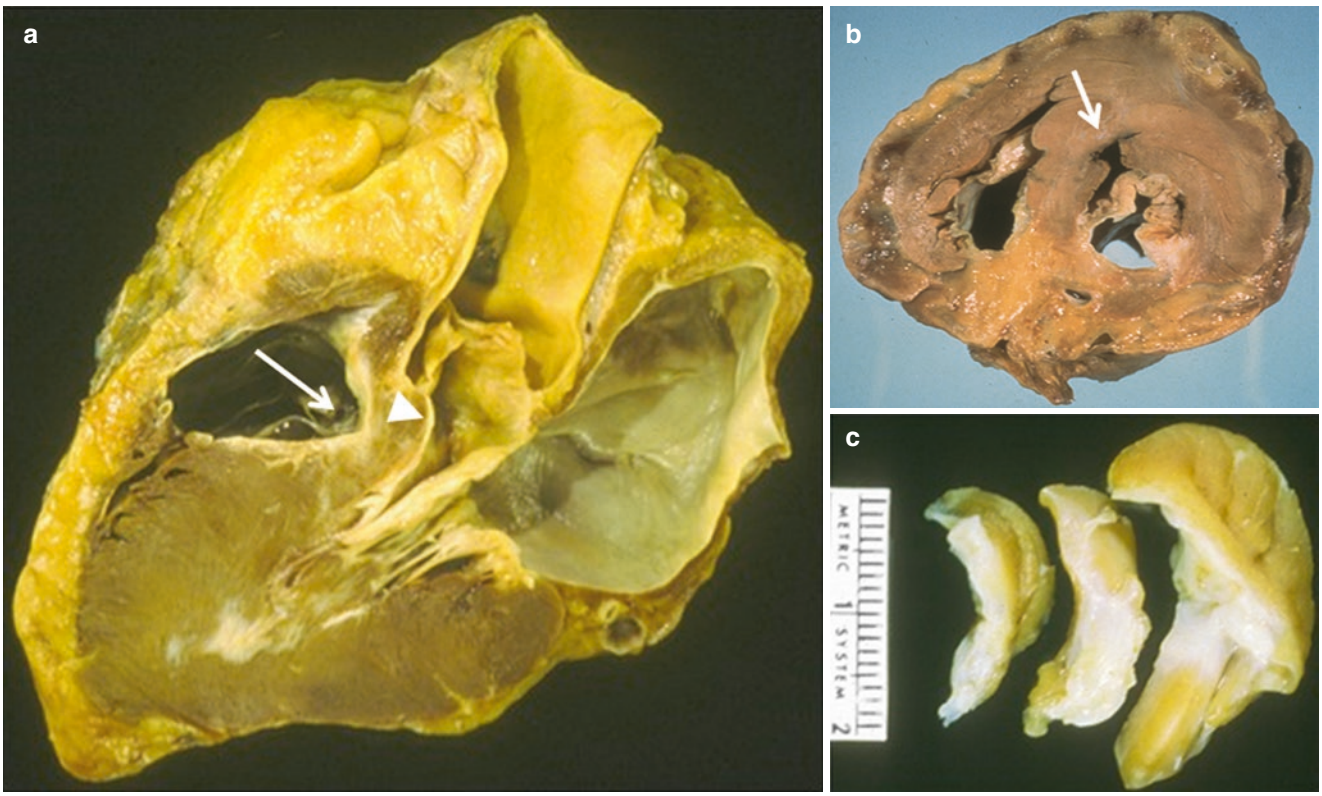

Fig. 3.12 Hypertrophic cardiomyopathy, myomectomy. (**a**) Hypertrophic cardiomyopathy treated by myomectomy. The right ventricular approach was used for the performance of myectomy (*arrow*). The discrete plaque in the left ventricular outflow tract (*arrowhead*). (**b**) Hypertrophic cardiomyopathy treated by myomectomy. The left ventricular approach was used for the performance of myectomy (*arrow*). (**c**) The myotomy specimen from the same patient from B showing three pieces of the myocardium with marked endocardial thickening. (Modified and reproduced from Virmani et al. [79])

Familial Hypertrophic Cardiomyopathy

The autosomal dominant inheritance of HCM was established 13 years after its initial description in 1958 [2, 8]. An echocardiographic study of 70 families of index cases demonstrated that in 55% of families, at least one member had echocardiographic evidence of HCM; however sporadic cases of de novo mutations are also seen [78].

Clinical Pearls

- Hypertrophic cardiomyopathy is characterized by asymmetric septal hypertrophy and accompanied by microscopic fibromuscular disarray, and when accompanied by fibrosis, there may be dilatation of the left ventricular cavity, and heart weight is twice the expected heart for weight and height of the individual.
- HCM is not uncommonly associated with sudden death, but it may not be the most common cause of sudden cardiac death in young trained athletes, especially outside the USA.
- HCM is most often familial, with a need for genotyping, but sporadic cases are well documented.

Posttest

1. Which of the following percent is representative of the actual incidence of HCM in the general population?
   A. 0.002%
   B. 0.02%
   C. 0.2%
   D. 2%
   E. 20%

   Answer: C
   Comment: Epidemiological studies from several parts of the world report a similar prevalence of LV hypertrophy, the quintessential phenotype of HCM, to be 0.2% in the general population, which is equivalent to at least 600,000 affected individuals in the USA.

2. Which of the following is *not* likely to be detected on gross pathologic examination of HCM?
   A. Left atrial dilatation
   B. Increased heart weight
   C. Ventricular scarring
   D. Left ventricular outflow tract plaque
   E. Myofiber disarray

Answer: E
Comment: HCM shows left atrial dilatation due to decreased left ventricular compliance, and, in a few cases, coexistence of atrial fibrillation may also result in left atrial dilatation. Scarring of the left ventricle increases as the disease progresses; also intramyocardial vessel thickening may result in left ventricle scarring, which can be grossly identified. In obstructive HCM, left ventricular outflow tract plaque is commonly observed grossly. Although myofibril disarray is observed in almost all cases of HCM, it can only be detected by histologic sectioning and staining following dehydration and embedding the ventricular septum from the heart in paraffin.

3. Which of the following is characteristic of apical HCM?
   A. Atrioventricular block
   B. Type III in echocardiographic Maron's classification
   C. High prevalence in Japanese
   D. Basal septal thinning
   E. High prevalence in Caucasian

Answer: C
Comment: Apical HCM is a rare variant of HCM which shows hypertrophy predominantly in the left ventricular apex. Apical aneurysm and ventricular tachyarrhythmias are observed in several cases. Even though apical HCM constitutes 13–25% of all cases of HCM in Japan, it is much less often observed in non-Japanese populations. This rare variant is not mentioned in Maron's original classification.

4. Which of the following is *not* a feature of HCM?
   A. Endocardial fibrosis on opposite site of the mitral posterior leaflet
   B. Left ventricular outflow tract plaque
   C. Subaortic stenosis
   D. Mitral valve elongation
   E. Enlargement of myocyte size

Answer: A
Comment: The frequency of a left ventricular outflow tract plaque is up to 73% in HCM patients. Furthermore, the frequency is 95% in patients with documented subaortic stenosis by catheterization. Endocardial fibrosis and mitral valve thickening and elongation are frequently observed; however, fibrosis of the ventricular septum in the LVOT is observed where the anterior leaflet hits the septum in systole. Enlargement of myocyte size is a typical finding on microscopic examination.

5. Which of the following is *the least* likely detected on histological examination of hearts with HCM?
   A. Hyperchromatic nuclei of myocyte
   B. Fibroblast disorganization
   C. Interstitial fibrosis
   D. Bizarre shape of mycytes
   E. Intramural coronary thickening

Answer: B
Comment: The characteristic histological features in HCM are the presence of marked myofiber disarray (also called myocyte disarray, myocardial disarray, and myocyte disorganization); myocyte hypertrophy, interstitial fibrosis, and intramural coronary artery thickening with severe narrowing have all been described in HCM hearts. Myocytes show hypertrophy with increase in transverse diameter, and the myocyte nuclei appear hyperchromatic and assume bizarre shapes. Fibroblast disorganization is not a feature of HCM.

6. Which of the following modalities is the most likely to detect mycardial fibrosis in HCM?
   A. Cardiac computed tomography
   B. Echocardiography
   C. Cardiac scintigraphy
   D. Left ventriculography
   E. Contrast-enhanced cardiac MRI

Answer: E
Comment: Delayed contrast-enhanced cardiac MRI is a well-recognized modality to detect areas of cardiac fibrosis in HCM. Several studies reported that the amount of fibrotic areas assessed by cardiac MRI can predict prognosis in patient with HCM.

7. Which of the following is a characteristic of late complication accompanying HCM?
   A. Mitral valve stenosis
   B. Pericardial calcification
   C. Thinning of ventricular basal septum
   D. Left ventricular dilation
   E. Aneurysmal coronary artery

Answer: D
Comment: Complications of hypertrophic cardiomyopathy are listed at Table 3.2. Left ventricular dilatation is a common manifestation of end-stage HCM which is accompanied by extensive myocardial fibrosis.

8. Which vessels in HCM demonstrate abnormal vascular wall thickening?
   A. Ascending aorta
   B. Epicardial coronary arteries
   C. Intramural coronary arteries
   D. Capillary vessel
   E. Coronary sinus

Answer: C

Comment: Intramural coronary artery thickening is present in the ventricular septum in 83% of HCM, and the location correlates well with areas of myofiber disarray. Intramural coronary artery thickening is more common in hearts with fibrosis than those without significant fibrosis.

9. Which of the following is *not* a characteristic of HCM when evaluated by echocardiography?
   A. Asymmetric hypertrophy
   B. Granular sparkling sign
   C. Ground-glass appearance
   D. Small ventricular cavity
   E. Systolic anterior motion

   Answer: B

   Comment: Echocardiographically, the hallmarks of HCM include left ventricular hypertrophy, a small ventricular cavity, systolic anterior motion of the anterior leaflet of the mitral valve, and a characteristic ground-glass appearance of the myocardium. Asymmetric hypertrophy is typical, occurring in 80–98% of cases. Granular sparkling sign is the typical feature of cardiac amyloidosis on echocardiography.

10. Which of the following is *not* a risk factor for SCD in HCM patients?
    A. Family history of sudden death due to HCM
    B. Hypertensive blood pressure response to exercise
    C. Unexplained recent syncope
    D. Left ventricular apical aneurysm and scarring
    E. Extensive and diffuse late gadolinium enhancement

    Answer: B

    Comment: Risk factors for SCD are listed in Table 3.6. *Hypotensive* or attenuated blood pressure response to exercise, mainly caused by the LVOT subaortic stenosis, is one of the risk factors of SCD in HCM.

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Approach to Diagnosis: Echocardiography

4

Beevash Ray and Matthew W. Martinez

Key Points

- Echocardiography is the primary initial imaging modality for diagnosing, evaluating, and monitoring those with suspected HCM.
- Precise thickness of multiple ventricular walls can be assessed with two-dimensional echocardiography.
- Obstruction, either at rest or with physiologic provocation, occurs in the majority of patients with HCM. "SAM septal contact" is the cause of the mechanical LVOT obstruction to blood flow between the septum and components of the mitral valve apparatus in the majority of patients. Gradients as result of the obstruction can be measured accurately with continuous wave Doppler.
- The ability to provoke and measure LVOT gradients is essential for the management of symptomatic HCM, and exercise stress echocardiography is the ideal modality for this assessment.
- SAM is not only responsible for LVOT obstruction but typically causes concomitant posteriorly directed mitral regurgitation. Patients with anteriorly directed mitral regurgitation require further investigation for intrinsic mitral valve pathology.
- In patients with hypertrophic cardiomyopathy, the TDI values are lower than expected for the age of the individual. This can be helpful to distinguish athletes from hypertrophic cardiomyopathy.
- Patients with apical HCM may require contrast administration. Contrast can be used to evaluate for an "apical pouch" or aneurysm which may contain a thrombus. It is also an important tool for assessment of septal perforator anatomy when considering alcohol septal ablation.

Introduction

Historically, during the 1960s, the diagnosis of HCM was suspected after a clinical examination suggested outflow tract obstruction. A cardiac catheterization was then required for confirmation of the subvalvular outflow tract obstruction and assessment of the pressure gradient [1, 2]. However, with the advent of M-mode and two-dimensional echocardiography, a modality for the precise characterization of the pattern and distribution of wall thickening became available [3]. Furthermore, with Doppler and stress echocardiography, additional information regarding diastolic as well as systolic changes in HCM was established [4, 5]. Today echocardiographic assessment requires a comprehensive assessment in several imaging planes. Careful attention to correct beam alignment in order to minimize errors in the measurement of LV wall thickness and appropriate identification of

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hypertrophy is required. Integration of all the imaging parameters including diastolic function is often required to distinguish cases without massive hypertrophy. Consequently, for the last 20–30 years, echocardiography has become the modality of choice for the diagnosis, monitoring, and therapeutic assessment of patients with HCM [6].

M-Mode Echocardiography

The first diagnostic criteria utilizing echocardiography for HCM was established using M-mode imaging. The high temporal resolution of M-mode echocardiography, which is superior to that of two-dimensional echocardiography, makes it ideal for the identification of timing [7]. Consequently, M-mode has been used for the measurement of dimensions at precise times during the cardiac cycle and is essential for the display of subtle abnormalities of specific cardiac structures [8]. Specifically, structures investigated with M-mode echocardiography for HCM include asymmetrical septal hypertrophy, systolic anterior motion of the mitral valve (SAM) (Fig. 4.1), left atrial size, and premature closure of the aortic valve (Fig. 4.2) [9].

The most important linear measurements made using M-mode echocardiography are that of the posterior wall and septal wall thickness. In the parasternal long axis view, a wall thickness of greater than 1.1 cm is considered abnormal; however, hypertrophy of greater than 1.5 cm is usually seen in patients suspected to have HCM [10]. Another important linear measurement made in the parasternal long axis is the

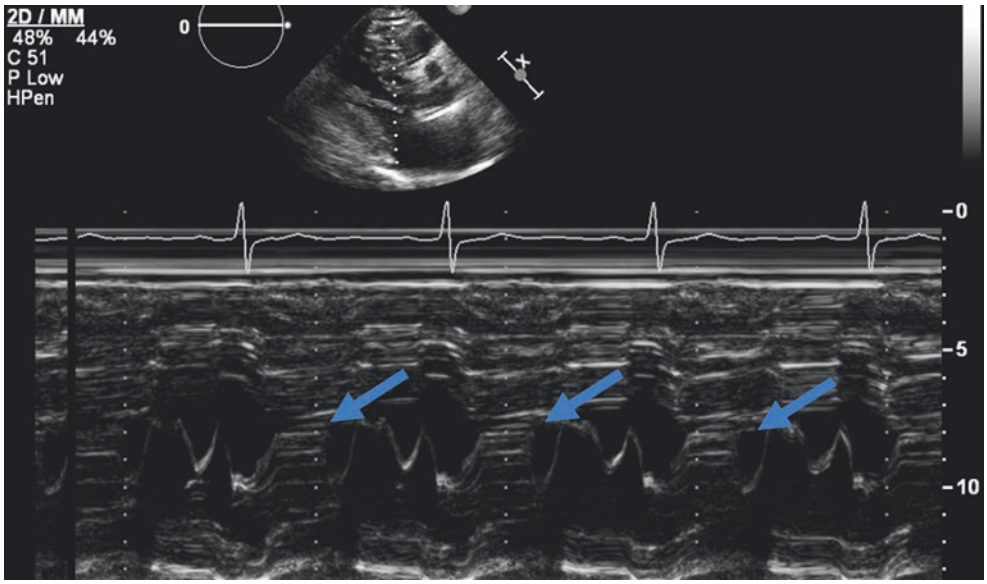


Fig. 4.1 Systolic anterior motion. Blue arrows show the movement of the anterior leaflet of the mitral valve toward the LVOT during systole

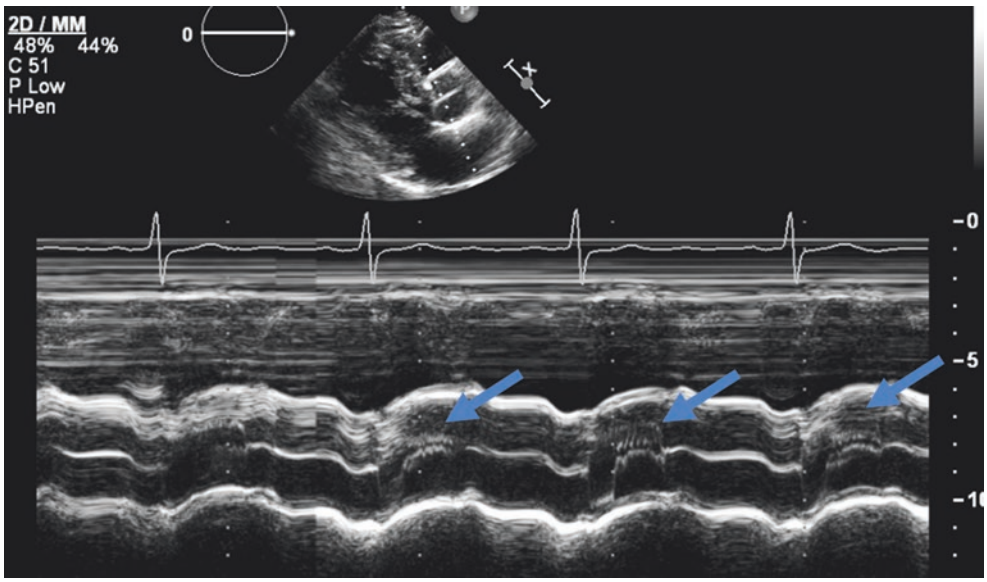


Fig. 4.2 Premature closure of the aortic valve (*blue arrows*) in a patient with HCM and obstructive SAM

anterior-posterior dimension of the left atrium (LA) which approximates left atrial size [11]. Left atrial (LA) diameter is usually increased in patients with HCM because of obstruction, mitral regurgitation, diastolic dysfunction, or concomitant atrial fibrillation. An LA size of greater than 48 mm has been shown to have higher risk of atrial fibrillation, congestive heart failure, and cardiac mortality [12]. Major pitfalls of utilizing M-mode echocardiography for linear measurements include finding a true minor axis dimension and measuring a representative portion of the LV.

In HCM, systolic anterior motion (SAM) of the mitral valve can cause left ventricular outflow tract (LVOT) obstruction, discussed later in the chapter [13]. M-mode echocardiography is well suited to demonstrate the presence and degree of SAM (Fig. 4.1). It is easily seen as contact of the anterior mitral valve leaflet/chordae with the septum when viewing M-mode through the mitral valve along with mid-systolic notching of the aortic valve when viewing the aortic valve (Fig. 4.2) [14]. The severity of SAM and subsequent LVOT obstruction can be inferred from the duration of leaflet/chordal contact with the septum. Mild obstruction is seen with contact for no more than 10% of systole and severe if greater than 30% of systole [15].

Two-Dimensional Echocardiography

Two-dimensional (2D) echocardiography is a powerful and important technique for diagnosis, prognosis, and treatment in HCM. It allowed for the first time visualization of the entire heart in one frame, thereby better illustrating the cardiac structural abnormalities associated with HCM. These include evaluation of LV systolic function, LV hypertrophy, LA volume, and SAM. Therefore, 2D echocardiography is the primary initial imaging modality for assessment of those with suspected HCM.

LV Hypertrophy

The diagnosis of HCM can be reliably made with the use of two-dimensional transthoracic echocardiography. Imaging features include LV hypertrophy with a non-dilated cavity in the absence of any systemic disease known to cause increased wall thickness [12, 13]. Traditionally, LV wall thickness of greater than 15 mm has been used to define HCM [10]. However, milder forms have been seen with hypertrophy of 13–15 mm, and the use of genetic testing has increased the proportion of HCM patients with milder degrees of hypertrophy seen in clinical practice. This degree of LV hypertrophy is the so-called "gray-zone" area as it can be seen in non-HCM groups such as highly trained athletes or people with hypertensive heart disease. Increased wall thickness in athletes has been described and can be difficult to discern from HCM; however even in the highly trained athlete, wall thickness rarely exceeds 15 mm [16]. Classically, LV wall thickness measurements are made at end diastole in the parasternal long or short axis views of the septal wall and/or posterior wall. The area of interest is usually the basal septum, but various patterns and distribution of LV hypertrophy (including diffuse and marked) have been reported in HCM [17]. The most clinically important measurement is the maximal wall thickness (MWT) at any LV level [18]. Extreme wall thickness of greater than 30 mm (Fig. 4.3) is associated with sudden cardiac death and is a class IIa indication for an implantable defibrillator [19]. Although M-mode has better temporal resolution to determine end diastole, the advantage of 2D echocardiography is that a true minor axis measurement can be made.

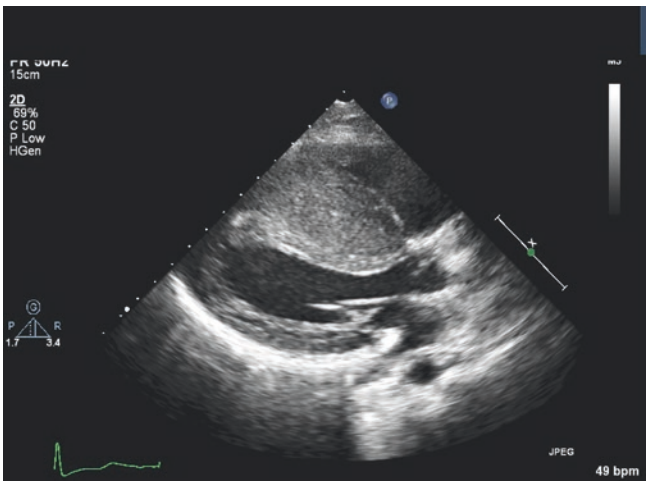


Fig. 4.3 Two-dimensional echocardiogram illustrating massive hypertrophy of the anterior septum (*blue arrow*)

The presence of LV hypertrophy in the anterior and anterolateral wall may be particularly difficult to detect and quantify. Acoustic windows and close proximity to the lungs account for some of the limited myocardial assessment, and alternative imaging may be required [20]. Sonographers and readers should also be careful to view the apex for discrete hypertrophy or extension of hypertrophy beyond the septum into the apex [21]. Focused views of the apex, including use of contrast agent, may be needed to adequately identify hypertrophy as well as the presence of an apical aneurysm. It has been established that apical aneurysms can be a complication of apical HCM or severe long-standing mid-ventricular obstruction. This has been associated with increased risk of adverse cardiovascular complications including sudden cardiac arrest and apical thrombus formation within the cavity, with potential for stroke. Focused views of the apex will also help identify LV non-compaction and is used to differentiate it from the apical form of HCM [22]. Right ventricular hypertrophy has also been described in patients with

HCM. In one study, right ventricular hypertrophy was seen in 44% of known HCM patients [23]. Cardiac MRI studies have also shown increased RV mass and hypertrophy [24]. The clinical and prognostic significance of right ventricular hypertrophy, however, is not known.

LV Systolic Function

Most HCM patients have hyperdynamic left ventricular systolic function and a relatively small LV cavity size. Along with 2D echocardiographic visual evaluation of LV function, techniques, such as Simpson's rule and fractional shortening, have been well validated for estimating ejection fraction [25]. Although ejection fractions above 70% are typical, LV systolic dysfunction can also be seen and defines end-stage HCM or the "burned-out" phase of HCM leading to progressive heart failure [26]. Two-dimensional echocardiographic evaluation in this scenario is characterized by substantial cardiac remodeling and gradual evolution from the typical hypertrophied, non-dilated, and hyperdynamic state to one of systolic dysfunction [26, 27]. However, left ventricular systolic dysfunction (ejection fraction ≤50%) occurs in only a small subset (~4%) of HCM patients during midlife and carries a poor prognosis and higher risk of sudden death (SCD) [28, 29]. Serial 2D echocardiograms to assess the ejection fraction, especially if there is a change in symptoms, can be used to evaluate for transition to end-stage HCM [30].

Left Atrial Volume

The LA volume as measured in 2D echocardiography is an important clinical and predictive dimension. It is usually measured in the four-chamber and two-chamber apical views at end systole. There are several approximations of LA volume involving long and short axes as well as area based on planimetry [31]. Left atrial volumetric remodeling as measured by increasing LA volumes has been shown to predict exercise capacity in nonobstructive HCM and may reflect chronic LV diastolic burden [32]. Furthermore, a left atrial indexed volume of greater than 34 mL/m^2 has been shown to prognosticate more serious cardiovascular events and greater LV hypertrophy, more diastolic dysfunction, and higher filling pressures [33].

Doppler Echocardiography

Two-dimensional echocardiography and Doppler echocardiography are effectively complementary diagnostic modalities. The former provides anatomic information while the latter provides hemodynamic and physiologic information. The Doppler effect, described by the Austrian scientist Christian Doppler in 1842, is the basis of Doppler echocardiography [34]. It essentially describes the relationship in mathematical terms between the increases in sound frequency as a sound source moves toward the observer and the decrease in sound frequency as the source moves away from the observer. Based on this principle, one can derive a multitude of hemodynamic variables of the heart including gradients between chambers, flow direction, and flow velocities. A comprehensive echocardiogram for HCM patients involves utilizing color Doppler, pulse wave Doppler, continuous wave Doppler, and tissue Doppler for hemodynamic and diastolic assessment of the heart.

Left Ventricular Outflow Tract Obstruction

In HCM, left ventricular outflow obstruction is often attributed to systolic anterior motion of the mitral valve. Most individuals with HCM do not exhibit significant resting obstruction, but a dynamic gradient can often be identified in the remaining patients. Therefore, obstruction, either at rest or with physiologic provocation, appears to be a basic characteristic of the majority of patients. LVOT obstruction and resulting pressure gradients are highly variable and strongly influenced by individual physiologic states. Symptomatic patients without a resting gradient must be evaluated further for inducible gradients. LVOT obstruction is most often a combination of mechanisms including narrowing of the LVOT by septal hypertrophy, anterior displacement of the mitral apparatus, and systolic anterior motion (SAM) of the mitral valve. Elongated mitral valve leaflets, or abnormally displaced, or attachments of papillary muscles may also contribute to obstruction. SAM is characterized by an anterior movement of the mitral valve leading to septal wall contact of the mitral valve leaflets. In a subset of patients, other structures of the mitral valve may contribute to obstruction, including abnormally thickened or displaced papillary muscles, with more distal or mid-ventricular obstruction.

The mechanism for LVOT obstruction is controversial, but most agree it is attributable to variations of the LVOT and mitral-aortic geometry. First, as already alluded to, papillary muscle displacement leads to diastolic downward vortex forces which pulls the mitral valve into the LVOT [35]. The anterior leaflet of the mitral valve has been found to be longer in patients with HCM and predisposed to act as a sail as it protrudes into the LVOT [36]. Systolic blood flow is directed toward the long anterior leaflet, and the acute mitral-aortic angle creates drag forces and moves the mitral valve anteriorly (SAM) making contact with the septal wall causing obstruction [37]. The "SAM septal contact" is the cause of the mechanical LVOT obstruction to the blood flow between the septum and components of the mitral valve apparatus in the majority of patients. The obstruction generates a gradient between

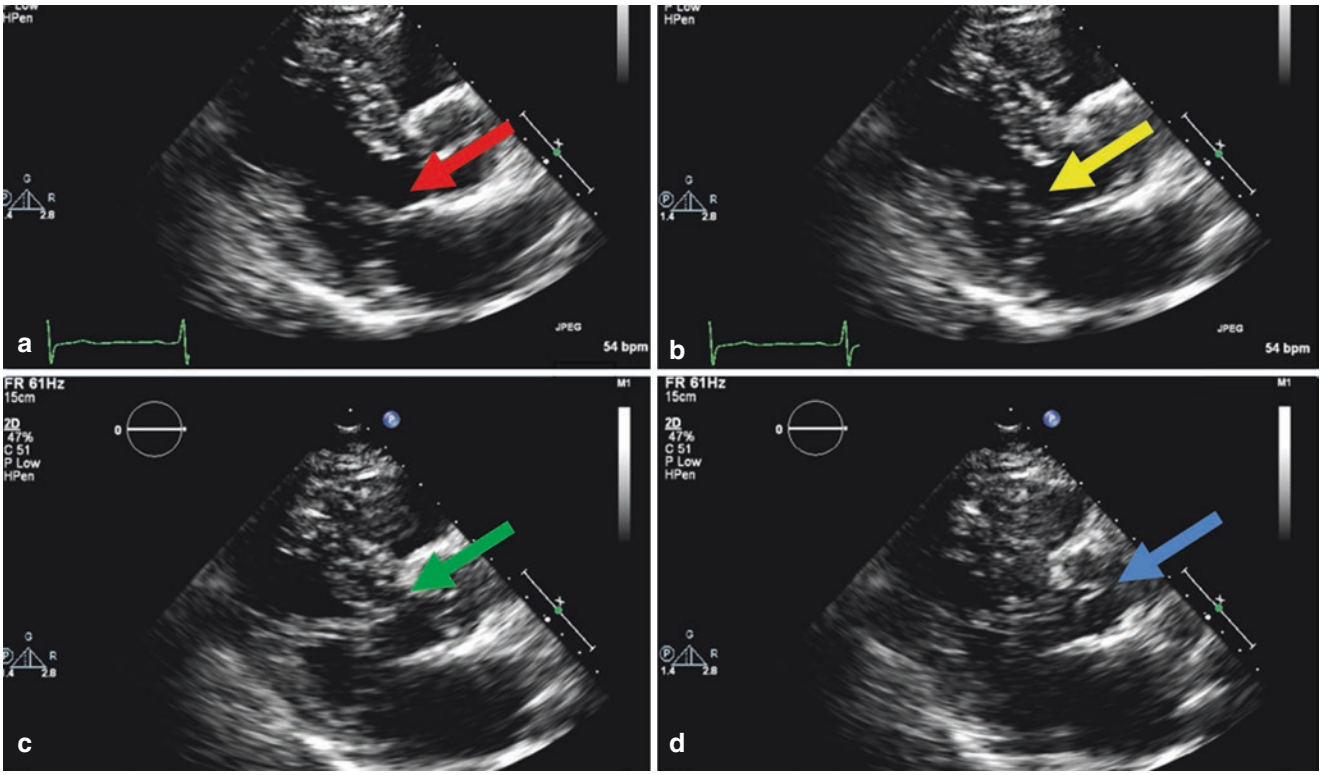


Fig. 4.4 (**a**) The mitral valve is closed in early systole (*red arrow*). (**b**) The anterior leaflet of the mitral valve begins to shift anteriorly (*yellow arrow*). (**c**) In the middle of systole, the mitral valve apparatus moves into the LVOT causing obstruction (*green arrow*). (**d**) The aortic valve closes prematurely (*blue arrow*)

the LV and aorta [38]. The hemodynamic consequences of SAM include prolongation of ejection time and a reduction in stroke volume. Typically, the anterior leaflet of the mitral valve is involved, but an extremely elongated posterior leaflet of the mitral valve can also be responsible for obstruction [39]. 2D echocardiography is an excellent modality and preferred method for visualizing SAM of the mitral valve and subsequent obstruction (Fig. 4.4). It is usually seen in the parasternal long axis during systole. After visualization of the obstruction, Doppler echocardiography is used to quantify gradients. If SAM is not readily visualized at rest, provocative maneuvers such as the Valsalva maneuver and/or administration of isoproterenol are undertaken.

SAM is not only responsible for LVOT obstruction but typically causes concomitant posteriorly (and laterally) directed mitral regurgitation. Coaptation of the mitral leaflets may be disrupted during SAM resulting in posteriorly directed mitral regurgitation. Complete assessment of the mitral valve should be performed in all patients, especially in those in whom septal reduction therapy is planned. It is well known that the anterior mitral valve leaflet is elongated when compared to those patients without HCM. Other abnormalities of the mitral valve may also include anterior displacement of the mitral apparatus and insertion of the papillary muscle directly into the anterior mitral valve leaflet. Papillary muscle abnormalities have been demonstrated in over 50% patients and may require attention and possible papillary muscle ligation at the time of the septal myectomy [40]. Depending on the age of the patient, concomitant degenerative mitral valve disease may be present in addition to SAM as the mechanism for mitral regurgitation. In addition, mitral calcification may contribute to anterior displacement of the mitral apparatus and worsening of SAM. These degenerated valves may require surgical repair or replacement. Careful attention to the direction of the mitral regurgitation can lend insight into the presence of intrinsic mitral valve disease [41]. Posteriorly directed mitral regurgitation is expected in those with SAM, whereas anteriorly directed or central mitral regurgitation suggests the presence of intrinsic mitral valve disease, and perhaps a flail segment or other etiology may be present [42]. Anteriorly directed regurgitation jets are usually evaluated further by transesophageal echocardiography.

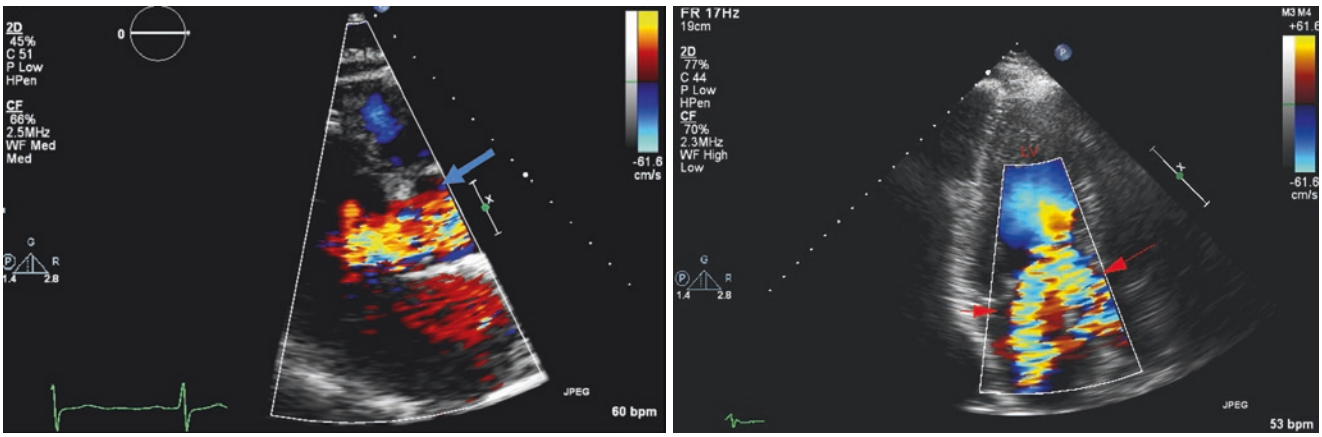
Color Doppler

Color flow Doppler displays intercavitary blood flow in different colors representing flow direction and velocity [43]. This makes color Doppler a powerful tool for the evaluation of valvular regurgitation. In obstructive HCM there usually

is abnormal mitral leaflet coaptation because of SAM which results in mitral regurgitation (MR) which is best seen in the parasternal long axis. As described above, it is essential to note the direction and severity of the mitral valve regurgitation as this is important when deciding about surgery or alcohol septal ablation; in particular any evidence for significant intrinsic mitral disease would favor surgical myectomy with valve repair or replacement. In the parasternal long axis, five-chamber view and three-chamber view turbulent blood flow due to SAM will be represented as a mixing of colors in the left ventricular outflow tract (Figs. 4.5 and 4.6). SAM tends to produce a mitral regurgitation jet directed posteriorly and laterally, whereas intrinsic mitral valve disease due to annular, papillary, or leaflet disease produces an anterior and medially directed jet [41]. Color flow Doppler can be utilized to view the apex for the presence of an apical aneurysm and corresponding flow reversals by continuous wave Doppler (Fig. 4.7). Mid-cavity obstruction may be present with the formation of an apical aneurysm, and this may be associated with ventricular arrhythmias and systemic embolism [44].

Pulse Wave Doppler

In the pulsed wave mode, a single ultrasound crystal sends and receives intermittent or "pulsed" sound beams. The maximal frequency shift that can be determined by pulsed wave Doppler is one-half the pulse repetition frequency which is called the Nyquist frequency. If the frequency shift is higher than the Nyquist frequency, then aliasing occurs [45]. Consequently, there is a maximum velocity that can be resolved using this modality. The advantage of pulse wave is that it determines blood flow velocities of a particular local-



Figs. 4.5 and 4.6 Color Doppler in the LVOT shows turbulent flow as indicated by the mosaic color pattern (*blue arrow*). Note the posteriorly directed mitral regurgitation present in the long axis view (*red arrow*) and turbulence across the outflow tract and into the aorta

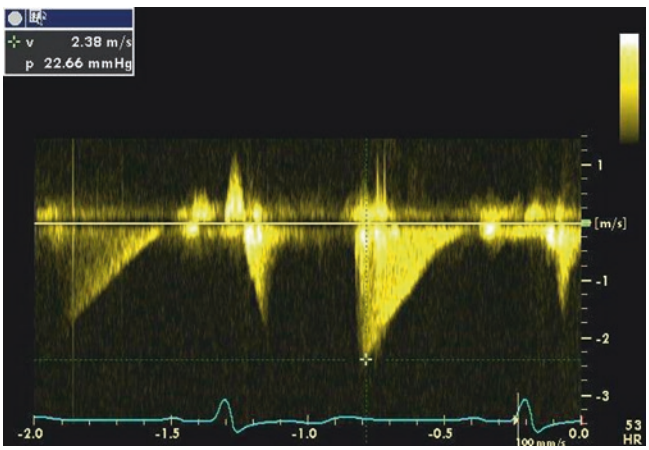


Fig. 4.7 Doppler signal illustrating flow in the apex suggestive of an apical aneurysm with reversal of flow

ized region but cannot resolve the high velocities that continuous wave Doppler is able to.

Pulse wave Doppler can be used to interrogate left ventricular outflow tract (LVOT) velocities accurately in HCM [46]. This measurement is made in the apical five-chamber and/or apical three-chamber view with careful effort to have the pulse wave beam as parallel to the direction of flow as possible. The velocity can be converted to pressure gradients using the Bernoulli equation thereby obtaining a precise measurement of LVOT pressures [34]. Furthermore, obstruction can occur in multiple areas within the LV cavity. Consequently, pulse wave Doppler is used to sequentially ascertain gradients from the LV apex down to the LVOT and across the aortic valve in order to confirm the anatomical level of obstruction. This is often referred to as "pulsing the septum" and allows the operator to identify the level for obstruction along with visualization of the obstruction with color Doppler. However, often the LVOT velocities exceed the Nyquist limit [47]. Thus, an accurate assessment of LVOT pressures via pulse wave Doppler is not often attainable in HCM patients, and typically maximum velocities are only identified by continuous wave Doppler. Pulse wave Doppler is also important in the determination of diastolic dysfunction (discussed later).

Continuous Wave Doppler

Continuous wave (CW) Doppler is dissimilar from pulse wave Doppler as the transducer utilizes two crystals. One of the crystals continuously transmits while the other continuously receives. Since the transmitted signal is not pulsed, the reflected signals all along the ultrasound beam are sampled concurrently. The major disadvantage of this mode is that velocities can come from anywhere along the ultrasound beam and thus cannot be localized. However, the advantage of this modality in HCM patients is that there is no aliasing, and therefore even high velocities can be accurately measured, making the modality particularly beneficial in determining peak velocities and gradients. Careful parallel alignment of the continuous wave beam with the direction of blood flow is necessary to eliminate underestimating the velocity.

As discussed earlier, HCM patients often have LVOT obstruction. This mechanical obstruction manifests as a pressure gradient through the LVOT which can be measured accurately with continuous wave Doppler (Fig. 4.8) [48]. The Doppler envelope is characteristically late-peaking and dagger-shaped, differentiating it from that of fixed aortic stenosis. Again, this measurement is made in the apical five-chamber and/or apical three-chamber view. About 25% of

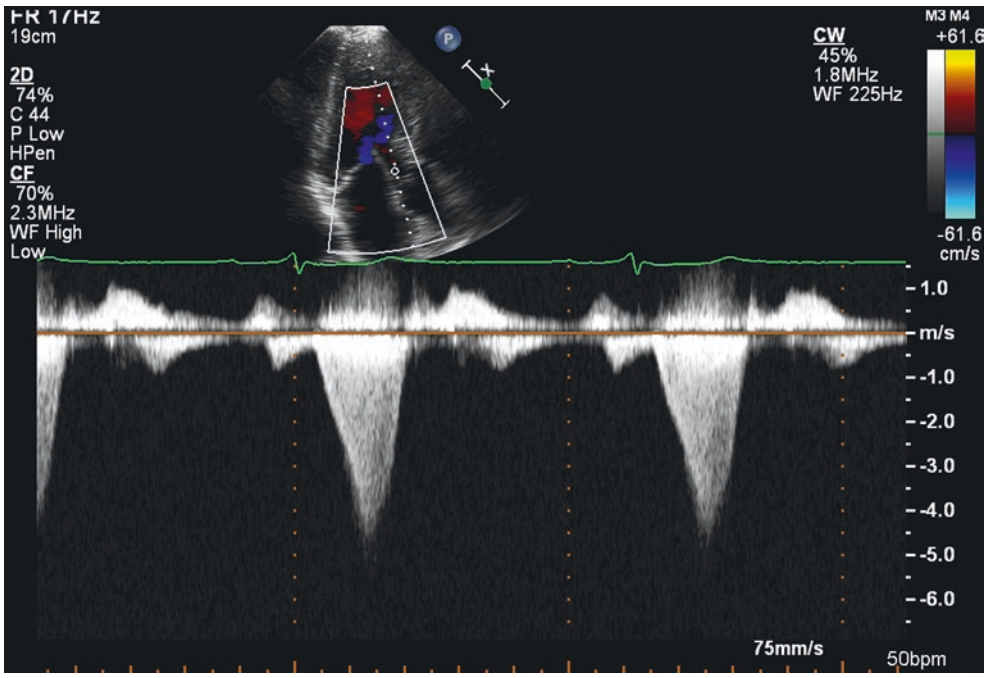


Fig. 4.8 Continuous wave (CW) Doppler with characteristic late-peaking dagger-shaped (*blue arrow*) LVOT obstruction and severe LVOT gradient (velocity approaching 5 m/sec or 100 mmHg)

patients have a significant LVOT pressure gradient at rest, which is defined as a pressure of greater than 30 mmHg. In symptomatic HCM patients who do not have significant pressure gradients at rest, a dynamic obstruction must be investigated. Maneuvers which can provoke a gradient include having the patient Valsalva, administering amyl nitrite, and exercising the patient. Exercise is preferred over the use of pharmacologic agents as these agents can cause gradients in even normal hearts, thus causing false positives [38]. Over 50% of true HCM patients without significant LVOT obstruction at rest will exhibit outflow gradients greater than 30 mmHg with exercise [49]. Therefore, the majority of patients have either resting or latent (provocable) obstruction. Provocable maneuvers can easily be carried out simultaneously with CW Doppler integration of the LVOT for gradient measurement.

Diastolic Function Evaluation

Nearly all HCM patients have some degree of diastolic dysfunction [50]. It is thought that the decrease in chamber compliance and increase in chamber stiffness because of increased LV mass and myocardial fibrosis in HCM play a prominent role in leading to diastolic dysfunction [51].

Doppler echocardiography with pulse wave and continuous wave evaluation and 2D echocardiography allows for an accurate assessment of diastolic function in HCM. Diastolic function measurements include pulse wave of the mitral inflow velocities (E for early rapid filling and A for atrial contraction), LA size, tricuspid regurgitation velocity, pulmonary vein reversal velocity, and TDI measurements of mitral annulus velocity (known as E' and A') [52]. These measurements are usually performed in the apical four-chamber view.

Although pulse wave variables by themselves, such as E/A and pulmonary vein predominance, do not correlate well with left ventricular end-diastolic pressure (LVEDP) in HCM, [53]. TDI in combination with pulse wave parameters have been shown to be instrumental in measuring diastolic dysfunction. For example, the E/E' ratio of >15 (using the TDI-derived E' velocity from the medial mitral annulus) has been shown to correlate with invasively measured left atrial pressures >15 mmHg 73% of the time [54]. Prognostically, E/E' ratio changes predict exercise tolerance in adults and children with HCM [55, 56].

The American Society of Echocardiography set out guidelines to determine diastolic function for HCM patients. There are four recommended parameters needed to evaluate diastolic dysfunction grade in HCM. These four parameters are average E/E' ratio of >14, LA volume index of >34 ml/m^2, pulmonary vein atrial reversal velocity time of >30 msec, and peak velocity of TR jet of >2.8 m/sec. The above parameters are valid even in patients with dynamic obstructive disease and mitral regurgitation. However, if there is more than moderate mitral regurgitation, then only pulmonary vein atrial reversal time and TR jet parameters are valid. If less than 50% of the parameters are met, then LA pressure is normal, and grade I diastolic dysfunction is present. If greater than 50% of the parameters are met, then the LA pressure is elevated, and grade II diastolic dysfunction is present. In the situation that exactly 50% of the parameters are met, estimated LA pressures and diastolic grade are indeterminate. Finally, there is grade III diastolic dysfunction in the presence of a restrictive filling pattern (E/A > 2.5, deceleration time of E velocity of <150 msec, and isovolumic relaxation time <50 msec) and reduced E' velocity [57].

Tissue Doppler Imaging

While color Doppler, pulse wave Doppler, and continuous wave Doppler are utilized to examine the velocity properties of red blood cell flow, tissue Doppler imaging (TDI) examines the velocity properties of the myocardium. TDI measures high amplitude, low velocity signals which is ideal for the quantification of radial and longitudinal myocardial motion. This is a highly important technique when evaluating patients for hypertrophic cardiomyopathy. In the apical four-chamber view, a pulsed TDI sample is placed within the myocardium adjacent to the medial or lateral mitral annulus to measure systolic and diastolic myocardial velocities [58]. In patients with hypertrophic cardiomyopathy, the TDI values are lower than expected for the age of the individual (Fig. 4.9). Normal or near normal values in younger patients should be considered abnormal. Furthermore, TDI is helpful to differentiate physiologic hypertrophy such as athlete's heart (normal or supernormal myocardial velocities, Fig. 4.10) and conditions of pathological hypertrophy (abnormal myocardial velocities) [59]. Finally, prognostically a mitral annular systolic velocity less than 4 cm/s measured using TDI has been shown to be an independent predictor of death or hospitalization for worsening heart failure in HCM [60].

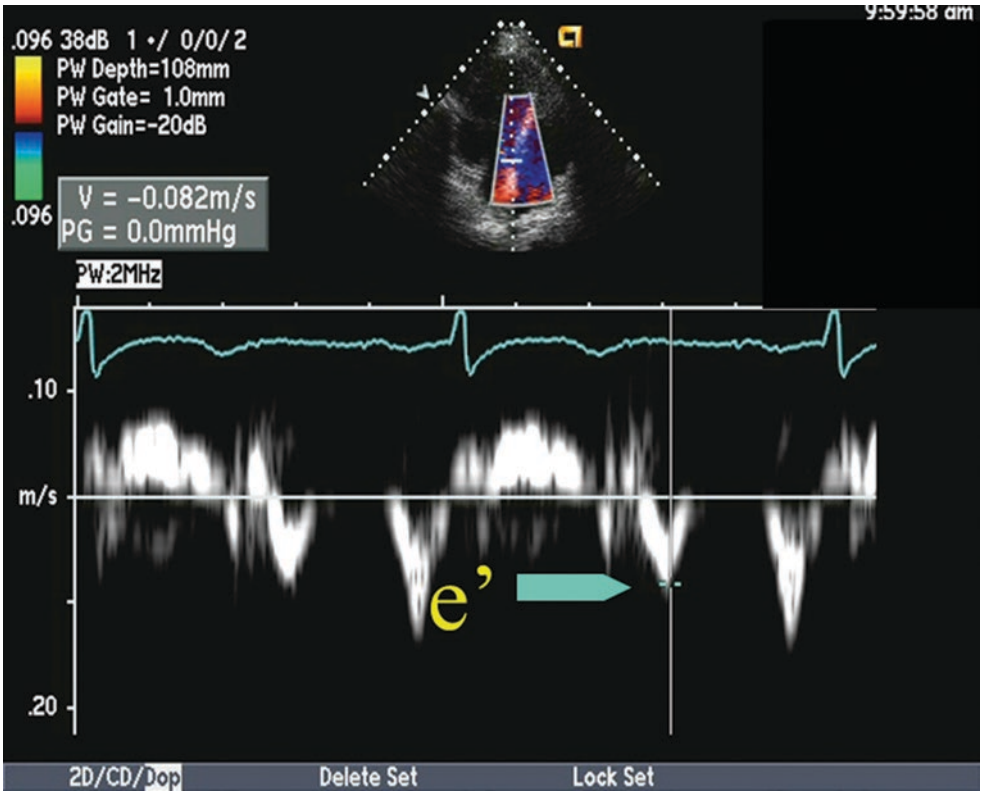


Fig. 4.9 Tissue Doppler images illustrating abnormal values that are reduced in a young person with HCM

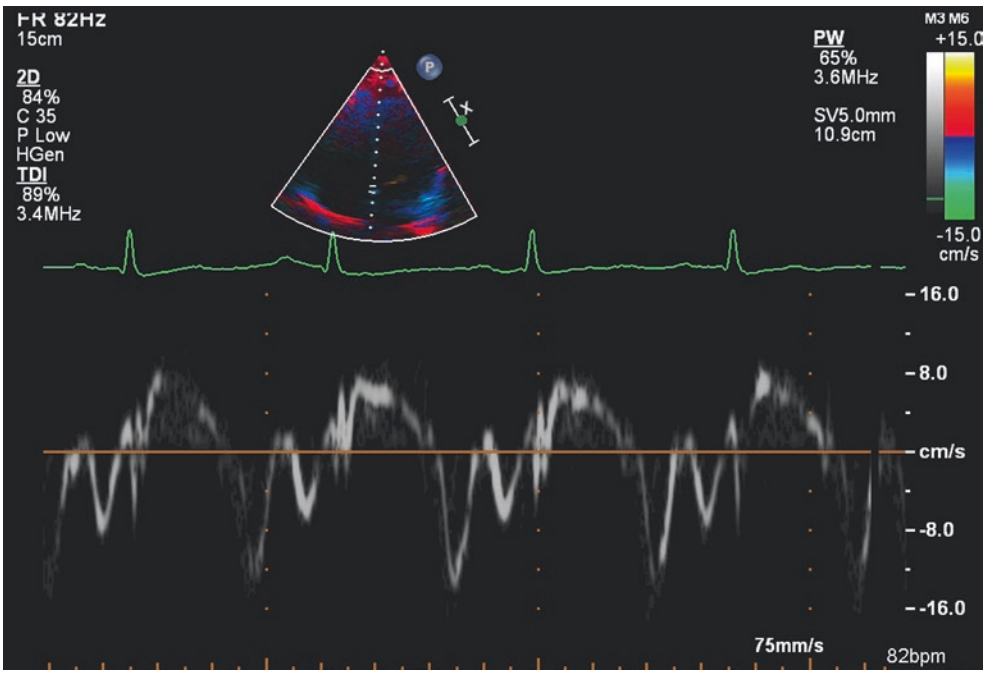


Fig. 4.10 Tissue Doppler images illustrating "supernormal" values in a young athlete

Strain and Strain Rate Imaging

Strain measurements assess myocardial motion relative to the adjacent myocardium and are unaffected by translational cardiac motion and tethering in the same way TDI measurements can be. Careful attention to how these measurements are obtained is important as they are angle-dependent measurements. While strain measures myocardial deformation, strain rate measures the local rate of deformation. This technique allows spatial and temporal tracking of longitudinal, circumferential, and radial deformation and the calculation of strain. Patients with HCM have significant reductions in strain in the septal segments and correlate with wall thickness [5] (Fig. 4.11). Studies in patients with HCM have demonstrated a reduction in longitudinal strain, an increase in circumferential strain, and normal systolic twist or torsion but a reduction in untwisting in diastole [61, 62]. Marked reduction in strain longitudinal measurements has been found to correlate to fibrosis identified by cardiac MRI [63].

Stress Echocardiography and LVOT Provocation

As previously discussed, patients with HCM may not have a significant resting obstruction. HCM is often a dynamic disease process with the presence of LVOT obstruction only present after provocation. Management of this group with a so-called labile obstruction requires further search for obstruction [64]. Consequently, the ability to provoke and then measure LVOT gradients is essential for the management of HCM with several options available to elicit the obstruction. Interventions are aimed to diminish LV volume and/or augment contractility. Various exercise and pharmacologic protocols have been proposed for the provocation of dynamic obstructions from a pharmacological stress standpoint. Dobutamine, isoproterenol, and amyl nitrite have all been proposed to provoke a gradient. The standard protocol of dobutamine doses of up to 30–40 mcg/kg/min [65] has been described; however LVOT obstruction is a known side effect of dobutamine and may occur in up to 20% of patients without known HCM or overt hypertrophy [66]. Therefore, dobutamine is not recommended in the evaluation of patients with suspected labile obstruction, and false positives are likely [67]. Isoproterenol doses of up to 0.005–0.02 mcg/kg/min for 5–10 min have been used safely in HCM patients and lead to LVOT obstruction by causing tachycardia [68]. Amyl nitrite use entails 2–6 inhalations of the vapor from one capsule over a period of 1–2 min. Inhaled amyl nitrite during simultaneous imaging of the LVOT leads to a rise in heart rate and a drop in the blood pressure with subsequent LVOT obstruction in patients with a labile obstruction. This can be repeated if needed but should be stopped if there is severe hypotension or marked symptoms of flushing and/or dizziness [69]. However, these methods are not physiologic assessments and do not mimic the same stresses produced with exercise. Therefore, exercise stress echocardiography is the ideal modality for this as changes in wall motion, outflow gradients, and systolic function can be assessed in simulated stress conditions that are similar to the physiologic stresses of activity that produce patient symptoms [70].

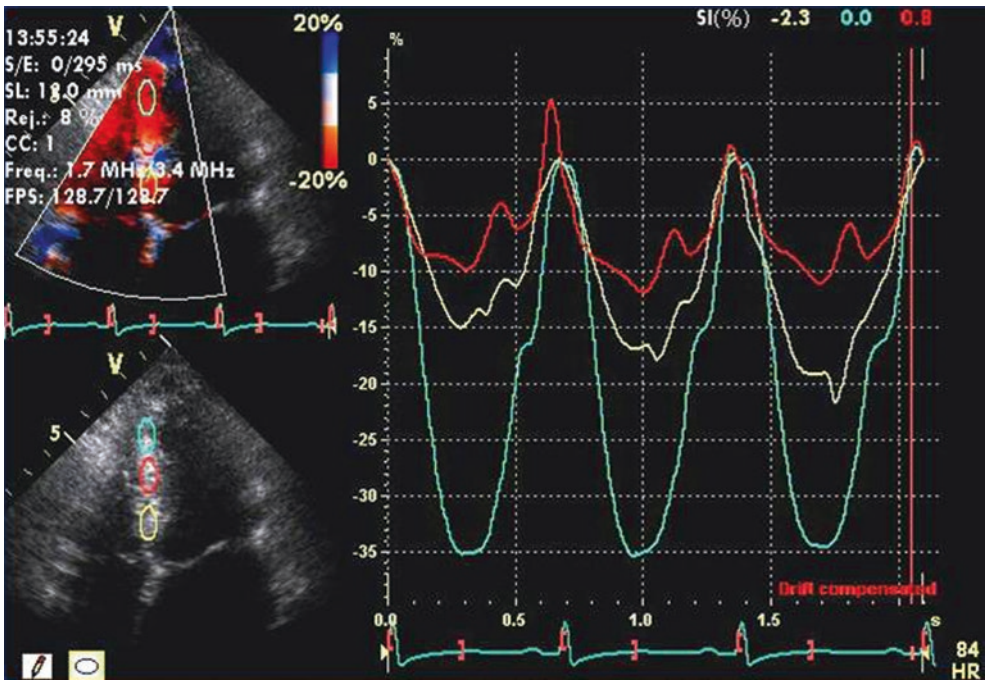


Fig. 4.11 Echocardiographic Doppler-derived strain images illustrating abnormal strain values in the area of left ventricular hypertrophy

These protocols are similar to routine exercise echocardiography with imaging prior to and during or immediately after the stress. Standard exercise protocols with the treadmill such as the Bruce or modified Bruce protocol as well as bicycle ergometry can be employed. Bicycle exercise may allow for easier acquisition of imaging data sets along with hemodynamic assessment; however, in this method increased venous return might decrease the likelihood and degree of LVOT obstruction. Of these protocols, stress with exercise is preferred since it most closely resembles physiologic states. Upright exercises are more likely to cause LVOT gradients during exercise than supine and are the preferred method for those with labile LVOT obstruction [71].

The 2011 ACCF/AHA guidelines for the diagnosis and treatment of HCM assign exercise echocardiography a class IIa recommendation for the detection and quantification of exercise-induced dynamic LVOT obstruction in patients who have a resting peak instantaneous gradient of 50 mmHg or less (level of evidence B). Stress echocardiography is not indicated in patients with gradients greater than 50 mmHg at rest or with Valsalva maneuver [72]. The following parameters can be evaluated during the test, especially during semi-supine exercise: electrocardiographic changes, symptoms, heart rate, LVOT obstruction, LV systolic/diastolic function, MR, blood pressure, and systolic pulmonary arterial pressure (SPAP). It is important to distinguish the subvalvular gradient from the MR jet. Other parameters that can be examined include 2D strain imaging [73]. With 2D strain a blunted increase in global longitudinal strain favors a HCM diagnosis over athlete's heart [74].

Provocable gradients ≥50 mmHg with exercise in those with symptoms that cannot be controlled with medications represent the conventional threshold for septal reduction intervention [67]. Finally, exercise echocardiography can be used to identify transient regional wall motion abnormalities due to functionally significant CAD. This is important since simultaneous presence of CAD with HCM carries a worse prognosis, may be present in older individuals with cardiovascular risk factors, and is treatable with revascularization techniques, either concomitant to septal reduction therapies or in isolation [75].

Contrast Echocardiography

Myocardial contrast media is typically given intravenously to opacify and view the ventricular cavities in those patients with difficult images. In particular, apical HCM may be difficult to appreciate in some cases, and contrast media can help for MWT measurement, and to identify the presence of an aneurysm as well as thrombus formation within the cavity (Fig. 4.12) [76]. Obese patients with poor acoustic windows may also benefit from contrast echocardiography, which can aid in assessing systolic function, cavity size, and wall thickness.

In patients with HCM, contrast utilization also takes on a different role. Alcohol septal ablation is performed for the relief of symptomatic medically refractory obstructive HCM in selected groups of patients [77]. Contrast media is injected into the coronary arteries to identify and confirm the appropriate septal branch that supplies the myocardium where SAM septal contact occurs (Fig. 4.13a, b). This is important to identify the desired area for ablation and to avoid alcohol injection into a papillary muscle or LV free wall. In addition, myocardial contrast can aid in understanding when additional more proximal or distal septal perforators should be

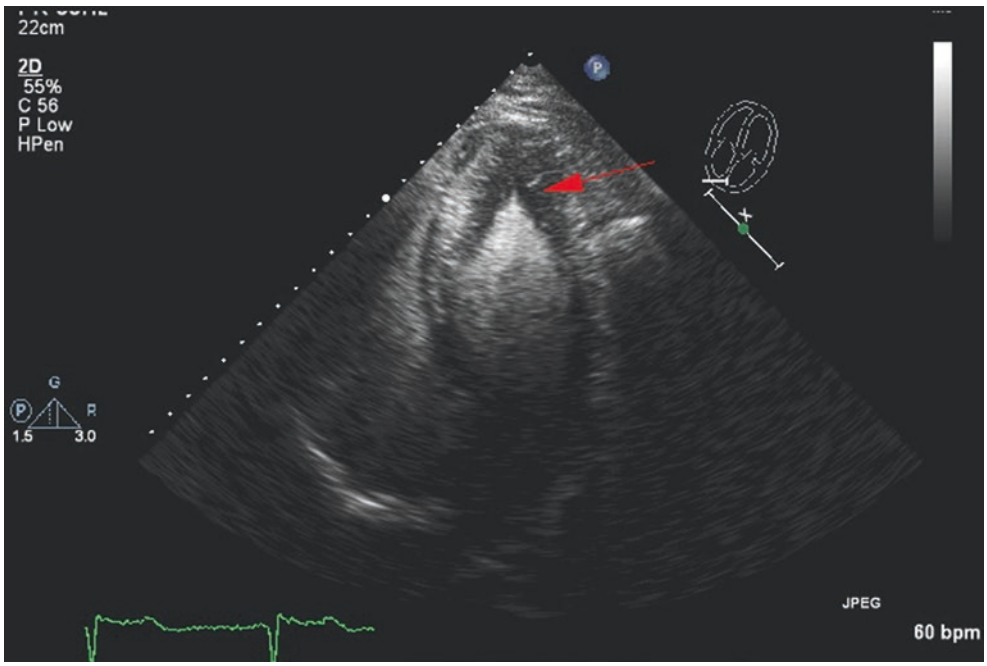


Fig. 4.12 Contrast media-enhanced echocardiogram illustrating apical hypertrophy (*red arrow*) with a classic "ace of spades" configuration. No aneurysm or apical thrombus is identified

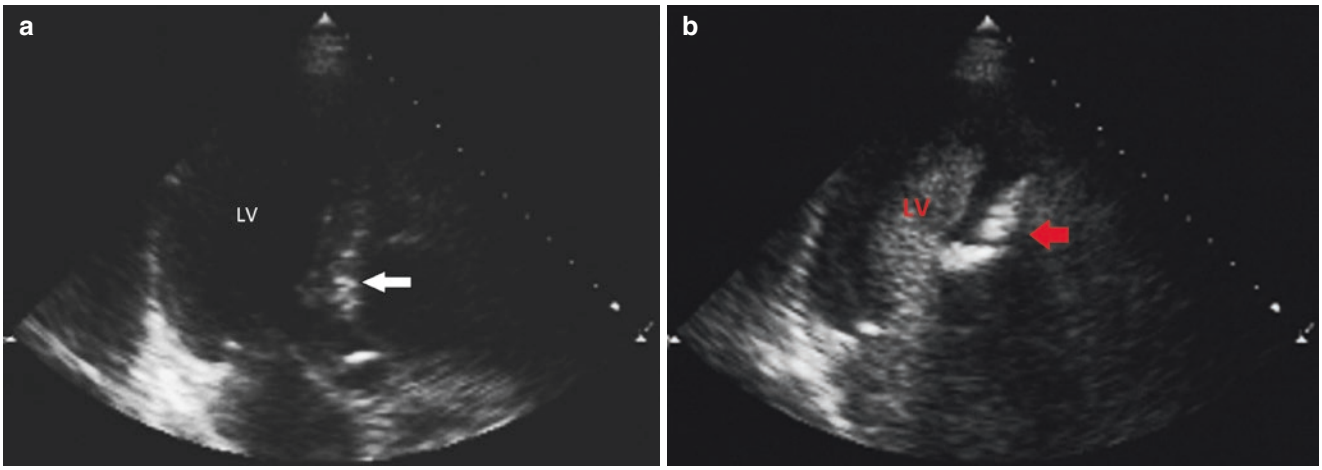


Fig. 4.13 (**a**, **b**) Two-dimensional echocardiogram pre (**a**)- and post (**b**)-contrast media injection. The contrast media-enhanced echocardiogram illustrates the area of myocardium supplied by the first septal perforator that will be affected during the alcohol ablation

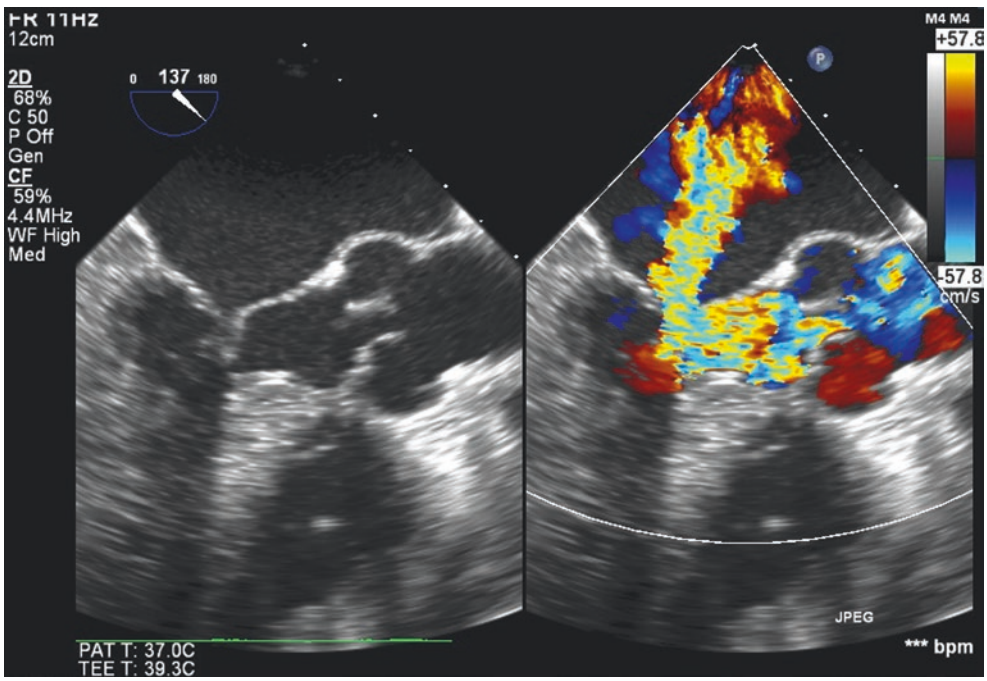


Fig. 4.14 Transesophageal two-dimensional echocardiogram illustrating systolic anterior motion (SAM) of the mitral valve with septal contact. Color Doppler illustrating LVOT obstruction with turbulence in the LVOT and corresponding posteriorly directed mitral regurgitation color Doppler signal

ablated, in order to effect a more efficacious and durable result. Contrast medium is injected into a septal branch of the left anterior descending artery resulting in opacification of the myocardium hopefully in the distribution of the proposed septal branch. Care should be taken to ensure that opacification of any cardiac structure other than the targeted septal area does not occur. Alcohol should not be injected in these cases, and alternative septal reduction therapy should be considered. When performed properly and with expertise, myocardial contrast reduced the total amount of ethanol injected and reduced complications including pacemaker implantation rates without impacting clinical efficacy and reduction of peak gradient [78].

Transesophageal Echocardiogram

Transesophageal echocardiography (TEE) is not often required in the evaluation of hypertrophic cardiomyopathy. TEE may be utilized preoperatively to evaluate SAM (Fig. 4.14) in patients with poor 2D echocardiography images or those unable to have a cardiac MRI. TEE evaluation would not be typically employed as a usual measurement tool in HCM but can be helpful in selected patients. For instance, in cases in which suspected intrinsic degenerative mitral valve disease is suspected, a TEE will be valuable, especially in cases when anteriorly or medially directed mitral regurgitation is identified and a flail or unsupported segment is suspected. Another area in which TEE is useful is

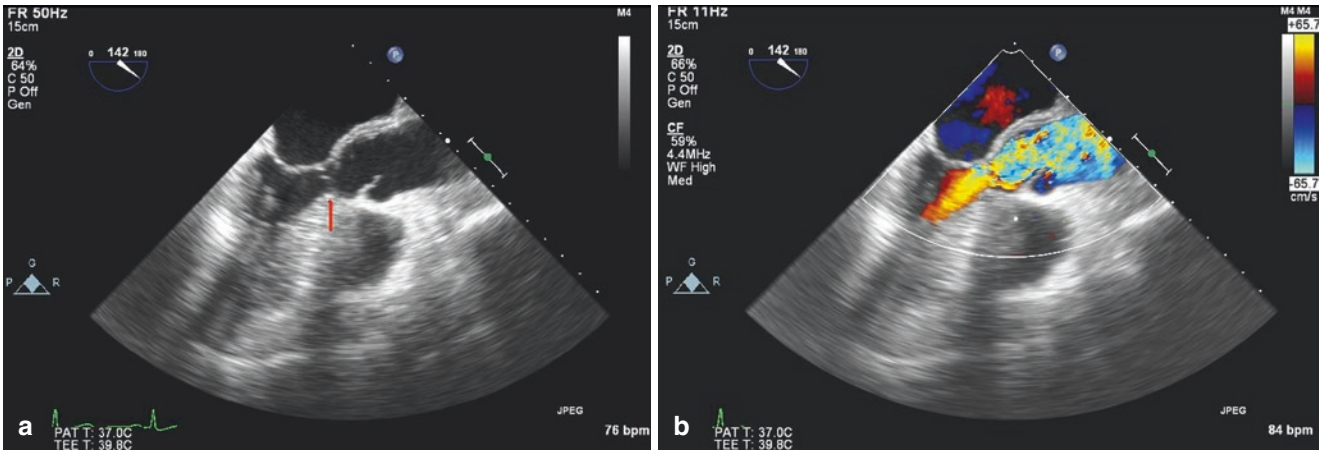


Fig. 4.15 (**a**) Transesophageal echocardiogram of a patient with a subaortic membrane (red arrow) (**b**) with severe LVOT obstruction illustrated by color Doppler. Note no systolic anterior motion of the mitral valve; the obstruction occurs at the level of the membrane

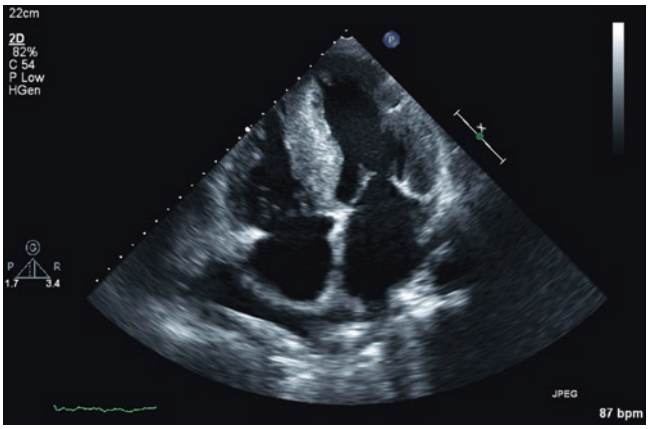


Fig. 4.16 Two-dimensional echocardiogram of a patient with amyloid cardiomyopathy. Note the thickened RV wall, pericardial effusion, and thickened valve leaflets

to rule out a subaortic or supra-aortic membrane or partial membrane. Although a subaortic membrane (Fig. 4.15a, b) is a rare condition, it remains an important differential diagnosis in hypertrophic cardiomyopathy with LVOT obstruction and in aortic stenosis, particularly at a young age or in the presence of family history, as diagnosis requires surgery in symptomatic patients [79]. TEE is also important intraoperatively during septal myectomy, in order to guide the procedure and confirm an optimal result with resolution of provocable gradient.

Diagnostic Caveats

Potential misdiagnosis may occur in diseases that mimic HCM. Left ventricular hypertrophy can be seen in many other diseases, and interpretation of imaging studies should always be done in context of the clinical history. Other forms of hypertrophy may mimic HCM and include but are not limited to physiologic hypertrophy of the highly trained athlete, hypertensive heart disease, aortic valve disease, infiltrative heart disease, and glycogen storage diseases. LVH is common in cardiac amyloid; several echocardiographic features may help to distinguish cardiac amyloid from HCM [80, 81]. These include biatrial dilatation, thickened interatrial septum, restrictive inflow pattern, thickening of the valve leaflets, and the presence of a pericardial effusion (Fig. 4.16). A longitudinal strain pattern of apical sparing using speckle tracking techniques has been shown to differentiate cardiac involvement from other cardiac pathologies [82]. A cardiac MRI or fat pad biopsy should be done when amyloid is suspected to confirm the diagnosis and ensure the correct treatment strategy. In addition, measurement error can be a common cause of misdiagnosis of HCM. The presence of left ventricular hypertrophy can be erroneously measured if an oblique section of the LV is measured or the right ventricular moderator band is included leading to overestimation of septal thickness.

Conclusions

Echocardiography is the primary method for the initial evaluation of patients with suspected hypertrophic cardiomyopathy. The diagnosis of HCM is challenging and is a clinical diagnosis utilizing historical features, physical examination, and echocardiographic assessment, which together promote a comprehensive clinical, anatomic, and physiologic understanding of a given patient. Echocardiography allows the clinician to evaluate for the presence and severity of LV wall thickness, diastolic dysfunction, the presence of LVOT obstruction, or mitral regurgitation and assist with therapeutic interventions in both the operating room and catheterization laboratory. Echocardiography is well suited to evaluate all aspects of patients with suspected HCM and those with HCM who are undergoing evaluation for new or changing symptoms.

Clinical Pearls

- Obstruction is a hallmark of symptomatic HCM. All patients should be evaluated by transthoracic echocardiography with provocation to identify the presence and severity of obstruction.
- The ability to provoke and measure LVOT gradients is essential for the management of symptomatic HCM, and exercise stress echocardiography is the ideal modality for evaluation of LVOT gradients, but care must be taken to avoid signal contamination with mitral regurgitation.
- Accurate measurement of ventricular wall thickness is important for both the diagnosis of HCM and management of massive hypertrophy for ICD decision-making. Careful attention must be given to the anterior and lateral walls which often underestimate the maximal wall thickness compared to cardiac MRI.
- Distinguishing adaptive athletic hypertrophy from pathologic hypertrophy in HCM is often accompanied by evaluating diastolic function. Athletes should not have abnormal diastolic function or lower TDI values for their age and degree of athleticism. This can be helpful to distinguish athletes from hypertrophic cardiomyopathy.

Questions

1. What advantage of M-mode echocardiography makes it ideal for measurements in HCM?
   A. High lateral resolution
   B. High temporal resolution
   C. High tissue penetration
   D. High axial resolution

   Answer: B. The advantage of M-mode echocardiography over other imaging modalities is the very high temporal resolution that it provides. As a result, it allows for the examination of high-frequency motion. For example, subtle abnormalities such as partial mid-systolic closure of the aortic valve due to subvalvular obstruction and systolic anterior motion of the mitral valve are demonstrated best using M-mode echocardiography. The axial resolution of an image is mostly affected by pulse length and frequency. The lateral resolution is affected by beam width, depth, and gain. The depth of penetration is directly related to the wavelength of US.

2. True or False. RV hypertrophy is rare in HCM.

   Answer: False. Right ventricular hypertrophy is often seen in HCM. In one study right ventricular hypertrophy was seen in 44% of known HCM patients. RVH on echo is best seen in the subcostal view. A greater than 5 mm measurement of the RV free wall is associated with RVH.

3. What is a pitfall of using M-mode echocardiography for linear measurements?
   A. Low temporal resolution
   B. Poor tissue penetration
   C. Finding a representative portion of the LV

   Answer: C. Since M-mode echocardiography is essentially an "ice pick" view of the heart, it is often difficult to determine which precise part of the heart is being visualized. Furthermore, M-mode may capture an off-axis cut, thus giving an oblique view of the LV wall. Temporal resolution is highest by M-mode echo.

4. Which of the following is true?
   A. Classically, LV wall thickness measurements are made at end diastole in the four-chamber view.
   B. The area of interest for the measurement is only the basal septum.
   C. Highly trained athlete wall thickness often exceeds 15 mm.
   D. Extreme wall thickness of greater than 30 mm is associated with sudden cardiac death.

   Answer: D. A greater than 30 mm wall thickness is associated with sudden death and is a Class 2a indication for an implantable defibrillator. The wall thicknesses of highly trained athletes are rarely greater than 15 mm. Typically one measures for LV hypertrophy in the parasternal long or short axis. The four-chamber view is never used. The area of interest is usually the basal septum, but various patterns and distribution of LV hypertrophy (including diffuse and marked) have been reported in HCM.

5. Which of the following statements about echocardiographic left atrial size and HCM is true?

   A. The left atrium is measured in the parasternal long axis view.
   B. The preferred measurement for left atrial size is area.
   C. A left atrial indexed volume of greater than 34ml/m^2 has prognostic implications.
   D. The left atrial volume can only be approximated by 3D echocardiography.

   C. The preferred size measurement for the left atrium is volume indexed by body surface area. 2D echo can be used to approximate left atrial volume by long-/short-axis measurements. These measurements should be done in the four-chamber and two-chamber apical views. A left atrial indexed volume of greater than 34 mL/m2

has been shown to prognosticate more serious cardiovascular events and greater LV hypertrophy, more diastolic dysfunction, and higher filling pressures.

6. In which views are the LVOT gradient checked?
   A. The apical five-chamber
   B. The apical three-chamber
   C. Both a and b
   D. Neither a nor b

   Answer: C. HCM patients often have LVOT obstruction. It is important to measure gradients properly to ascertain the level and location of the obstruction. The best way to measure LVOT gradients is in the apical four- and five-chamber views. In symptomatic HCM patients who do not have significant pressure gradients at rest, a dynamic obstruction must be investigated.

7. Which of the following is not a recommended parameter to evaluate for diastolic dysfunction grade in HCM patients?
   A. Pulmonary vein atrial reversal velocity <30 msec.
   B. E/E' ratio >14.
   C. LA volume index of >34 ml/m^2.
   D. Peak velocity of the TR jet >2.8m/sec.

   A. The American Society of Echocardiography established new guidelines for the determination of diastolic dysfunction in 2016. There are now four recommended parameters needed to determine diastolic dysfunction grade. These four parameters are average E/E′ ratio of >14, LA volume index of >34 ml/m^2, pulmonary vein atrial reversal velocity time of >30 msec (not <30 msec), and peak velocity of TR jet of >2.8 m/sec.

8. Your patient's echocardiogram has the following values: E/E′ ratio of 16, LA volume of 37 ml/m^2, pulmonary vein reversal velocity time of 25 msec, and TR jet velocity of 2.5 m/sec. What grade diastolic function does the patient have?
   A. Grade I
   B. Grade II
   C. Grade III
   D. Indeterminate

   Answer: D. The recommended parameters needed to evaluate diastolic dysfunction grade in HCM are average E/E′ ratio of >14, LA volume index of >34 ml/m^2, pulmonary vein atrial reversal velocity time of >30 msec, and peak velocity of TR jet of >2.8 m/sec. If less than 50% of the parameters are met, then LA pressure is normal, and grade I diastolic dysfunction is present. If greater than 50% of the parameters are met, then the LA pressure is elevated, and grade II diastolic dysfunction is present. In the situation that exactly 50% of the parameters are met, estimated LA pressures and diastolic grade are indeterminate. Finally, there is grade III diastolic dysfunction in the presence of a restrictive filling pattern (E/A > 2.5, deceleration time of E velocity of <150 msec, and isovolumic relaxation time <50 msec) and reduced E′ velocity. This patient had 50% of the criteria; thus the grade is indeterminate.

9. Contrast echocardiography media plays an important role in hypertrophic cardiomyopathy assessment in all of the following except:
   A. The evaluation of SAM
   B. Apical HCM
   C. Thrombus formation in a "burned-out" reduced LVEF HCM patient
   D. To identify appropriate coronary vessels for alcohol septal ablation

   Answer: A. Contrast echocardiography plays an important role in HCM evaluation. Often the apical walls are not well visualized on a TTE. The classic spade appearance of the ventricular lumen of an apical HCM patient is well recognized with contrast. In later stages of HCM, one can have severely reduced LVEF. These patients are susceptible to forming LV thrombus which is best identified with contrast. Finally, contrast media is injected into the coronary arteries, to identify and confirm the appropriate septal branch that supplies the myocardium for alcohol septal ablation. It is important to identify the desired area for ablation and to avoid alcohol injection into a papillary muscle or LV free wall. Contrast media does not play a major role in evaluating SAM.

10. TEE is an important tool in HCM evaluation in the following situations except:
    A. Patient with HCM and concomitant intrinsic degenerative mitral valve disease
    B. Differentiating HCM from a subaortic membrane
    C. Intraoperatively during septal myectomy
    D. Checking LVOT and aortic valve gradients in a patient with HCM and aortic stenosis

    Answer: D. HCM patients often have mitral regurgitation. However, it may be difficult to discern intrinsic mitral valve disease versus MR secondary to SAM in an HCM on a TTE. TEE is the best tool to evaluate for intrinsic mitral valve disease in these patients. Although rare, an important differential of LVOT gradients is subaortic membrane. These are often missed on TTE. Having TEE imaging is a class I indication during intracardiac surgery. HCM evaluation with concomitant AS is often challenging. Checking LVOT and AS gradients in TEE, although possible, is not ideal because it is often difficult to obtain Doppler measurements parallel to flow. TEE can be valuable in these

patients when evaluating the aortic valve structure and measuring aortic valve area by planimetry in the setting of high gradients.

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Cardiac MRI in Diagnosis and Management

5

Daniele Massera, Jonathan Kahan, Juan Gaztanaga, and Mario J. Garcia

Key Points

- Application of a strong magnetic field to hydrogen atoms in myocytes causes protons to align in higher energy states. When a perpendicular magnet is applied, the energy given off and absorbed by the surrounding tissue is detected as the protons relax. This is called spin-lattice or T1 relaxation. If energy is absorbed and detected from one proton to another, this is known as spin-spin or T2 relaxation.
- Cardiac MRI (CMR) has many applications in the field of cardiology and is the gold standard for quantification of ventricular volumes, masses, fibrosis, and ejection fraction, with excellent spatial resolution, accuracy, and reproducibility. Additionally, it is not limited by body habitus or poor acoustic windows. Cardiac stents, grafts, and closure devices are generally safe, and MRI-conditional implantable cardiac defibrillators and pacemakers are available.
- Chelated gadolinium is the main contrast agent used in CMR. It has an excellent safety profile; nephrogenic systemic fibrosis is the most serious but rare complication. Late gadolinium enhancement is used to detect areas of fibrosis, which may be associated with increased risk for sudden cardiac death.
- Hypertrophic cardiomyopathy (HCM) has many phenotypes, the most common being asymmetric septal hypertrophy. CMR can diagnose and detect the extent of various HCM presentations, especially in areas that are difficult to evaluate on echocardiography, such as the apex and lateral wall.
- A variety of cardiac diseases can mimic HCM, especially hypertensive heart disease, athlete's heart, infiltrative cardiomyopathies, and valvular diseases. CMR has the ability to help distinguish between these differential diagnoses.
- Mitral valve regurgitation is the most common valve disorder in HCM. Systolic anterior motion, papillary muscle dysfunction, and fibrosis can readily be detected and quantified by CMR. Papillary muscle abnormalities, including hypertrophy or abnormal positioning or attachment, as well as membranes, can be distinguished by CMR.
- Patients with HCM are at increased risk for myocardial microvascular ischemia, which can lead to heart failure and sudden cardiac death. Delayed enhancement CMR can detect myocardial perfusion defects and fibrosis, allowing for improved diagnosis and risk stratification, enabling personalized treatment plans.

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Introduction

A variety of noninvasive modalities are used for the diagnosis and management of hypertrophic cardiomyopathy (HCM). Appropriate imaging should be utilized when HCM is suspected based on relevant signs and symptoms. Imaging can not only help to establish the diagnosis but also for risk stratification of sudden cardiac death (SCD) and evaluation of treatment options, making its use critical for proper

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management. Advances in imaging technology through cardiac magnetic resonance imaging (CMR) have given new insight and understanding into the morphologic diversity of HCM patients. Assessing global and regional left ventricular (LV) function, location and extent of hypertrophy, distribution and burden of fibrosis, as well as anatomy and physiology of the mitral valve (MV), is key to establishing a firm diagnosis, prognosis, and treatment plan. This chapter will outline the basic principles of CMR and its role in the diagnosis and treatment of HCM, with a special emphasis on current and future clinical applications.

General Principles of CMR

Magnetic resonance imaging (MRI) is one of the most widely used diagnostic techniques in medicine. Cardiac MRI (CMR) has emerged as a valuable modality for detection of both static and dynamic cardiovascular processes.

MR Physical Principles

All materials in nature have magnetic properties; movement of electrical charge creates magnetic field lines perpendicular to the charge. Furthermore, any nucleus with an odd number of protons and neutrons will have magnetic moments, where a magnetic field with direction surrounds it based on movement of charges within the atom. In order to create a uniform magnetic field with parallel field lines, it needs to have a solenoid configuration, where an electric charge creates a magnetic field surrounding the object that the field passes over. Since the body largely consists of water, hydrogen atoms with a single positively charged proton can be used to generate electrical charge and therefore can create a magnetic dipole (bi-directional magnetic impulses originating from a single plane). Normally, these electrical charges and magnetic fields are pointed in random directions, canceling each other out. However, when a strong magnetic field is applied, the vectors of all of the magnetic momenta line up either parallel (low energy state) or antiparallel (high energy state) to the direction of the magnetic field source. In other words, when a strong, external magnetic field is applied to the hydrogen atoms in the form of water in the human body, those protons align either facing toward or away from the field. Furthermore, a strong external magnet does not just line up the molecules, but causes them to resonate (rotate). Another name for this rotation is precession. Each nucleus has a unique frequency proportional to the strength of the magnetic field to which it resonates, which is called resonant frequency. It can be calculated by using the Larmor equation:

$$\text{Resonant frequency}\left(\text{F}\right) = \text{B}_0 \times \text{Larmor constant}\left(42.57\,\text{MHz / T for a H}^1\text{ nucleus}\right)$$

B_0 is the strength of the external magnetic field, and T is a tesla unit, which equals 10,000 times the strength of the earth's magnetic field.

Therefore, another way to look at precession is that all protons will wobble or rotate around the plane of B_0 in an either parallel or antiparallel fashion.

All images are detections of energy from a given source. In order to obtain CMR images, it is necessary to detect the energy given off by the protons. This is accomplished by briefly applying a second magnetic field (B_1) perpendicular to the initial strong magnetic field and measuring the energy (in the form of absorption of energy into surrounding tissue) as protons return from a high to low energy state (antiparallel to parallel) and as they slow down their rotation (resonance). The energy given off by these relaxations is called spin and can be detected by radio-frequency (RF) signals or echo.

It is important to note that an atom can relax or "spin" in two different ways. When a strong magnetic field is applied, and all protons are aligned around B_0, the magnetic moments of each individual proton can be measured in either the longitudinal (z-axis) or transverse axis (x- and y-axis). It makes sense that if protons are essentially in line with each other, there is no statistical transverse movement, and therefore all transverse vectors cancel out, leaving a total of either parallel or antiparallel-oriented protons; the sum of these vectors is called net magnetization M. Note that net magnetization in the longitudinal plane is called M_Z and in the transverse plane M_{XY}.

When a brief radio-frequency (electromagnetic) pulse is applied, protons will suddenly align toward the transverse (higher energy state), instead of the longitudinal plane. After the electromagnetic pulse is turned off, the protons relax (spin) from a high to a lower energy state, and excess energy given off is absorbed by the surroundings, also known as the lattice. This spin-lattice relaxation is also known as T1 relaxation, and different relaxation times reflect different sizes and consistencies of molecules in tissue. In technical terms, T1 is the amount of time it takes for 63.2% of the original M_Z to recover. T2 (spin-spin) relaxation works similarly, except that it detects the effect of one proton's magnetic field on another and therefore is not influenced by the strong external magnetic field like the T1 relaxation time. Of note, T2 is the time it takes for 63.2% of the initial M_{XY} to disappear. After one RF pulse and a magnetic field, a gradient echo (GRE) is created from the spin of the energy-decayed protons. After two successive RF pulses, a spin echo is created.

Instrumentation

The main components of an MRI system include the magnet, magnetic field gradients (RF pulses), a radio-frequency system, and cardiac receiver coils, in addition to software to control the components and monitor the patient.

The superconducting magnet is stationary and creates the strong homogenous magnetic field. Superconducting magnets are made of niobium-titanium alloy wire to create 1.5–3 tesla (T) magnetic fields (although up to 10 T magnets have been created for experimental purposes). The radiofrequency system generates RF pulses leading to the excitation of protons and then uses a receiver to obtain signals from the protons. Note that these two actions occur through coils, which are usually numerous and small in order to eliminate background noise. It is also possible to activate more than one gradient coil at the same time, leading to oblique RF pulses and allowing different angles of measurement from 90 and 180 degrees.

Images obtained are stored in a k-space, or temporary image space. This is usually a matrix where the raw image data from the RF signals are stored. At the end of the scan, the data collected in k-space from different pulse sequences is used to produce an image. This concept becomes important when discussing different imaging modes (see below). From the k-space matrix, near limitless sequences can be applied to the raw data to transform it into images that contain different structural and functional information. A few types of these images, as applied to HCM, are discussed in a later section.

Contrast Agents

Most MRI contrast agents use various compounds of chelated gadolinium, and their use is similar to iodinated contrast agents in computed tomography. Most commonly, gadolinium is injected at 0.2 mmol/kg; however, single (0.1 mmol/kg) and triple (0.3 mmol/kg) doses can be used. Initially, gadolinium is injected intravenously, where it then partitions to the extracellular matrix. In tissues with increased vascularity, more gadolinium will bind to these structures. Once gadolinium is bound to extravascular spaces, it shortens both T1 and T2 (increasing relaxation) leading to an increase in signal intensity. Some compounds have the ability to lead to signal loss. Thus, it is important to understand that the same contrast agent can both increase and decrease the signal intensity depending on which imaging sequence is being used.

There are currently nine gadolinium-based agents approved by the Food and Drug Administration (FDA), although none are specifically labeled for CMR use. Most have similar T1 relaxivity, while Gadobenate dimeglumine (Multihance®) has a higher T1 relaxivity and therefore requires protocols with smaller dosing. Gadoterate (Dotarem®) is a newer agent that has lower T1 relaxivity and is considered safer for patients with lower glomerular filtration rates; however, it is still not used regularly in CMR.

Chelated gadolinium has an excellent safety profile, with a <1% adverse reaction rate, most commonly flushing, headache, and nausea. Allergic reactions are reported at <0.05%, while severe anaphylaxis has only been shown in isolated case reports. At larger doses, however, acute renal failure may develop, especially in patients with underlying renal dysfunction. Gadolinium carries an FDA warning for nephrogenic systemic fibrosis, a potentially lethal reaction involving fibrosis of the skin, joints, and internal organs. However, the EuroCMR study, which analyzed over 11,000 patients undergoing CMR with gadolinium, found no cases of nephrogenic systemic fibrosis [1]. Nevertheless, it is important to measure a patient's kidney function to avoid the risk of developing fibrosis, as patients with end-stage renal disease have a higher risk of developing this rare but frequently fatal complication.

MR Protocols and Cardiovascular Applications

Cardiac MRI (CMR) can be used to evaluate the structure, perfusion, function, and metabolism of the heart. This is achieved through a multitude of imaging protocols, each designed to detect a certain component of the heart. In most cases, images are collected and analyzed in segments, most commonly following the American Heart Association 17-segment model [2]. Most sequences can further be divided into bright blood (gradient echo) sequences and black blood (spin echo) sequences. Both bright and black blood sequences are named after the appearance of blood and refer to the method of obtaining these images (generically called T1 and T2; see section "MR Physical Principles").

Initially, the patient completes an MRI safety screen to avoid most of the possible complications/contraindications (see section "Absolute and Relative Contraindications"). Once inside the scanner, an electrocardiographic (EKG) signal is attached for gating purposes. If EKG monitoring cannot be obtained, then the peripheral pulse signal can be used. If stress testing is done, a blood pressure cuff must also be attached. Hearing protection should be given, as the magnetic gradients deliver loud tapping noises.

Once the patient is inside the CMR scanner, a low-resolution localizer image is obtained with single-shot steady-state free precession (SSFP), acquiring a single image in the axial, coronal, and sagittal planes. Not only does this help to localize the heart, but these fast images can show gross abnormalities, e.g., aortic aneurysms, masses, or congenital defects.

Another concept applied to numerous sequences is phase contrast (PC) imaging, which is used to obtain velocities through an area (i.e., valves) from which gradients can be calculated (see section on valvular stenosis). In this technique, blood is given a magnetic energy pulse before the valve and its spin are measured immediately after the excitation plane, allowing measurement of flow velocity.

Cine imaging involves the use of segmented SSFP images, determining the T2/T1 ratio of tissues and is therefore less dependent on inflowing blood. This leads to excellent endocardial definition, as well as increased temporal resolution, quality, and reproducibility [3]. Each heartbeat or segment leads to acquisition of a k-space, and temporal resolution is determined by the time between two consecutive k-spaces or, in other words, the product of the repetition time by the number of k-spaces acquired per heartbeat. In general, temporal resolution for CMR should be less than 45 ms. Spatial resolution in cine imaging is determined by the imaging matrix size, and the field of view should be <2 mm in the x- and y-axis [4]. During a cine image, the patient must hold their breath for 5–10 s or 8–12 heartbeats. If patients have limited breath hold capacity, images can be obtained with averages of three to four numbers of excitations per cycle or with respiratory navigators during free breathing. Gating can be accomplished both retrospectively and prospectively. In prospective gating, the QRS complex triggers imaging acquisition, while in retrospective gating, images are obtained throughout the cardiac cycle, which is therefore the preferred method for CMR image acquisition [5]. In patients with severe arrhythmias or limited breath holding capability, real-time cardiac function can be ascertained using variations of SSFP and echo planar imaging (EPI) [6].

Ventricular function is obtained in cine imaging through multiple short-axis slices that are approximately 6–10 mm thick and usually contiguous but can be separated by <5 mm gaps. Images in Figure 5.1 are also obtained in multiple dimensions, with standard 4-, 3-, and 2-chamber views as well as the long axis of the right ventricle. Figure 5.2 These images allow accurate determination of size, shape, and wall thickness of both ventricles, as well as visualization of dyskinesia, remodeling, or other structural abnormalities. Newer sequences have been able to recreate the full three-dimensional anatomy in a single breath hold [7].

First-pass perfusion imaging is a useful technique that enables detection of perfusion and microvascular obstruction in the myocardium. In this technique, saturation recovery gradient-echo images are obtained following injection of chelated gadolinium into the bloodstream in order to trace the passage of contrast through the myocardium and tissue [8]. In cases where detection of ischemia is desired, such as in acute myocardial infarction and coronary artery disease, adenosine or dipyridamole is given to dilate resistant arterioles before the injection of contrast [8]. Areas of reversible ischemia will appear as hypoperfusion on stress images but not at rest.

Exact quantification of perfusion can be obtained for each myocardial segment by creating signal versus time curves during contrast first pass. However, exact analysis of perfusion is time-consuming due to extensive post-processing and complex mathematics [9]. Myocardial signal intensity is then corrected for background noise, baseline, and blood

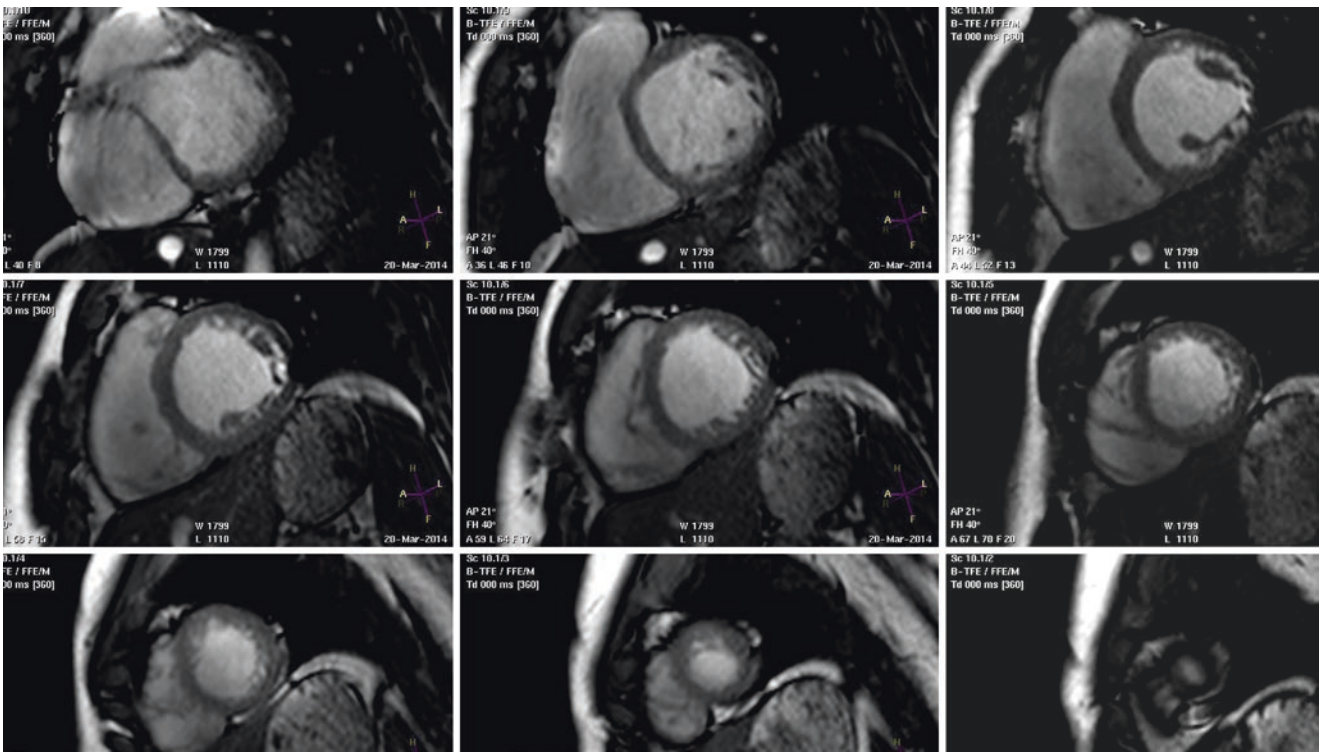

Fig. 5.1 Image of short-axis stack cine from base to the apex of a normal heart using steady-state free precession (SSFP) sequence

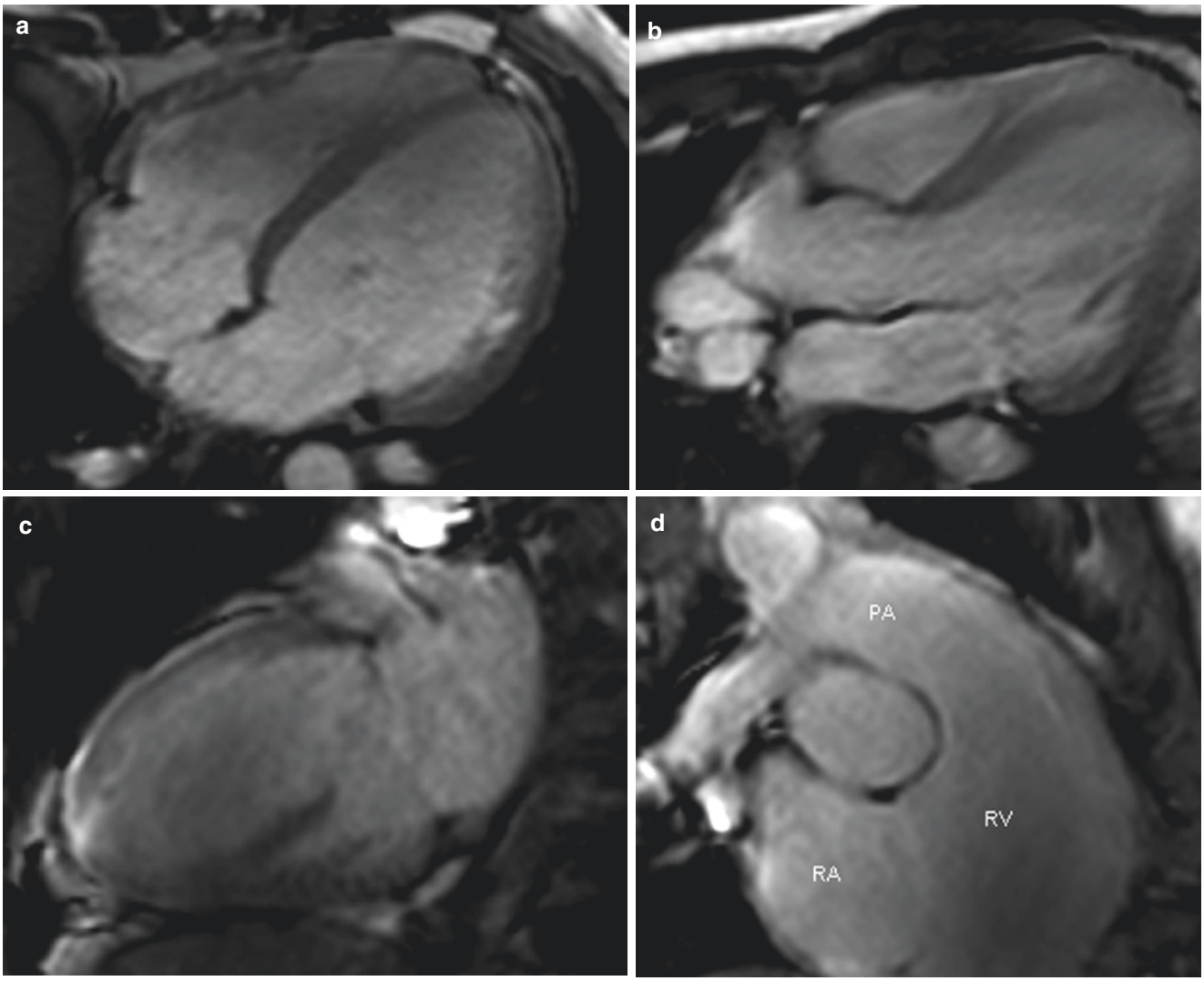

Fig. 5.2 SSFP long-axis cine images of (**a**) the four-chamber view, (**b**) three-chamber view, (**c**) two-chamber view, and (**d**) right-sided two-chamber view demonstrating the right atrium (RA), right ventricle (RV), and pulmonary artery (PA)

pool signals and given a percentage of hypodensity in each segment. Small doses of contrast are used due to a nonlinear relationship between signal intensity and contrast dose. Dual-bolus injection protocols and other sequences may be used to overcome this limitation [8]. Image acquisition is rapid during both rest and stress because a large part of the contrast diffuses quickly into extracellular tissues. Subsequently, semiquantitative analyses can be performed, most commonly by measuring the upslope of perfusion during stress versus rest and comparing it to an established perfusion reserve index.

Delayed enhancement CMR is a sequence that is used to detect scar or fibrosis. Figure 5.3 In this modality, images are typically obtained 10–20 min after gadolinium contrast injection, in order to allow diffusion into the tissue. In normal myocardium with an intact cell membrane, gadolinium is unable to diffuse into the cell. In damaged cells, e.g., after an acute myocardial infarction, the cell membranes are disrupted, allowing gadolinium to enter the cells [10]. This leads to hyperenhancement that can easily be detected. In scar formation, such as in an old myocardial infarction, gadolinium will bind to the collagen matrix and therefore appear as hyperenhancement.

Absolute and Relative Contraindications

Before any MRI procedure, patients should complete a screening checklist questionnaire and remove any metal from their body such as piercings, glasses, watches, hearing aids, etc. The checklist should include any internal metals such as pacemakers, stents, shrapnel, etc. In addition, patients should be asked about claustrophobia, because most MRI scanners consist of large, enclosed tubes and generate loud

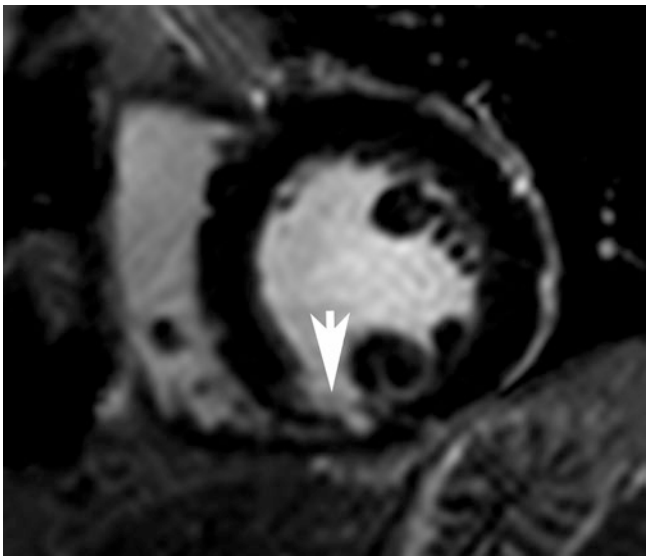

Fig. 5.3 Delayed enhancement short-axis image demonstrating subendocardial enhancement of the inferior wall (*arrow*) segments representing scar/infarction

noises; claustrophobia is considered a relative contraindication to MRI (estimated to occur in 2–4% of patients [11]).

Due to the relatively long duration of CMR scans and the inability to perform cardiopulmonary resuscitation and other lifesaving techniques during scanning, clinical instability is generally considered to be an absolute contraindication to undergoing a CMR. Note that MRI-safe ventilators are available and mechanical ventilation is not a contraindication for CMR.

According to the US Food and Drug Administration, the fetal effects of MRI are unknown, based on lack of long-term studies on fetuses exposed to MRI [12]. The 2013 American College of Radiology Guidelines, however, state that pregnant patients may undergo MRI scans if the benefit outweighs risks to mother and fetus [13]. Therefore, it is prudent to discuss the potential benefits of CMR and the potential risks to the fetus, including possible teratogenicity during the first trimester (although this has yet to be demonstrated in human studies) and theoretical acoustic damage [14].

Gadolinium has demonstrated clear teratogenic properties in pregnant patients and has been labeled pregnancy class C by the Food and Drug Administration (= adverse effect on fetus shown in animal studies) [15]. Gadolinium is recommended only if use is "absolutely necessary" and the benefit outweighs the potential harm. It is important to wait 24 h after gadolinium contrast administration before breastfeeding and to discard any milk expressed during this time period.

External and internal foreign bodies can be affected by CMR. Patient preparation can easily avoid complications, and all rings/jewelry, hearing aids, glasses, and medications such as patches should be removed before imaging. Most relevant to the cardiologist are coronary stents and implanted pacemakers. It is important to note that devices are tested at a specific tesla level, and those labeled safe at 1.5 T may not be safe at a higher magnetic field level. Most coronary stents (even immediately following implantation), graft closure devices, PFO/ASD closure devices, inferior vena cava filters, coils, and prosthetic/metal valves are labeled as MR safe according to the American Heart Association 2007 statement and can undergo ≤3T MRIs following a brief manufacturing check [16]. The website www.mrisafety.com can be an excellent resource. If devices are weakly ferrogenic, MRI safety should be individualized, and it is prudent to wait for up to 6 weeks following implantation if possible.

Pulmonary artery catheters (e.g., Swan-Ganz catheter) and retained pacemaker leads are generally considered unsafe due to possible movement and heating of the catheter/leads within the pulmonary artery/cardiac tissue. Pacemakers and defibrillators have largely been considered an absolute contraindication to CMR, although newer studies have demonstrated safety, especially at the 1.5 T magnetic level [15]. MRI-conditional systems are available, but also non-MRI-conditional devices implanted after the year 2001 have been shown to be safe when following a dedicated protocol [17]. It is estimated that 50–75% of patients will have an indication for MRI during the lifetime of their device, and it is an important area of research to find MRI safe devices and protocols for implantation [18]. This may be especially true in HCM, since patients often require both ICD and CMR imaging.

Further relative contraindications include the patient's ability to perform breath-hold maneuvers, follow simple instructions, and lie in the supine position, as well as morbid obesity (weight limit 200 kg in most scanners).

CMR Applications in HCM

Noninvasive imaging is paramount to the diagnosis and management of HCM. CMR can accurately assess ventricular size and function and help the clinician with differentiating HCM from other causes of ventricular hypertrophy, as well as enable assessment of valvular pathology in three dimensions, especially of the aortic and mitral valves. Gradients and flows across valves can also be obtained, thus guiding the management of valvular lesions and disease-specific phenotypes.

Assessment of LV Volumes, Mass, and Function

CMR is considered the gold standard for the quantification of ventricular volumes, masses, and ejection fraction, demonstrating excellent spatial resolution, accuracy, and reproducibility [19]. In CMR, short-axis images are stacked using

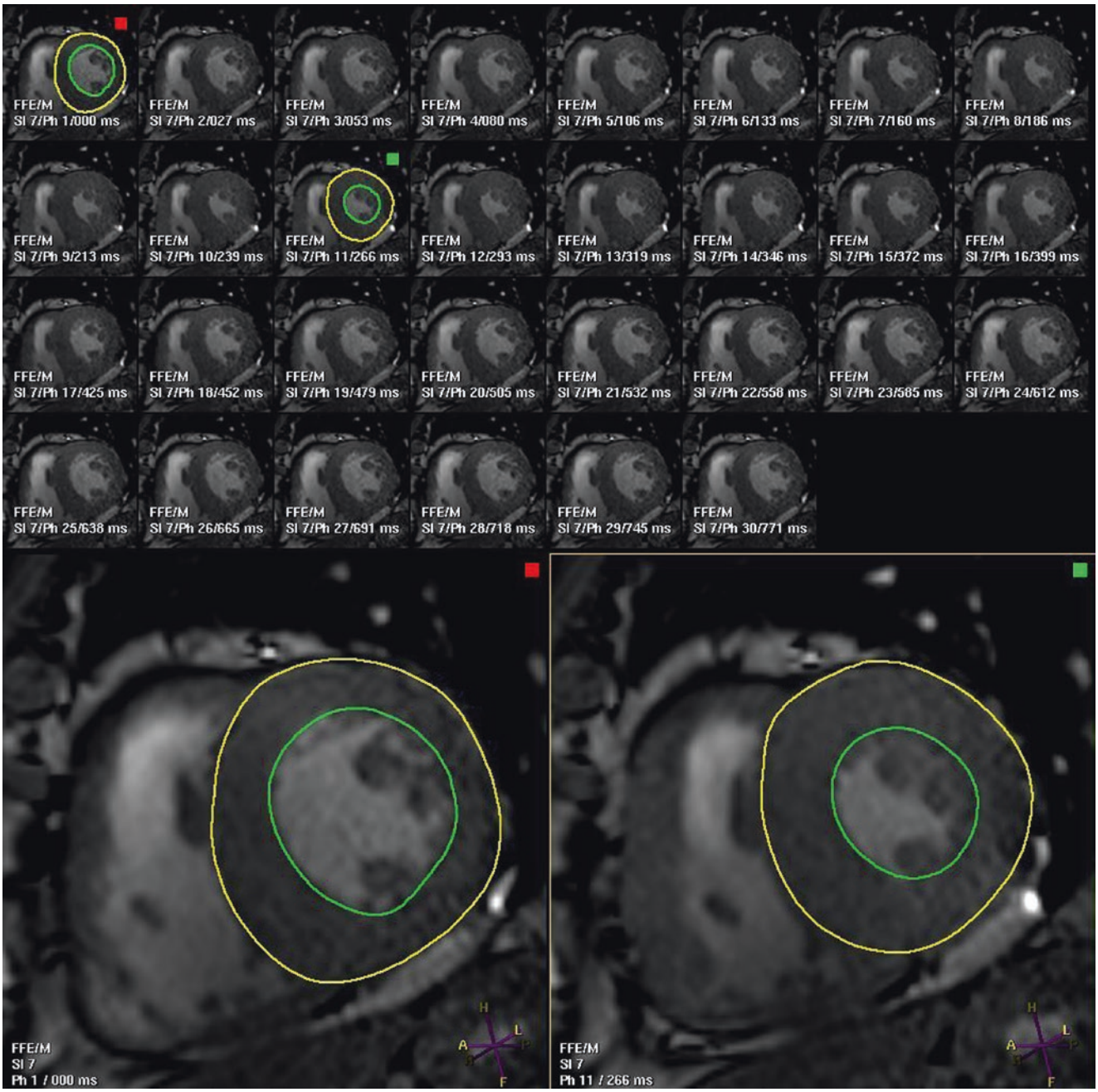

Fig. 5.4 Short-axis cine stack demonstrating endocardial and epicardial contours in end-diastole and end-systole for functional and volumetric analysis

Simpson's method to obtain the minimum and maximum ventricular dimensions and to define endocardial and epicardial borders. Figure 5.4 The volume of each ventricular cavity can then be assessed by multiplying the difference between the maximum and minimum area and the slice thickness. Once this has been obtained, end-diastolic and end-systolic volumes (EDV and ESV, respectively) can be derived by adding the cavity volumes of different slices. Ejection fraction and stroke volume can be calculated from EDV and ESV.

Ventricular mass is calculated by multiplying the volume of the total myocardium (mL^3) by the density of the myocardium (1.05 g/mL). Note that papillary muscles are excluded from such calculations and are not considered to contribute significant mass overall. However, this may not always be true in patients with HCM, some of whom have extensive papillary hypertrophy [20] (Fig. 5.5).

Similarly to echocardiography, a 17-segment model of the LV is used, and each region is given a score based on the radial thickening.

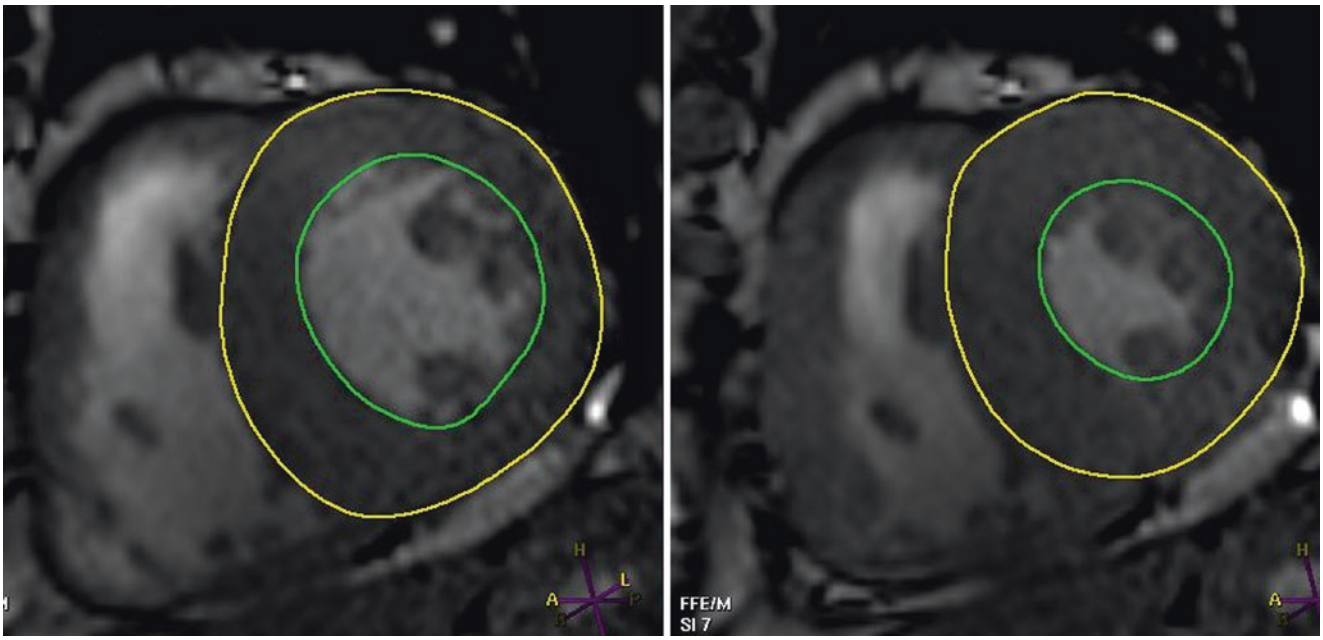

Fig. 5.5 Short-axis cine image showing end-diastole and end-systole excluding papillary muscles for functional and volumetric analysis

Regional Morphology and Functional Assessment

Chamber morphology and function are usually evaluated simultaneously using cine images with steady-state free precession (SSFP). SSFP with contrast can determine T2/T1 ratios, allowing for better definition of the endocardial border, and is less dependent on blood inflow. HCM can present with various different morphologies (characterized below). Hypertrophy in HCM can be focal or diffuse; asymmetric septal hypertrophy is the most common phenotype. In fact, more than 80% of HCM patients have septal hypertrophy; 9% have anterolateral free wall hypertrophy; apical, mass-like, and mid-LV hypertrophy make up the rest of the HCM morphologic expressions [21]. In Asia, however, the apical phenotype may be more common than in the United States [22] (Fig. 5.6).

Asymmetric Septal Hypertrophy

Asymmetric septal hypertrophy is the most common morphologic presentation of HCM. Patients may present asymptomatic, or with dyspnea, syncope, chest pain, or sudden death [23, 24]. About 70% of patients with asymmetric septal hypertrophy have systolic left ventricular outflow tract (LVOT) obstruction [58]. Obstruction can be present at rest, provoked by hemodynamic alterations, or labile and occurring at random times [25]. Its presence can be affected by preload, afterload, and contractility [26]. Diagnosis of HCM based on CMR is made when the interventricular septum is ≥15 mm in end diastole or when the ratio of septum to lateral LV wall is ≥1.3 in normotensive patients or ≥1.5 in hypertensive patients without left ventricular hypertrophy [27]. Asymmetry in and of itself, in the absence of qualifying maximal thickness, is not considered diagnostic of HCM. Figure 5.7 These findings correlate with echocardiography, where similar criteria apply. Valente et al. [28] and Devlin et al. [29] examined the utility of echocardiography and CMR to diagnose HCM in patients with and without left ventricular hypertrophy. While both CMR and echocardiography reached the same conclusion 90% of the time, both authors concurred that CMR is superior to echocardiography in diagnosing HCM, likely due to increased detail in anatomical reading as well as less geometric assumptions and miss with CMR. In a more recent study, Hindieh et al. reported a ≥10% intermodal discrepancy in approximately half of their contemporary cohort, supporting a more widespread use of CMR [30]. CMR excels at imaging areas of the heart typically difficult to visualize with echocardiography, such as the apex and lateral wall. In addition, RV structure and function, including RV outflow tract obstruction, can also be better visualized.

Apical HCM

Apical HCM is more common in Asian populations compared with Caucasians, and the proportion of apical HCM among all patients with HCM varies from as high as 25% in Japan to less than 2% in Western regions [31]. In up to half of cases, EKG demonstrates deeply negative T waves in precordial leads (>10 mV), although there is no correlation between the extent of the T wave depressions and wall thickness [31, 32]. Apical HCM is commonly missed on

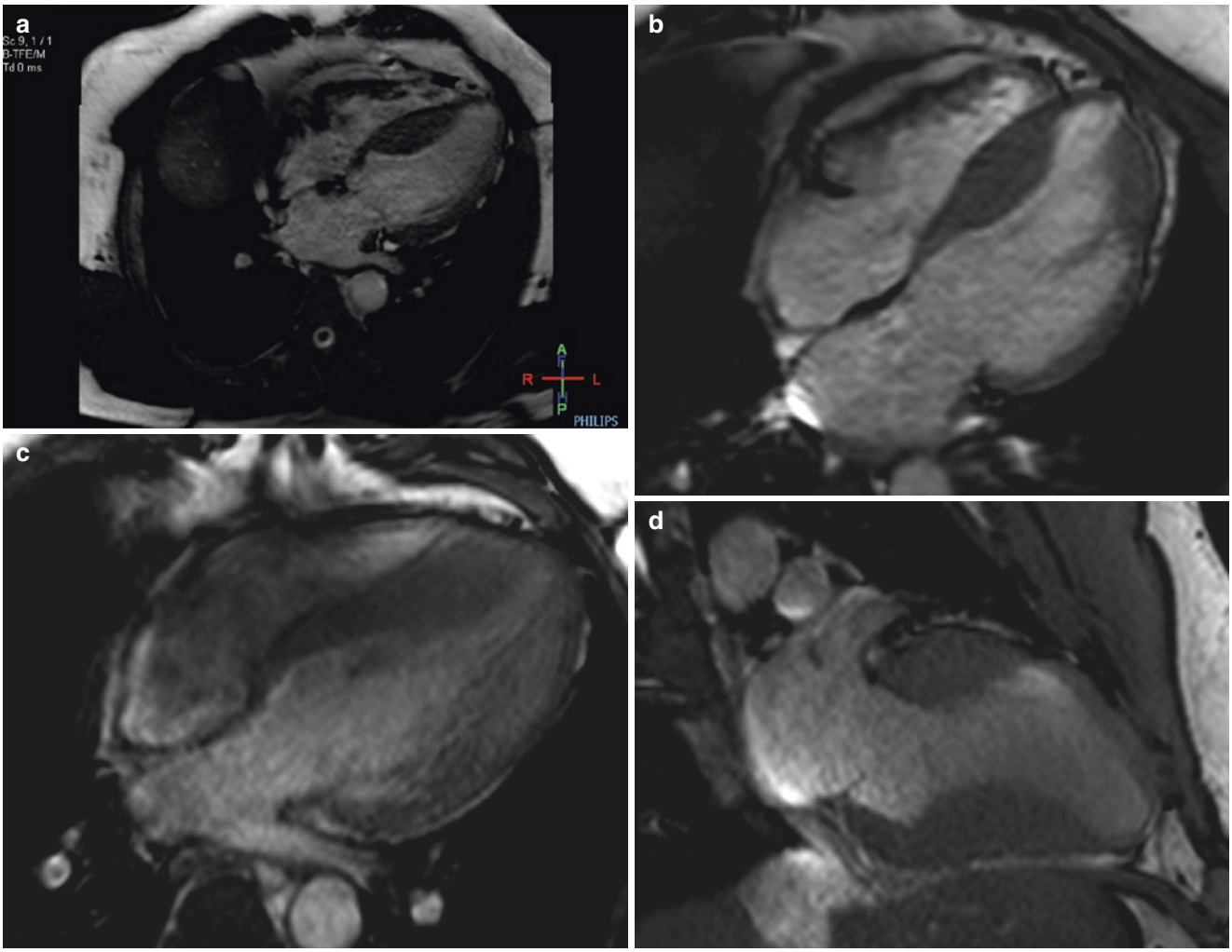

Fig. 5.6 SSFP cine image demonstrating (**a**) four-chamber view with mid-septal hypertrophic cardiomyopathy, (**b**) four-chamber view with mid-septal and distal lateral wall hypertrophic cardiomyopathy, (**c**) four-chamber view with apical hypertrophic cardiomyopathy, and (**d**) two-chamber view with basal anterior and mid inferior hypertrophic cardiomyopathy

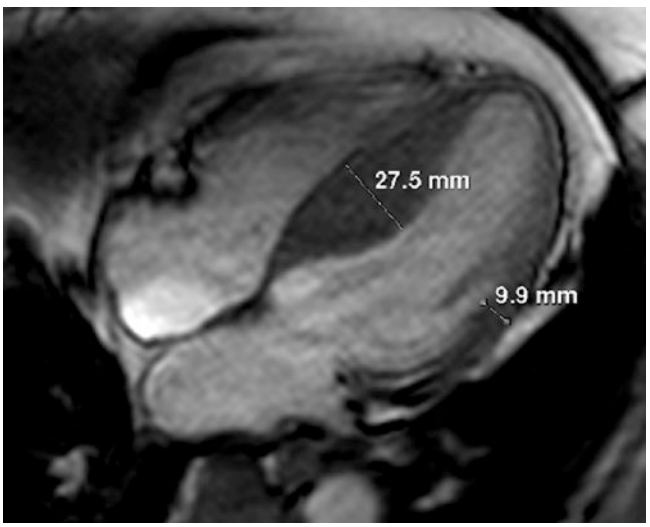

Fig. 5.7 SSFP cine image showing >1.5 cm thickness in the septum with a > 1.3 ratio of septum to lateral LV wall

standard echocardiography, e.g., due to foreshortening of the apex [32]. Use of contrast echocardiography can substantially improve endocardial border definition. The diagnostic criteria for apical HCM is an absolute apical wall thickness of >15 mm or the ratio of apical LV and basal LV wall thickness ≥1.3–1.5 [32]. Figure 5.8 Other possible signs include a failure to identify increased wall thickness toward the apex and obliteration of the LV apical cavity during systole. Patients with apical HCM have been described as carrying a more favorable prognosis, with lower symptom burden and a higher long-term survival, possibly because hypertrophy does not extend beyond the mid-ventricular level and generally does not cause LVOT obstruction [33]. However, more recent studies have called this notion into question, reporting a similar prognosis as with the other phenotypes [33, 34]. Pathophysiologic determinants are diastolic dysfunction, substrate predisposing to arrhythmia, mid-ventricular obstruction, and apical aneurysm formation [35].

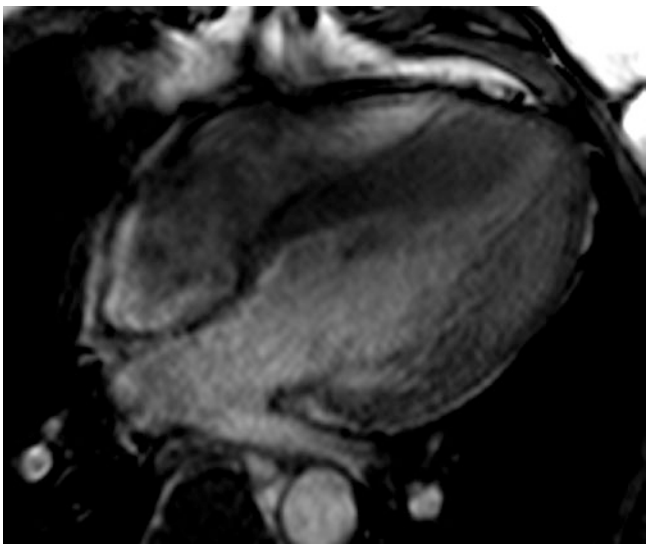

Fig. 5.8 SSFP cine image of apical hypertrophic cardiomyopathy

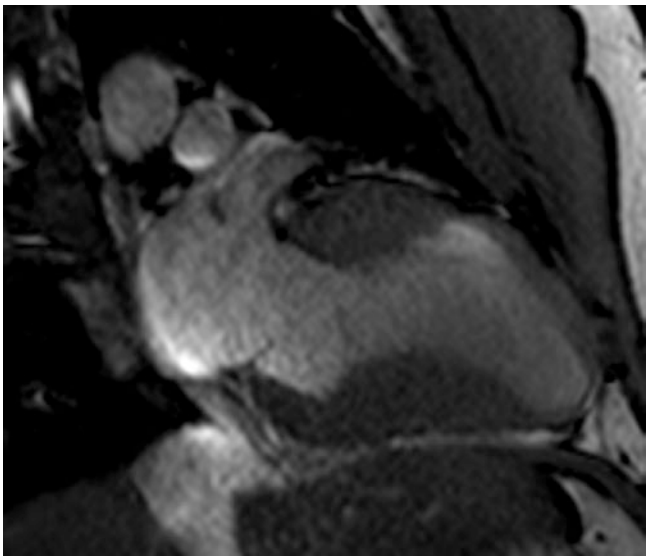

Fig. 5.9 SSFP cine image demonstrating hypertrophic cardiomyopathy involving two different (anterior and inferior) myocardial regions

Atypical Presentations

In the past, it was assumed that asymmetric septal hypertrophy was the only phenotype of HCM. However, it has been shown that HCM can present as diffuse global hypertrophy or focal segmental hypertrophy, as well as many other atypical patterns.

Focal segmental hypertrophy may involve only one or two segments, occasionally with hypertrophied segments separated by normal regional wall thickness; this phenotype has been described in up to 13% of patients with HCM [36]. Figure 5.9 Limitations of transthoracic echocardiography may lead to underestimation of LV thickness and subsequently to a missed diagnosis of HCM [30, 36, 37].

Mid-LV concentric hypertrophy is another uncommon form of HCM, leading to mid-LV obstruction and apical akinesis or aneurysms. Concentric hypertrophy can lead to intracavitary pressure gradient formation in the LV apex, which may result in aneurysm formation in 4.8% of patients and increased risk of progressive heart failure, thromboembolic phenomena, and sudden death [38, 39].

Rarely, HCM can present as mass-like thickening of the LV, which unlike a true mass (e.g., vegetation, tumor) will demonstrate contractile properties. MR tagging is a useful tool in this scenario (see below) because it highlights a contractile mass in HCM but does not tag a tumor [40].

While echocardiography remains the reference standard for evaluation of the mitral valve leaflets, quantification of LVOT gradients, and dynamic assessment during exercise and load-altering maneuvers, CMR provides more complete assessment of the subvalvular apparatus, including the papillary muscles.

Abnormal Papillary Muscle Morphology

Abnormal papillary muscle morphology, such as bifid or multiple accessory papillary muscles, are common in HCM [41]. Abnormal position of a papillary muscle, e.g., anteroapical displacement, can lead to systolic anterior motion (SAM) of the mitral valve and LVOT obstruction [41, 42]. Moreover, SAM and elevated LVOT gradients can be present independently of increased septal wall thickness, which in some cases can be normal [43]. In fact, papillary muscle alterations may be the only abnormality seen on CMR, resulting in LVOT obstruction without cardiac muscle hypertrophy.

Mitral Valve Anomalies

Mitral valve pathology is the most common valve lesion associated with HCM. CMR can be of value in detecting and defining its abnormalities [44]. Furthermore, unrelated primary pathologies such as rheumatic heart disease or myxomatous degeneration may confound the diagnosis. Common disorders of the mitral valve related to HCM include increased leaflet area (with elongation of one or both leaflets), abnormal origination, and/or insertion of the papillary muscles and abnormal systolic anterior motion, which is the most common abnormality seen [45–47] (Fig. 5.10).

Systolic anterior motion (SAM) results from elongation of the anterior leaflet, leading to exaggerated anterior motion and obstruction of the LVOT. The papillary muscle inserts directly into the anterior leaflet in 10% of patients with obstructive HCM without chordae tendineae connecting to it [48]. Severity of the resulting mitral regurgitation (MR) secondary to SAM is directly proportional to the severity of the LVOT gradient [49]. Alternative diagnoses, such as valvular vegetations, mitral valve prolapse, and mitral annular calcification (MAC), should be excluded and are readily differentiated on CMR. Elongated and redundant cords that may contribute to LVOT obstruction and mitral regurgitation can also be evaluated by CMR.

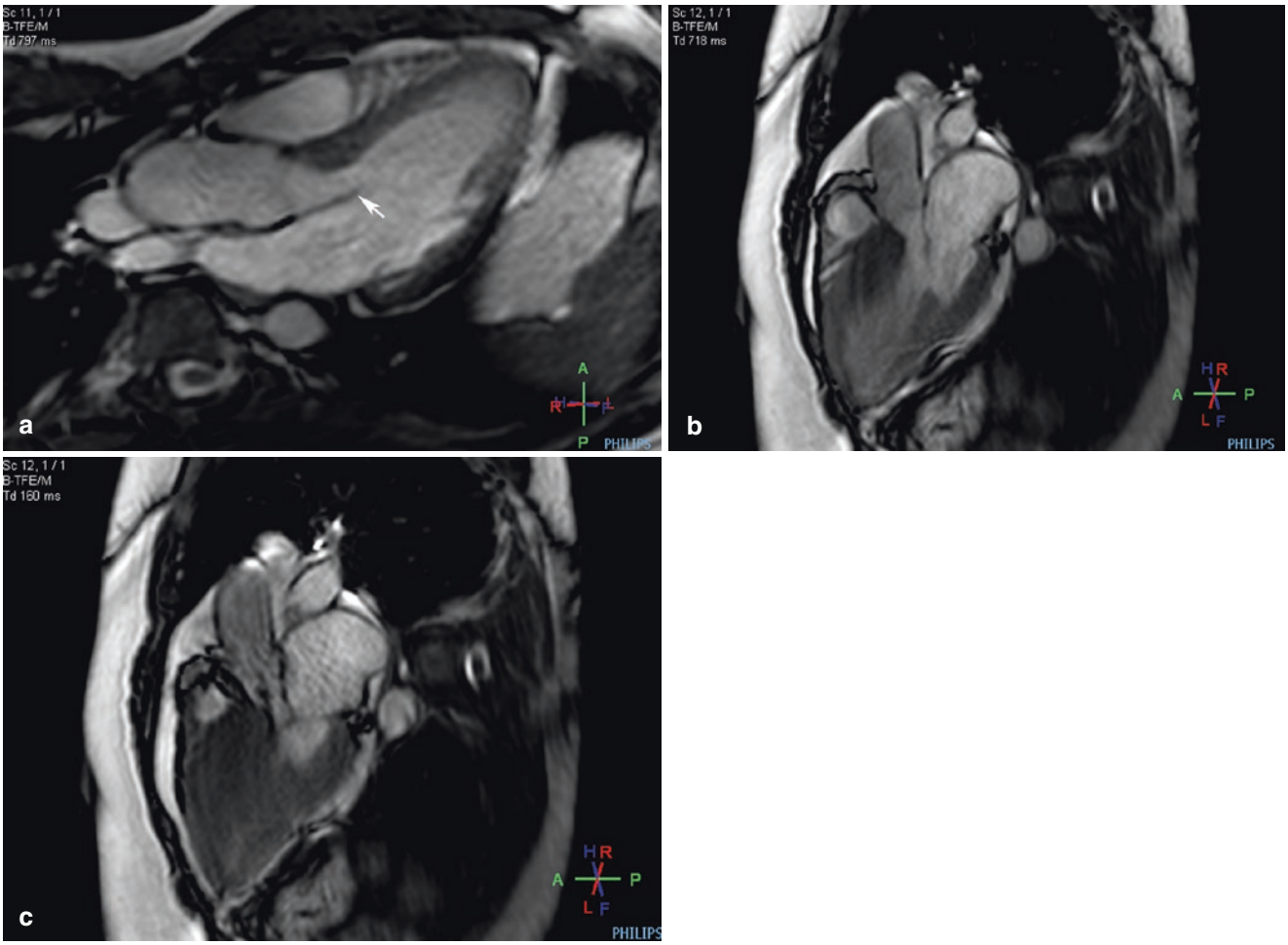

Fig. 5.10 SSFP three-chamber cine image showing (**a**) redundant anterior mitral valve leaflet (*arrow*), (**b**) narrowed left ventricular outflow tract during diastole, and (**c**) significant left ventricular outflow obstruction during systole

MR Tagging for Strain Analysis and T1 Mapping

MR tagging is a technique that can be used to assess myocardial function. In this technique, RF pulses are delivered immediately after the QRS complex. This nulls the signal in planes perpendicular to the image leading to a grid of dark lines (tags) that can be visualized and tracked during the cardiac cycle. Figure 5.11 Quantification of tag changes reveals deformation and displacement of the myocardium, enabling accurate evaluation of regional and overall systolic, as well as diastolic function. With this technique, radial, longitudinal, and circumferential strain, ventricular torsion, and strain rates can be obtained. Harmonic phase analysis greatly reduces the post-processing time. Therefore, this is a valuable tool for assessment of myocardial function and strain. Strain quantification with phase displacement encoding can further lead to increased spatial and temporal resolution [50].

Myocardial T1 mapping has emerged as an experimental technique that allows quantification of the extracellular volume fraction reflecting interstitial disease and may enable detection of earlier stages of fibrosis before development of LGE [51]. It does not require gadolinium contrast administration and has been found to distinguish HCM patients with LV hypertrophy and mutation carriers without LV hypertrophy from normal controls [52]. Furthermore, native T1 has been described as independent discriminator between HCM and hypertensive heart disease, despite controlling for LGE, suggesting that T1 mapping may be a powerful tool to discriminate between morphologically similar cardiomyopathy phenotypes [53]. Further research encompassing a variety of morphological phenotypes is required before widespread clinical use.

Miscellaneous

More recently, additional morphological features in HCM have been described owing to detailed assessment with CMR. Accessory apical-basal muscle bundles, which may contribute to LVOT obstruction, were observed in 60% of patients with HCM, as well as in family members who are genotype-positive but phenotype-negative, but only in 10% of control subjects [54]. Myocardial crypts described as nar-

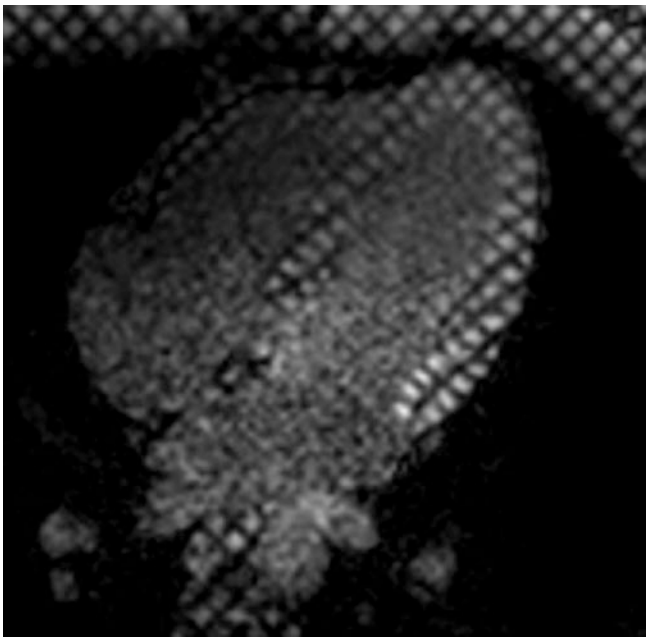

Fig. 5.11 Four-chamber view with MRI tagging sequence

row, blood-filled invaginations that are not visualized by echocardiography have also been described in a similar proportion of genotype-positive phenotype-negative family members but only in a small proportion of patients with HCM [55]. Their clinical significance is unknown. Lastly, left atrial remodeling and dysfunction identified on CMR have been shown to predict development of atrial fibrillation in patients with HCM [56].

Evaluation of LV Outflow Tract Obstruction

Left ventricular outflow tract obstruction (at baseline or provocable) is present in 70% of patients with HCM and directly relates to pathophysiology as well as treatment considerations [57, 58]. In most patients, septal hypertrophy leads directly to LVOT obstruction, although patients can have hypertrophy without obstruction and vice versa. LVOT obstruction without hypertrophy is commonly due to papillary muscle or other subvalvular abnormalities, such as membranes [42]. Mid-ventricular obstruction due to concentric hypertrophy should also be considered. While transthoracic (or transesophageal) echocardiography is initially used to quantify LVOT gradients, CMR has superior ability to define papillary muscle anatomy, systolic anterior motion contact, concomitant mid-ventricular hypertrophy, as well as membranes, leading to definition of the subvalvular apparatus with greater detail. Short-axis cine images are used to evaluate the LVOT, while long-axis cine images can demonstrate the subvalvular anatomy, especially in patients without asymmetric septal hypertrophy but with LVOT obstruction. Three-dimensional images of the LV are created by gating of the entire heart, allowing for reconstruction of the papillary muscles and the subvalvular apparatus. Accurate evaluation of the level of obstruction is crucial when planning septal reduction therapy, since alcohol septal ablation is typically reserved for patients with outflow tract obstruction due to asymmetric basal septal hypertrophy and SAM.

While LVOT gradients, acceleration, and flow turbulence can be measured using CMR, echocardiography remains the gold standard. Flow-sensitive gradient echo in CMR is used to define flow turbulence and acceleration, while phase contrast flow-sensitive sequences are used to estimate the LVOT gradient. Figure 5.12 Precise alignment, signal loss, and provocation during exercise can impede utility of the techniques described above. Newer CMR sequences, such as three-dimensional flow pattern/velocities not limited to imaging planes, real-time velocity encoding, and accurate sequence-enhanced turbulent jet velocities, may contribute to the accurate assessment of LVOT parameters [59–61]. Despite the dynamic nature of the LVOT, gradients >30 mmHg are associated with increased risks of stroke, heart failure, arrhythmia, and sudden cardiac death [57].

Qualitative and Quantitative Assessment of Mitral Regurgitation

CMR has the ability to image valve morphology in any plane without the limitation of poor acoustic windows or confounding by supra- or subvalvular disease (i.e., membranes). However, echocardiography has a high temporal and spatial resolution (especially transesophageal echocardiography) for highly mobile structures, such as leaflet abnormalities, vegetations, and ruptured chordae tendineae, and can be obtained in real time, making it the test of choice for these diagnoses. CMR images are obtained through SSFP, although fast GRE sequences can result in less artifact in areas of pulsatile flow. Turbulent flow, such as in mitral regurgitation, are seen as areas of signal void (spin dephasing) in SSFP and fast GRE bright blood images [62]. Figure 5.13 By measuring the size of the signal void, valve regurgitation can be defined in a semiquantitative fashion. However, similarly to echocardiography, imaging parameters such as angle, jet velocity, and dispersion of flow can alter the true size of the regurgitant jet. CMR, however, is able to truly quantify valve regurgitation using volumes determined from the difference in left and right ventricular stroke volume (SV) calculations obtained through cine imaging (see section "Assessment of LV Volumes, Mass and Function"). For the mitral valve, the difference between LV SV (from cine images) and forward SV (from phase contrast images of the ascending aorta (Fig. 5.14)) is obtained. By using the following equation, mitral regurgitation can be quantified:

$$\text{Regurgitation Fraction} = \text{Regurgitation Volume} / \text{Total SV}$$

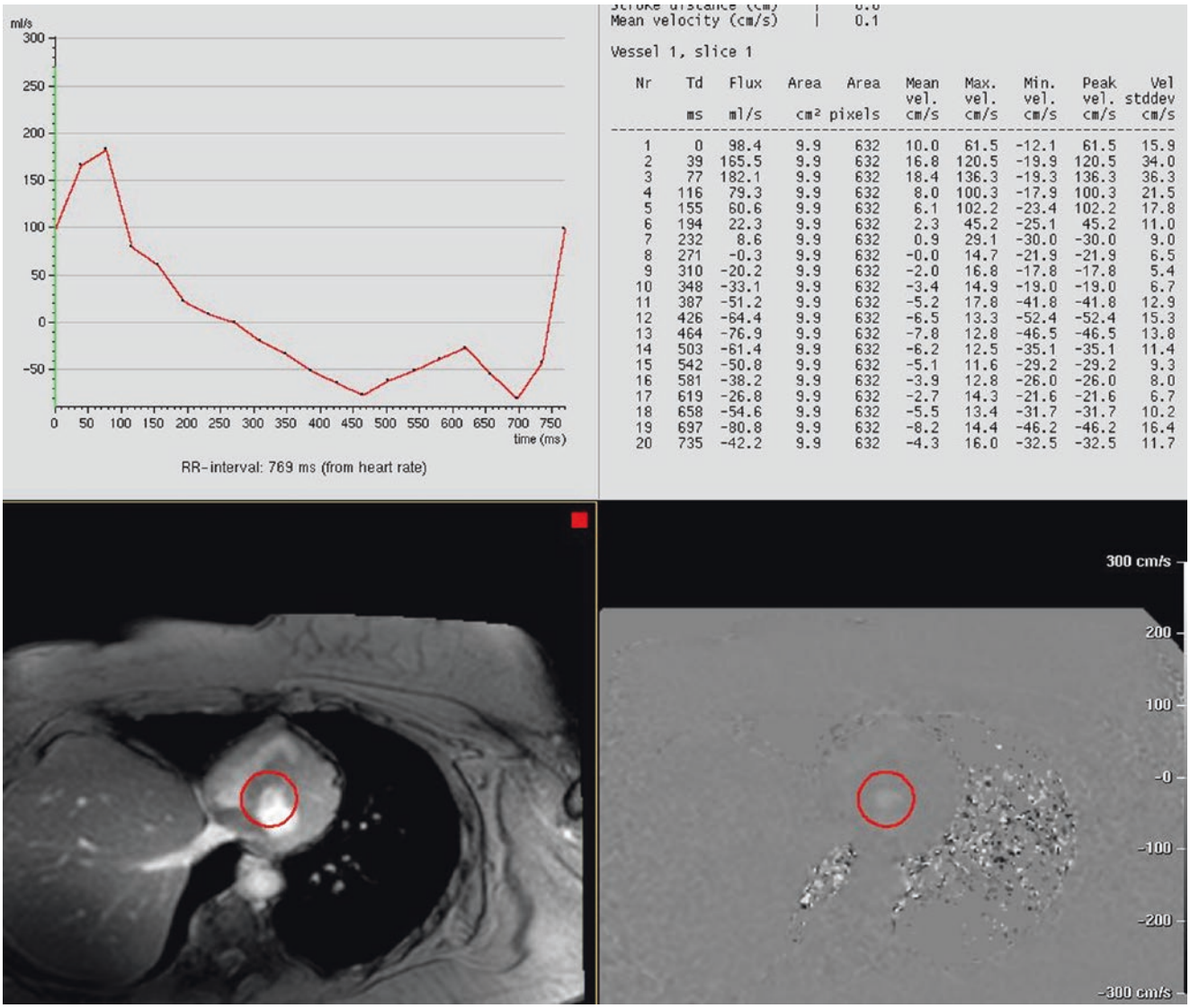

Fig. 5.12 Phase contrast imaging of a short-axis view with the region of interest at the left ventricular outflow tract demonstrating no significant gradient with a maximum velocity of 136.3 cm/sec

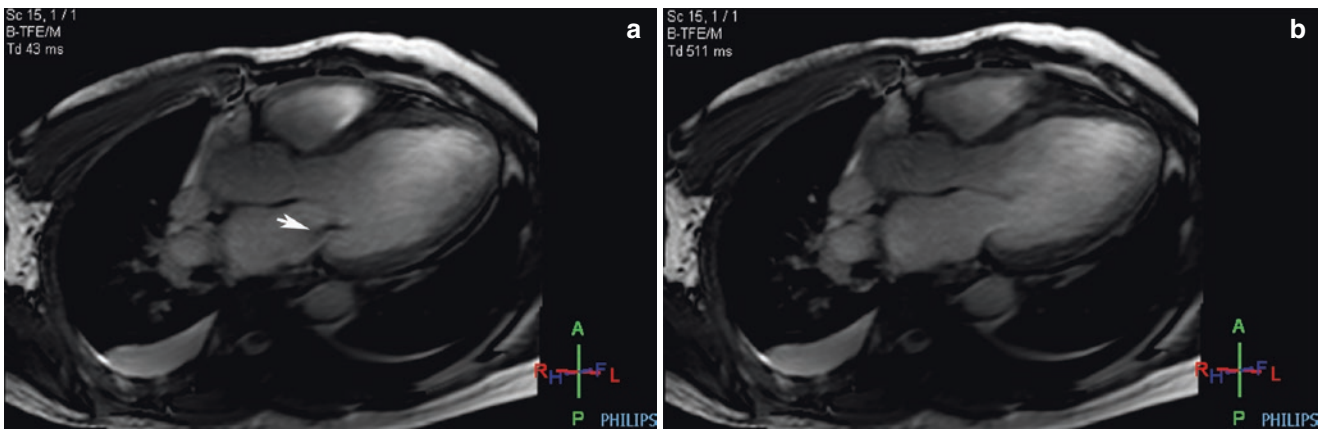

Fig. 5.13 SSFP three-chamber cine image demonstrating significant mitral regurgitation with turbulent flow (arrow) during systole (**a**) in comparison to in diastole (**b**)

Important clues regarding the MR jet can lead to phenotypic information for HCM patients. For example, if the MR jet is posteriorly directed, the most likely etiology is SAM, while an anterior/medial jet is a sign of posterior leaflet pathology [63]. As discussed above, if MR is related to SAM, treatment of LVOT obstruction will correct both MR and LVOT obstruction. However, if MR is independent of SAM, surgical treatment directed at the concomitant valve pathology may be required.

Myocardial Perfusion and Delayed Enhancement

Myocardial perfusion and delayed enhancement imaging are increasingly used in the risk stratification of HCM patients, and it is well known that myocardial ischemia contributes to angina, dyspnea, heart failure, arrhythmias, and sudden death [64]. Ischemia is commonly detected by visual interpretation, with the main limitation of dark rim artifact, which is thought to be caused by blood at the endocardium border resulting in hypointensity. Common causes of this artifact are insufficient k-space sampling, motion artifact, or contrast-related magnetic susceptibility, especially using SSFP sequences, high dye load, and fast injection rates [8]. To eliminate dark rim artifact, stress and rest images are compared to see if the dark rim artifact is present in both types of imaging.

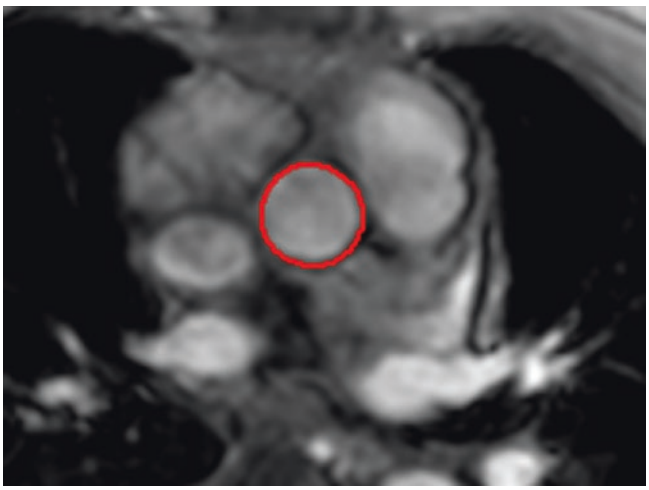

Fig. 5.14 Phase contrast imaging of the ascending aorta

Perfusion abnormalities can be demonstrated with single-photon computed tomography (SPECT), positron emission tomography (PET), and CMR via first-pass perfusion. In the absence of significant coronary artery disease, midwall perfusion defects during adenosine stress can be seen in the hypertrophied segments, which signify microvascular obstruction. Figure 5.15 The presence of perfusion abnormalities correlates with a poor prognosis. A prospective study of 51 patients with HCM found that abnormal vasodilator response was strongly predictive of mortality [64].

Late gadolinium enhancement (LGE) is used to assess normal myocyte uptake and architecture and has the ability to distinguish normal from infarcted myocardium and fibrosis [10]. In HCM, LGE can be used to assess increased myocardial fibrosis due to collagen deposition. LGE can be performed in a qualitative or quantitative fashion; quantification and phase-sensitive inversion recovery (STIR) sequences may improve accuracy. Fibrosis in the setting of HCM has been associated with microvascular ischemia, coronary arteriole dysplasia, and/or sarcomere gene mutations [65]. Owing to the heterogeneity of HCM, multiple patterns of LGE have been described: subendocardial and transmural LGE, which may be difficult to distinguish from coronary artery disease; LGE at the right ventricular insertion point into the ventricular septum;

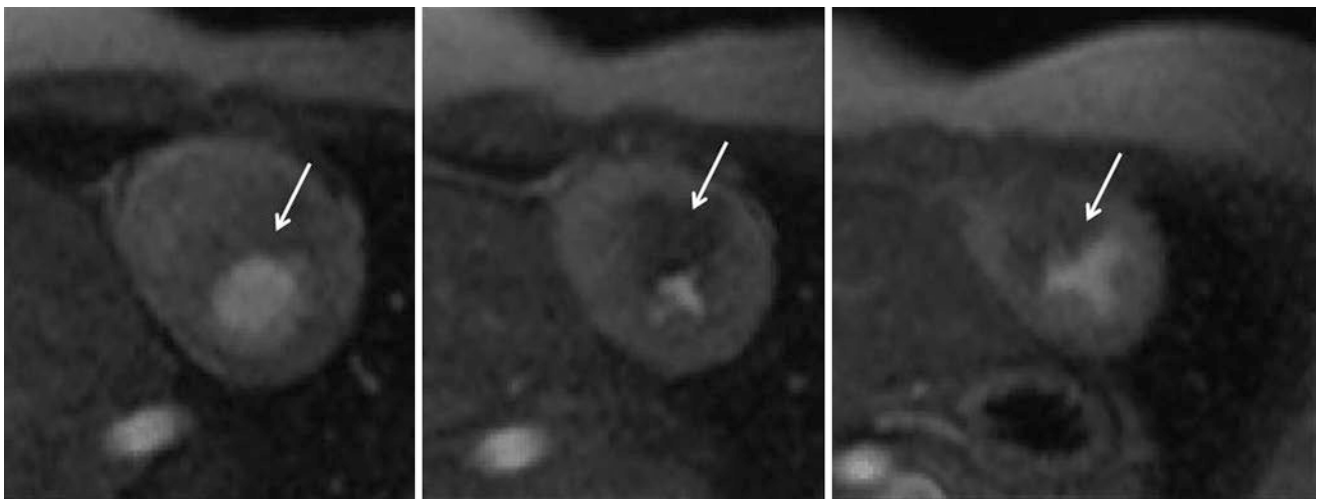

Fig. 5.15 Stress adenosine MRI showing basal to apical short-axis views with perfusion defects (*arrows*) in the hypertrophied mid-septum demonstrating microvascular ischemia

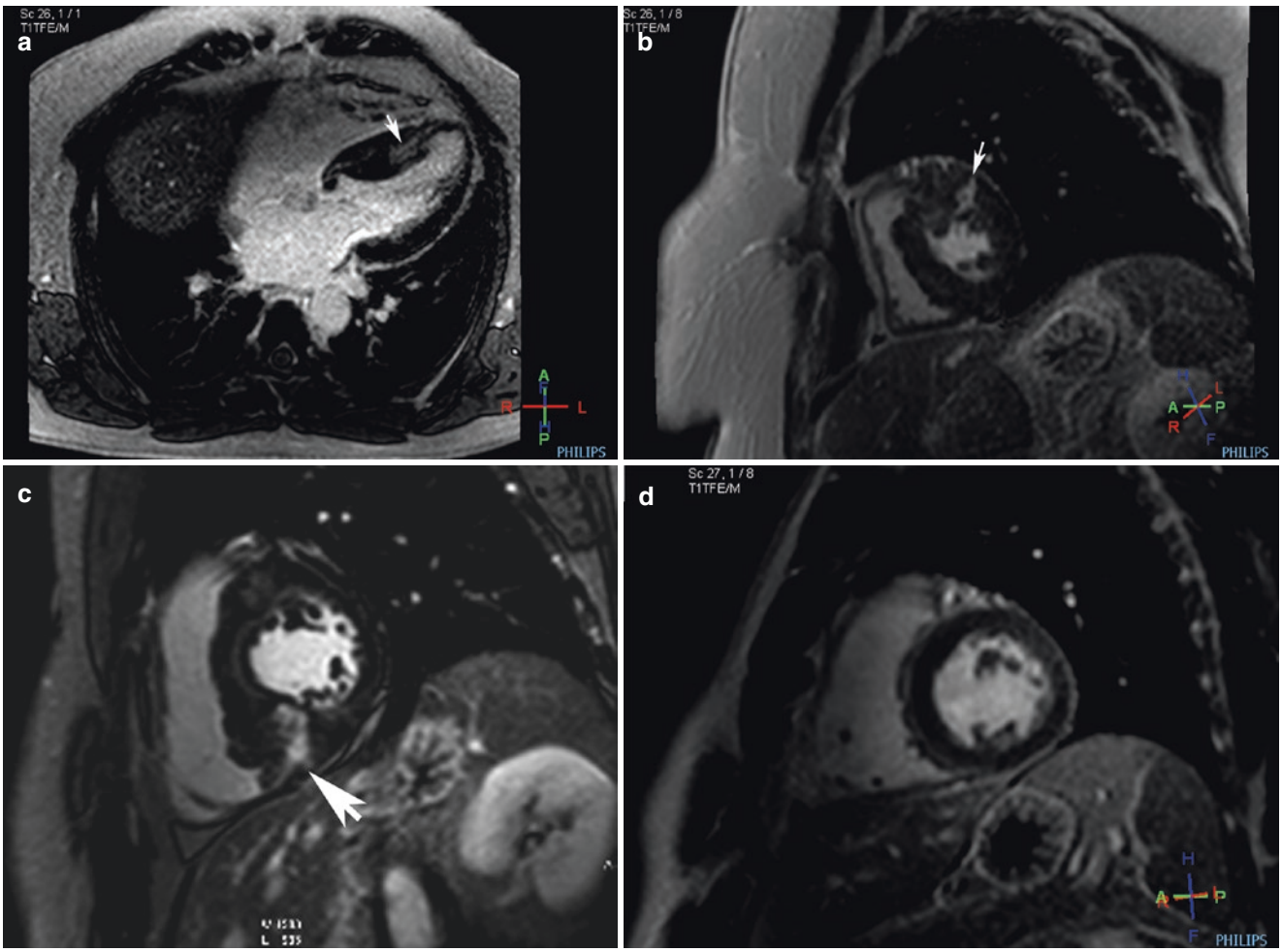

Fig. 5.16 Delayed enhancement imaging demonstrating (**a**) four-chamber view with intramyocardial patchy fibrosis (*arrow*) of the septal wall, (**b**) short-axis view with patchy intramyocardial fibrosis of the anterior wall (*arrow*), (**c**) short-axis view with patchy fibrosis of the right ventricular insertion points (*arrow*), and (**d**) short-axis view with linear midwall fibrosis of the septal wall

and most commonly, patchy intramyocardial LGE, which may appear similar to infiltrative diseases [66]. Figure 5.16 Interestingly, areas of increased fibrosis tend to correlate with areas of wall motion abnormalities and to occur in the thickest segments of the heart affected by HCM [67]. Similarly, hyperenhancement has been found in a majority of HCM patients corresponding to areas of hypertrophy and scarring, mainly in the middle third of the ventricle in a multifocal distribution, although the right ventricle can also be involved [68, 69]. This is thought to be associated with areas of myocardium susceptible to ventricular ectopy and arrhythmias and may be associated with ICD discharges [70]. Initial studies demonstrated that LGE is associated with the risk of sudden cardiac death, albeit with a low predictive value [71]. The largest series to date by Chan et al. reported a linear relationship between LGE extent and SCD risk and introduced LGE extent >15% of LV mass as conferring a greater than two-fold increased risk among those who were considered low risk by traditional risk stratification [72]. A pooled analysis of five available studies confirmed the association between presence of LGE, as well as LGE extent, with risk of SCD [73]. According to the most recent ACC/AHA guidelines published in 2011, however, there is no consensus regarding the use of LGE in the clinical assessment of HCM, although it is increasingly utilized by experts in the field [70]. Indeed, the extent of LGE is gaining traction as a marker of increased risk for ICD allocation in individuals with borderline assessment by traditional means.

Differential Diagnosis

A multitude of conditions can mimic HCM, both by symptoms and on EKG, as well as on echocardiography

and CMR imaging. The most common diseases that are confused with HCM are hypertensive heart disease and aortic stenosis, which both present with concentric hypertrophy. Figure 5.17 In general, hypertension leads to an increase in LV wall thickness that rarely exceeds 15 mm. Note that myocardial fibrosis on LGE sequences can occur in hypertensive heart disease, HCM, as well as in aortic stenosis [74, 75]. In rare cases of HCM with aortic stenosis, CMR can identify the jet turbulence to distinguish if it predominantly originates from the ventricle or the aortic valve.

Since most patients with HCM are diagnosed at a young age, athlete's heart is also part of the differential diagnosis. Athlete's heart is characterized by symmetric LV thickening usually less than 15 mm, and normal function on Doppler echocardiography. CMR is able to accurately measure LV volumes, mass, and function, with the wall thickness indexed to the end-diastolic ventricular volume allowing for distinction between athlete's heart and HCM [76].

Ventricular noncompaction is another disease that can mimic HCM, where prominent LV trabeculations are the pathognomonic feature. Figure 5.18 CMR can distinguish between noncompacted and compacted layers, with an end-diastolic ratio of noncompacted to compacted layers of >2.3 being diagnostic [77]. Additionally, CMR can reveal the transition zone between the two layers.

Valvular Aortic Stenosis

The approach to valvular aortic stenosis in CMR is similar to echocardiography. Phase contrast images and velocities can be used along with the modified Bernoulli equation

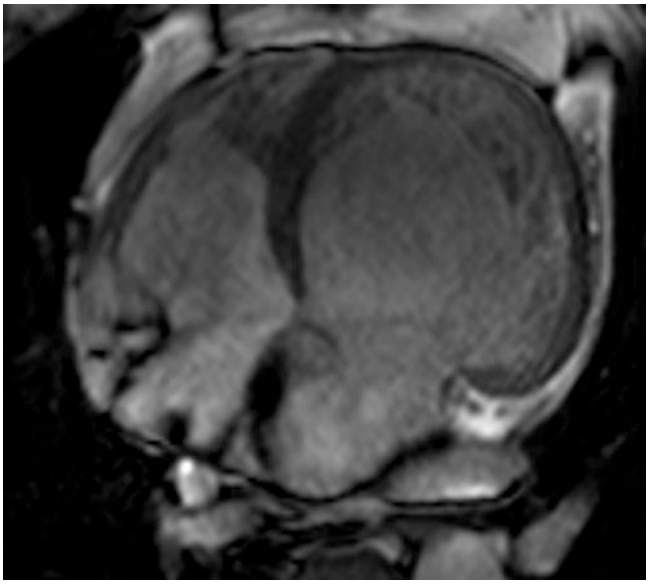

Fig. 5.18 SSFP four-chamber cine image demonstrating left ventricular noncompaction

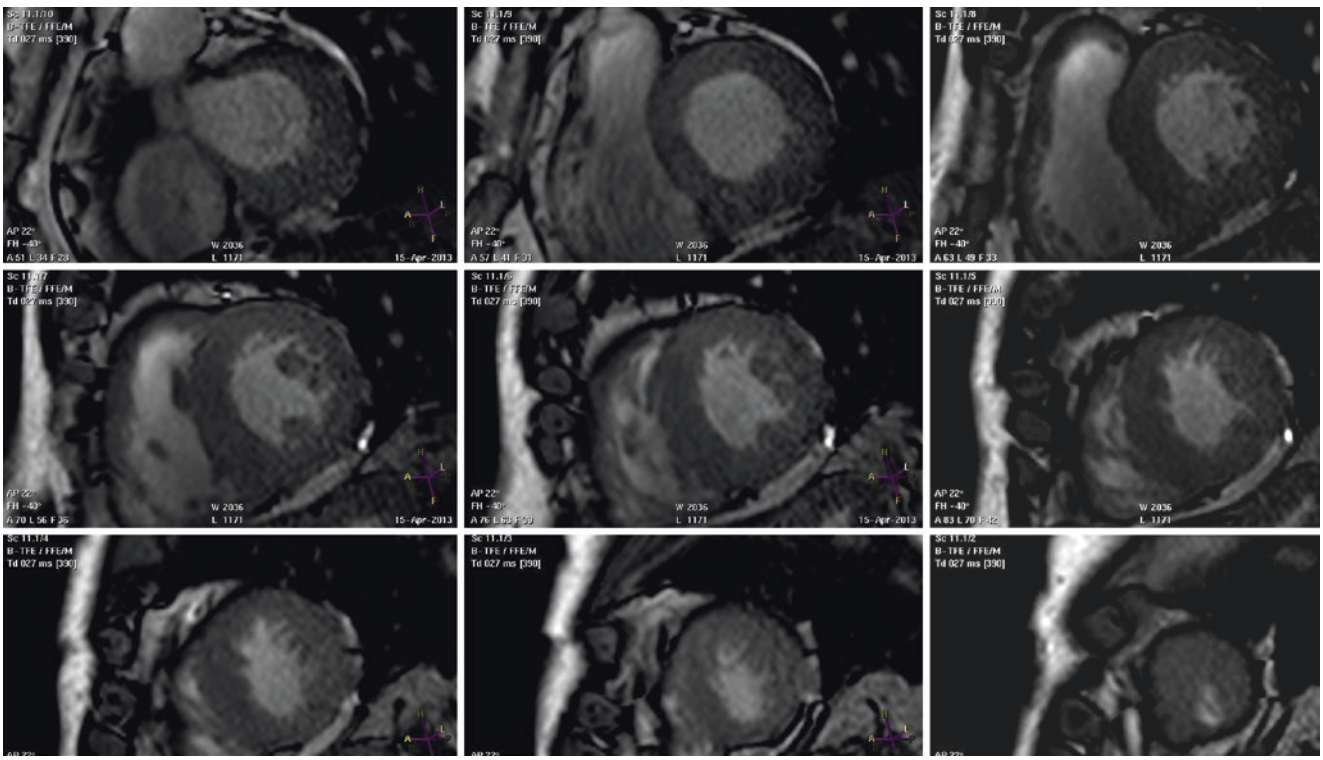

Fig. 5.17 SSFP short-axis cine stack demonstrating concentric left ventricular hypertrophy

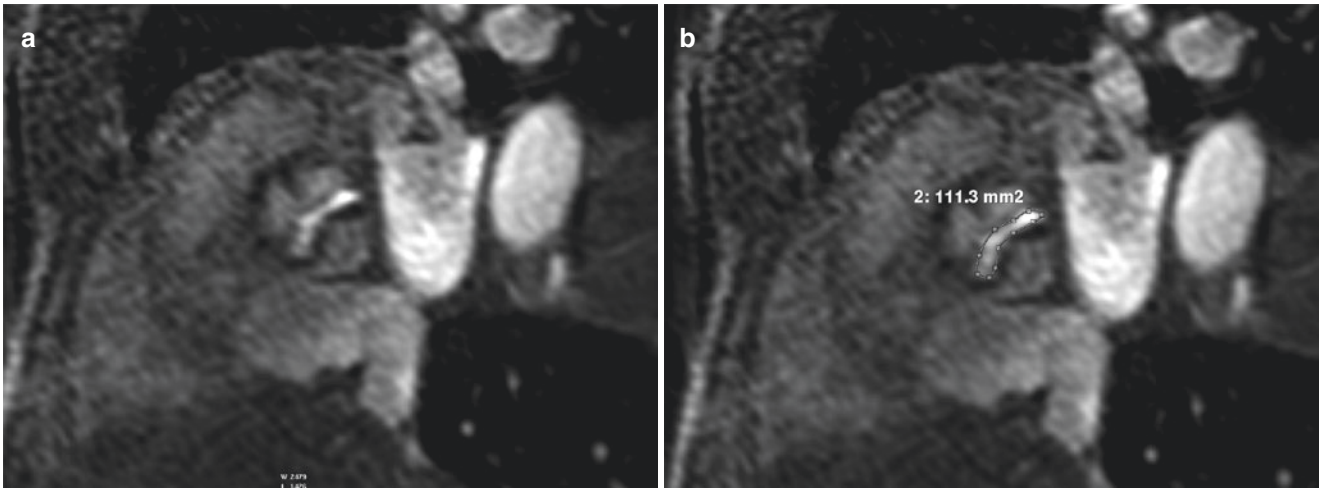

Fig. 5.19 Short-axis SSFP view during systole (a) showing a bicuspid aortic valve and (**b**) planimetry of the valve demonstrating moderate aortic stenosis

($\Delta P = 4\ V^2$) to obtain mean and peak pressure gradients. The point of maximum velocity can be obtained through in-plane, as well as through phase-contrast imaging, or by measuring the flow at the LVOT and the tip of the aortic leaflets to obtain the velocity-time integrals (VTI). With LVOT measurements (mentioned above), the aortic valve area (AVA) can be calculated using the continuity equation in the same fashion as in echocardiography [78].

By utilizing SSFP images, direct planimetry cine images can be obtained, most commonly by using several thin (5 mm) contiguous images parallel to the annulus and extending across the valve in order to capture the tips of the leaflets. Figure 5.19 The valvular orifice is traced during maximal opening in the most distal slice; foci of calcification resulting in signal void are generally included.

Subaortic Membrane

Once thought to be a pediatric disease, subaortic membranes leading to discrete subaortic stenosis and aortic valve regurgitation have been described in adult populations [79]. In this disorder, a congenital or acquired subaortic membrane leads to fixed obstruction of the LVOT that often results in aortic valve regurgitation. Associated pathologies are rheumatic mitral valve disease, ventricular septal defect, coarctation of the aorta, and bicuspid aortic valve [79]. Subaortic membranes usually lead to progressive LVOT obstruction and require surgical resection. Although the membranes themselves may be difficult to visualize by CMR due to limitations in spatial resolution, the diagnosis can be easily established by the detection of abnormal turbulent flow in the absence of valvular, muscular (i.e., asymmetric hypertrophy with SAM), or abnormal papillary/chordal substrate.

Infiltrative Cardiomyopathies

Infiltrative heart diseases can also mimic HCM, with various CMR techniques allowing for distinction between the two entities. Amyloidosis causes diffuse LV wall thickening and diffuse LGE, with shortening of the null time on inversion recovery sequences [80, 81]. Figure 5.20 Sarcoidosis presents as restrictive cardiomyopathy with generalized LV thickening. The LGE pattern usually involves the basal and lateral segments, and asymmetric basal septal involvement is possible [82]. Anderson-Fabry disease, an X-linked glycolipid storage disease, results in concentric hypertrophy with 50% of patients demonstrating LGE, usually in the basal inferolateral wall on CMR [83]. Genetic testing may be useful to distinguish these entities. Hypereosinophilic syndrome can lead to apical fibrosis, cavitary obliteration, and apical mural thrombus, mimicking apical HCM on TTE [84]. The pattern of LGE is typically diffuse and subendocardial.

Practical Implications

In clinical practice, there is variation in the use of CMR, with some HCM centers electing to perform CMR on all patients and others invoking a more selective strategy. Routine CMR at the time of initial diagnosis can lead to a more robust understanding of structure and function, elimination of alternative diagnoses, as well as more accurate definition of the LV maximal thickness in all segments. In addition, LGE can help with risk stratification and supplement decision-making, especially with regard to ICD implantation. On the other hand, CMR is costly leading to a more selective approach in other centers, which utilize CMR in patients who are at borderline risk for SCD, and in situations where the added

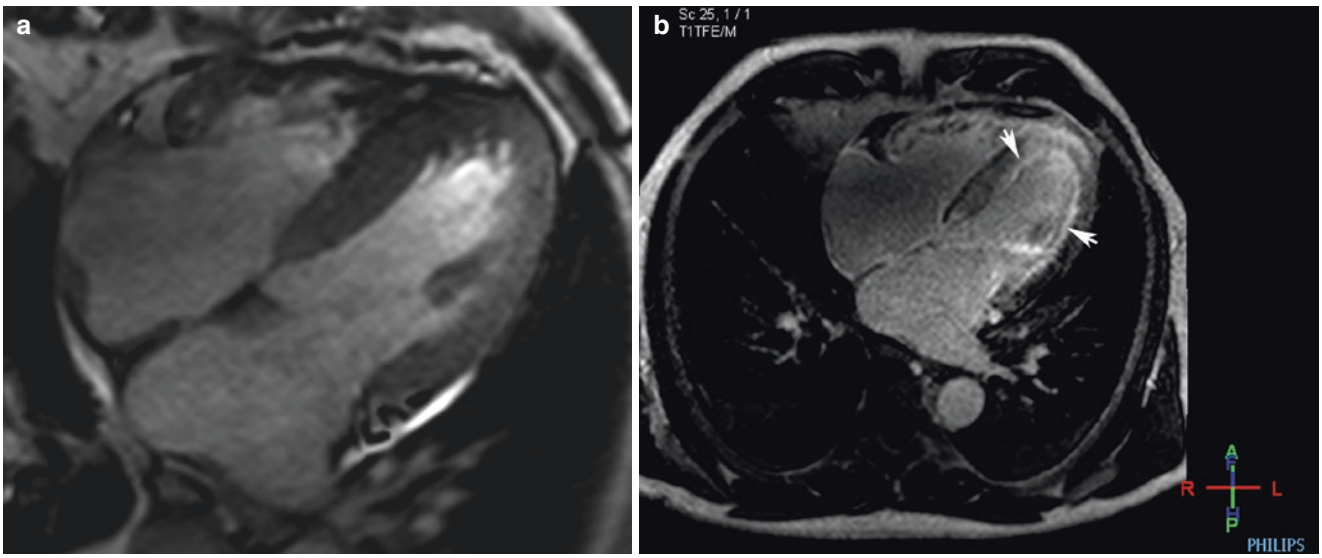

Fig. 5.20 (**a**) Four-chamber SSFP image of a patient with cardiac amyloidosis. (**b**) Delayed enhancement four-chamber image of diffuse subendocardial enhancement (*arrows*) in the same patient with amyloidosis

information of LGE extent may help with risk stratification. In addition, patients with mild or borderline LVH by echocardiography may have a discrepant degree of LVH by CMR, thereby confirming the diagnosis [30]. Patients who are genotype-positive but phenotype-negative by echocardiography may actually become phenotype-positive on CMR, with implications for further treatment, including lifestyle modification. This is important given that the number of patients identified as carriers has increased with the advent of commercial gene testing. On the other end of the spectrum, patients with LV thickness > 2.5 cm may have higher degrees of hypertrophy by CMR that would place them at high enough risk of SCD to warrant ICD implantation. Finally, patients in whom an alternate diagnosis is suspected, such as amyloidosis, sarcoid, or noncompaction cardiomyopathy, or in whom areas of the heart are poorly visualized by echo due to body habitus or acoustic windows, are good examples of when selective CMR may be helpful. According to the guidelines, a routine application is currently not recommended; rather MRI is advised in a more selective approach, as described above.

Future Directions

Noninvasive cardiac imaging has provided important insights into the phenotypic expression, natural history, prognosis, and treatment of hypertrophic cardiomyopathy. Evolution of CMR technology, such as real-time imaging, inversion recovery, and delayed enhancement may lead to a better understanding of the clinical significance of various phenotypic expressions in HCM. Genetic testing coupled with advanced imaging may allow earlier detection of disease before overt symptoms are present. This may help facilitate treatment monitoring and strategies, as well as improved prognostication for entire families. Future CMR techniques may enable better quantification of gradients, rotation, torsion, and twist, which will further improve diagnosis and personalized treatment. Finally, the Hypertrophic Cardiomyopathy Registry (NCT01915615) is an international multicenter observational study funded by the National Heart, Lung, and Blood Institute (NHLBI), which completed enrollment of 2750 participants between 2014 and 2017 with an expected follow-up period until 2022. All study participants underwent CMR scanning, as well as detailed genetic and biomarker testing. This study is expected to improve risk stratification of individuals with HCM by integrating a wide variety of clinical and experimental biomarkers, including detailed CMR data.

Clinical Pearls

- In patients with signs and symptoms of HCM, including abnormal electrocardiography, but without typical echocardiographic findings, CMR may detect atypical presentations such as apical or focal segmental HCM. This is especially true in patients of Asian descent, where apical HCM in particular has a higher prevalence. Patients who are genotype-positive but phenotype-negative by echocardiography may be particularly well served by CMR.
- In HCM patients with angina or heart failure symptoms, assessment of perfusion and scar by CMR may be valuable. HCM patients are at increased risk

for microvascular obstruction, which can lead to symptoms and sudden cardiac death. Furthermore, delayed enhancement can aid in ICD implantation decisions, as significant delayed enhancement is a risk modifier.

- CMR is invaluable at distinguishing HCM from other cardiac diseases which can mimic HCM, such as hypertensive heart disease, athlete's heart, ventricular noncompaction, infiltrative heart diseases, and aortic stenosis. In cases of HCM with aortic stenosis, CMR can identify the location of the turbulent jet to assess origin from the ventricle or aortic valve.
- Guidelines have not yet defined absolute indications for when to perform CMR in patients with HCM. In genotype-positive individuals without echocardiographic evidence of HCM, cases with borderline LV hypertrophy on echocardiography, or borderline wall thickness meeting criteria for ICD implantation, CMR can help categorize patients as truly having HCM or needing ICD therapy.
- Studies linking scar burden with prognosis are ongoing, especially with regard to the incidence of end-stage systolic dysfunction and sudden cardiac death. To this end, patients should have CMR performed prior to implantation of ICD, so that such information is available for them in the future as the field evolves.

Questions

1. The manipulation of which of the following particles is responsible for MRI technology?
   A. Electrons
   B. Protons
   C. Neutrons
   D. X-rays
   E. Magnets

   The correct answer is B. In magnetic resonance imaging, protons (in the form of hydrogen atoms contained in water) are aligned by application of a strong magnetic field. The energy emitted by the aligned protons is measured and used to generate MRI images.

2. Cardiac MR is superior to echocardiography at all of the following except:
   A. Measurement of left ventricular outflow tract gradients
   B. Ventricular volume measurement
   C. Detection of myocardial crypts
   D. Diagnosis of apical variant hypertrophic cardiomyopathy
   E. Evaluation of fibrosis

   The correct answer is A. CMR is superior to echocardiography at measuring atrial and ventricular volumes and identifying LV wall thickness, segments of hypertrophy, as well as associated features, such as myocardial crypts. Late gadolinium enhancement enables identification and quantification of myocardial fibrosis. Echocardiography is superior to CMR at measuring LVOT gradients.

3. The most dangerous adverse reaction of gadolinium contrast media is
   A. Contrast-induced nephropathy
   B. Angioedema
   C. Ototoxicity
   D. Nephrogenic systemic fibrosis
   E. Osteoporosis

   The correct answer is D. Nephrogenic systemic fibrosis is a dreaded complication of gadolinium contrast media and has only been seen in individuals with decreased glomerular filtration rate. While contrast-induced nephropathy is an adverse reaction to iodinated contrast radiocontrast media, it is not seen after administration of gadolinium contrast agents.

4. Which of the following is an absolute contraindication to cardiac MRI?
   A. Implantable cardioverter defibrillator
   B. Claustrophobia
   C. End-stage renal disease
   D. Pregnancy
   E. None of the above

   The correct answer is E. Safe MRI imaging is possible in all of the above scenarios, provided that safety precautions are taken. MRI-conditional implantable cardioverter defibrillators are on the market, but devices that have been implanted after the year 2001 have been shown to be safe when following a dedicated protocol involving reprograming of the device and careful monitoring by skilled personnel. Claustrophobia is considered a relative contraindication, and end-stage renal disease is not a contraindication for MRI, unless gadolinium contrast media is used. Pregnancy is not a contraindication to non-contrast MRI imaging, though administration of gadolinium contrast agents should be avoided given the risk of teratogenicity.

5. Delayed enhancement sequences are obtained ___ min after administration of gadolinium contrast media.
   A. 1–3
   B. 5–10
   C. 10–20
   D. 20–30
   E. 45

   The correct answer is C. First-pass perfusion images are obtained immediately following injection of gadolinium contrast agents, though delayed enhancement sequences are taken 10–20 min after injection.

6. Which of the following answers is correct?
   A. Late gadolinium enhancement extent >15% of LV mass is associated with a twofold increase in sudden cardiac death in patients with HCM.
   B. Late gadolinium enhancement is associated with fourfold increase in dynamic LVOT gradients.
   C. There is no linear relationship of LGE extent and sudden cardiac death.
   D. Absence of LGE confers a worse prognosis.

   The correct answer is A. There is a linear relationship between late gadolinium enhancement extent and sudden cardiac death risk. More specifically, LGE extent >15% of LV mass is associated with twofold increase in sudden cardiac death in patients with HCM. LGE extent is not associated with LVOT gradients.

7. CMR can help distinguish HCM from the following phenocopies, except:
   A. Anderson-Fabry disease
   B. Hypereosinophilic syndrome
   C. Hypertensive heart disease
   D. Left ventricular noncompaction cardiomyopathy
   E. None of the above

   The correct answer is E. All of the above mimickers of HCM can be distinguished on CMR. Anderson-Fabry disease typically exhibits LGE in the basal inferolateral wall. Hypereosinophilic syndrome is characterized by diffuse subendocardial LGE and LV apical thrombus. In hypertensive heart disease, the LV wall thickness usually does not exceed 15 mm. Left ventricular noncompaction cardiomyopathy presents with an abnormally thick layer of noncompacted myocardium.

8. Which of the following findings on CMR is associated with increased risk of sudden cardiac death?
   A. Myocardial crypt
   B. Accessory apical-basal muscle bundle
   C. Accessory papillary muscle
   D. Apical aneurysm
   E. Apical-variant HCM

   The correct answer is D. Apical aneurysm is a high-risk feature and has been found to be associated with increased risk of sudden cardiac death. All other findings are not currently known to be associated with an increased risk of sudden cardiac death.

9. In HCM, abnormal papillary morphology can cause systolic anterior motion of the mitral valve and left ventricular outflow tract obstruction in the presence of normal septal wall thickness.
   A. True
   B. False

   The correct answer is A. Abnormal positioning of a papillary muscle, e.g., anteroapical displacement, can lead to systolic anterior motion of the mitral valve and left ventricular outflow tract obstruction, even when septal wall thickness is normal or only mildly increased.

10. CMR is recommended in all patients with HCM by current guidelines.
    A. True
    B. False

    The correct answer is B. Current guidelines do not recommend CMR in all patients. However, CMR can provide additional information by better characterizing morphology and pattern of LV hypertrophy, mitral valve and subvalvular anatomy, associated pathologies, presence and extent of myocardial fibrosis, and distinguish between other causes of myocardial hypertrophy.

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Genetics of HCM and Role of Genetic Testing

6

Christopher Semsarian and Jodie Ingles

Key Points

- Genetic testing is commercially available for HCM patients.
- Accurate phenotyping should be performed prior to genetic testing to ensure a correct clinical diagnosis of HCM.
- Cardiac genetic counselling is essential, especially pre- and post-genetic testing.
- Genetic variants identified need to be carefully interpreted to ensure DNA variants are correctly classified as pathogenic.
- The greatest value of genetic diagnosis is for cascade testing of asymptomatic relatives.
- There is a high rate of uncertain variants identified, especially when a broad gene panel is ordered, adding complexity to interpretation and communication with family.
- The multidisciplinary specialized clinic is the preferred model of care in HCM families.

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Introduction

Major advances have been made over the last 30 years that have defined the genetic basis of many medical diseases. There are now over 40 different cardiovascular diseases directly caused by variants in genes that encode cardiac proteins. These cardiovascular diseases include the inherited cardiomyopathies, primary arrhythmogenic diseases, metabolic disorders, and the congenital heart diseases. Identification of the genetic causes of cardiovascular disease has led to improved and earlier diagnosis of at-risk individuals and, in some cases, is helping to guide therapies as well as inform prognosis. This chapter will provide an overview of the current knowledge related to the genetics, and the role of genetic testing specifically, in the most common genetic heart disorder, hypertrophic cardiomyopathy (HCM).

Genetic Basis of HCM

Since 1989, major advances have been made in our understanding of the genetic basis of HCM. In a disease that was defined as a "tumor of the heart" by Donald Teare in 1958 [1], our genetic advances have led to a complete redefinition of HCM as a complex medical genetic disorder of the sarcomere. To date, over 1300 causative variants in at least 8 disease genes have been identified in patients with HCM, with variants in other less well-described genes also reported [2, 3]. Variants in phenocopy (HCM "mimicker" diseases) genes also comprise an important proportion of genetic causes. The key genes are summarized in Table 6.1. These disease genes encode primarily sarcomere, and sarcomere-related proteins, and are almost exclusively inherited in an autosomal dominant pattern, with offspring of an affected individual having a 50% chance of inheriting the disease gene. Collectively, these findings have led to the description of HCM as a "disease of the sarcomere."

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Table 6.1 Causative Genes in HCM

Causative gene	Gene symbol
Key 8 HCM genes	
β-myosin heavy chain	*MYH7*
Regulatory myosin light chain	*MYL2*
Essential myosin light chain	*MYL3*
Cardiac troponin T	*TNNT2*
Cardiac troponin I	*TNNI3*
α-tropomyosin	*TPM1*
α-cardiac actin	*ACTC*
Cardiac myosin-binding protein c	*MYBPC3*
Other genes implicated (less evidence)	
α-actinin2	*ACTN2*
Myozenin2	*ACTN2*
Muscle LIM protein	*CSRP3*
Filamin C	*FLNC*
Telethonin	*TCAP*
Calsequestrin	*CASQ2*
Junctophilin 2	*JPH2*

Among the causative genes, the β-myosin heavy chain (*MYH7*) and myosin-binding protein C (*MYBPC3*) genes are the most commonly described in HCM populations worldwide, accounting for approximately 70% of all mutations identified. Major advances in defining the genetic basis of HCM have led to commercially available genetic testing for HCM since 2002 [4]. While there is variability among testing providers, mainstream HCM testing currently includes testing of comprehensive cardiac panels (including most of the main genes listed in Table 6.1). For a new proband with a definite diagnosis of HCM, the detection rate for identifying a causative variant is currently up to 40–60%. The presence of a positive family history of HCM, as well as a family history of sudden death due to HCM, may increase this pickup rate to beyond 80% [5].

Most of the causative gene variants in HCM are of the *missense* type, in which a single base pair change results in the change (or replacement) of one amino acid (so called non-synonymous mutations). These are usually rare (less than 0.02%) or completely absent from control populations such as the Exome Aggregation Consortium [6]. Other variant types may exist that cause more significant disruptions to the encoded protein, so-called *"frameshift"* or *"truncation"* mutations, which can lead to a major change in the protein sequence or a loss of amino acids resulting in a shortened protein. The latter mutations are often caused by deletions or insertions of nucleic acids in the coding region and are commonly identified in *MYBPC3*. Some of the common Dutch founder mutations cause a frameshift in *MYBPC3* [7].

Genetics and Prognosis in HCM

While the identification of a HCM disease-causing mutation has significant diagnostic benefits in patients and family members, so far there is no prognostic role of a gene result for the proband in the clinic. Excitingly, recent studies are beginning to suggest future applications where genetics might be used to guide management and treatments in HCM, but these are a way off. Historically, studies suggested there may exist overall trends in clinical outcomes with specific disease genes. For example, mutations in *MYH7* were generally more severe with earlier age of presentation [8], while mutations in *MYBPC3* lead to a more benign clinical outcome at later age of onset of disease [9]. These early findings also referred to some mutations being classed as "malignant" (e.g., Arg403Gln in *MYH7* gene) and others "benign" (Arg502Trp in *MYBPC3* gene). However many subsequent studies have shown a lack of correlation of specific mutations with disease outcome [10], and this reflects the clinical heterogeneity *within* HCM families. Similarly, other studies have postulated specific genes and mutations are associated with early onset of HCM in children and late onset in the elderly, as well as links to variant forms of HCM such as apical, or end-stage "burnt-out" HCM.

Role of Genetic Testing in HCM

When considering genetic testing in HCM, a number of basic genetic testing principles, applicable to all genetic heart diseases, need to be considered. These considerations are important to ensure optimal and most effective care of families with HCM.

General Principles

Genetic testing is not a simple blood test. There are many considerations that arise with every family. A complete clinical genetic evaluation is required, which includes being certain of the clinical diagnosis in the proband, understanding the probabilistic nature of genetic testing, the need for genetic counseling, and taking a detailed family history to get a sense of disease penetrance and patterns of disease [11].

Importance of Detailed and Accurate Phenotyping

The cornerstone of genetic testing is accurately defining the clinical phenotype both in the individual patient and the family. The highest yields from genetic testing are often based on patient cohorts with confirmed disease. In HCM, careful attention to the family history, clinical symptoms, and defining the extent, distribution, and severity of hypertrophy are all considered essential in clinically distinguishing HCM from other HCM phenocopies, such as Fabry disease or glycogen storage diseases, which have different genetic etiologies.

Genetic Counseling and Informed Consent

In all patients and families with HCM, genetic counseling is essential. Genetic testing options span all stages of life, from the preimplanted embryo or fetus to children and adults [12]. Appropriate pre- and post-test genetic counseling is a vital component of genetic testing. The cardiac genetic counselor plays a key role in the HCM genetic testing process, ensuring that the individual understands the clinical and psychosocial implications of every possible result, limitations of the tests including difficulties in interpretation of the results, as well as discussion of other issues such as genetic testing of children, prenatal and preimplantation genetic diagnosis, and access to insurance [13]. This is an increasingly important aspect of management as genetic test results more commonly include a greater level of uncertainty and information, reflecting the probabilistic nature of these results.

Commercially Available Genetic Testing in HCM

Over the last decade, commercially available genetic testing for inherited cardiac diseases, including HCM, has expanded significantly. Genetic testing has moved from single gene testing to concurrent testing of multiple genes in "panels" of 20 or more genes. Development of "cardiomyopathy panels," which test for over 50 cardiac genes involved in the pathogenesis of a variety of cardiomyopathies including HCM, is now commonplace. Such approaches have expanded our knowledge about causative genes in HCM. Importantly, increased size of a gene panel, i.e., more genes tested, has not been shown to result in an improvement in diagnostic yield [14]. Indeed, we have shown identification of uncertain variants soon out number truly causative variants as panel sizes increase (Fig. 6.1). The increased likelihood of uncertain and incidental genetic findings further highlight the essential need of cardiac genetic counseling including patient education and informed consent prior to testing [15].

Proband Genetic Testing in HCM

The genetic testing process most frequently begins with testing the proband (or index case). This is often the first person in the family who presents, and the clinical diagnosis of HCM is established. Following genetic counseling and informed consent, genetic testing is performed. The outcomes can be divided into (1) those where a variant(s) is identified that is deemed to be *likely pathogenic* or *pathogenic* (disease-causing), (2) no rare variants are found (an *indeterminate result*), and (3) uncertain rare variants are identified (*variant of uncertain significance*; VUS).

Determining whether a DNA variant is disease-causing in HCM is a major challenge and remains the *Achilles heel* of genetic testing. In most genetic testing reports, an effort will be made to determine the likelihood that a variant that has been identified is pathogenic. The important and often misunderstood point is that genetic tests are probabilistic tests rather than deterministic, and this can be difficult to convey to the patient. For the attending cardiologist or geneticist interpreting the genetic result, the evidence for the variant being causative or benign is considered and classified across a spectrum from most confident of causation (pathogenic) to most confident of not being the cause (benign; Fig. 6.2). Determining pathogenicity is a challenging task, and standardized criteria and public sharing of data are critical in reaching agreement among centers and testing laboratories [16, 17]. The American College of Medical Genetics and Genomics and Association of Medical Pathologists (ACMG/

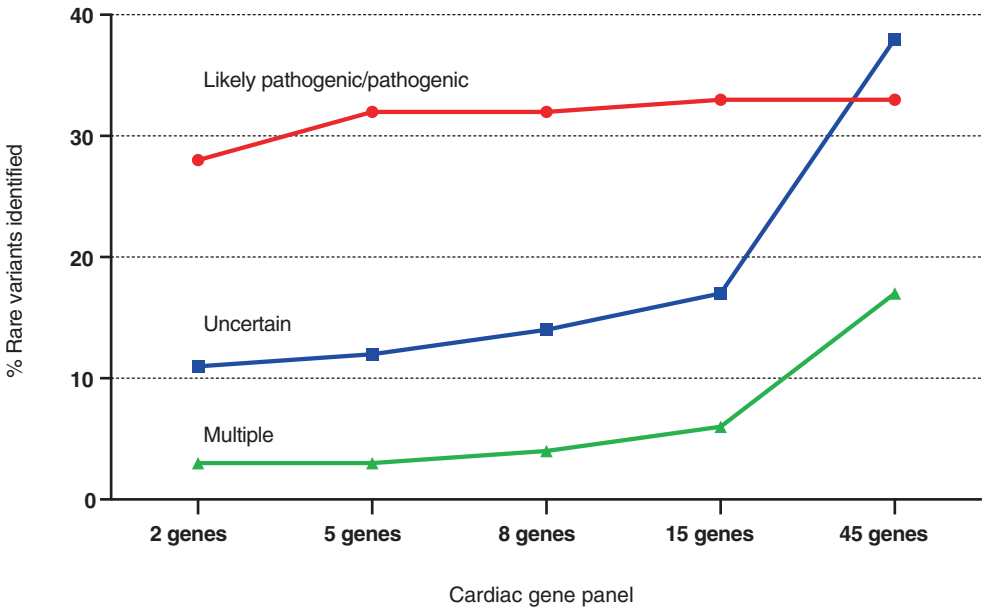

Fig. 6.1 Genetic testing yield based on increasing gene panel size. As the number of genes tested increases, the diagnostic yield does not increase; however, the rate of uncertain variants identified does [14]

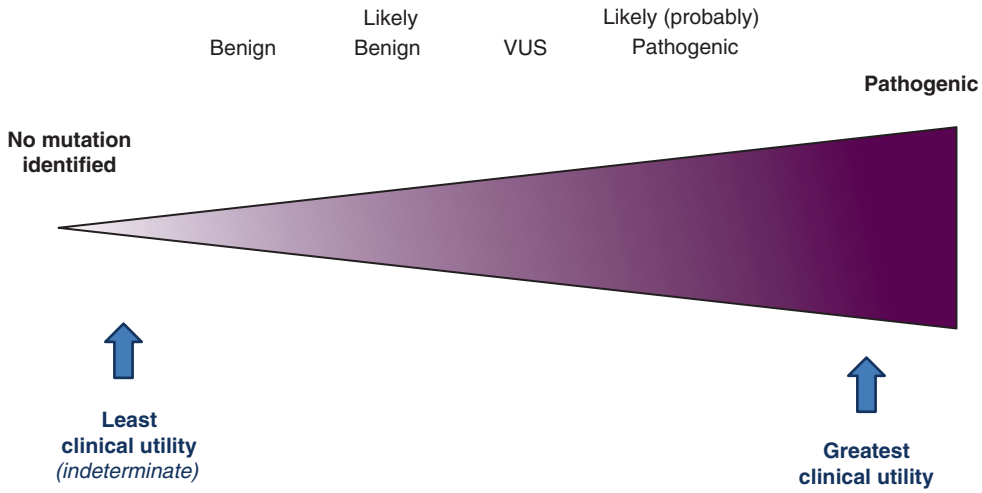

Fig. 6.2 Spectrum of pathogenicity: Determining the probability that a DNA variant is pathogenic relies on a consideration of clinical, genetic, and in silico information. Determining pathogenicity is probabilistic. (Adapted from Maron et al. [4])

Table 6.2 Key aspects of determining variant pathogenicity

Rare (<0.02%) or absent in control populations, such as ExAC
In a gene with robust evidence of disease association (see Table 6.1)
Previously seen in multiple unrelated individuals with the same phenotype
Multiple in silico prediction tools in agreement and suggestive of a deleterious impact
Strong evidence of segregation of the variant to other affected relatives
Robust functional studies that suggest a role in disease

AMP) released a document to guide variant interpretation in 2015, providing increased stringency and standardization [18]. While these are a big step forward, disease-specific modifications will be the next stage toward more accurate and careful variant classification. Key aspects of variant classification are shown in Table 6.2.

Even after applying the criteria listed above, situations arise where the clinical significance and pathogenicity of a variant remains unknown. In these cases, the variant is termed a variant of uncertain significance (VUS). Given this current ambiguity, a VUS is considered an indeterminate result and is not considered reliable to be used for cascade genetic testing of asymptomatic family members (Fig. 6.3). Importantly, with the recent emergence of large whole exome and genome datasets, reclassification of variants, e.g., downgrading of a DNA change from pathogenic to benign due to new genetic information, is an important consideration for previously tested HCM families. Periodic reevaluation of DNA variants is therefore recommended in HCM families [19].

Cascade Genetic Testing of HCM Family Members

The greatest utility of genetic testing is for early diagnosis of family members. Once a likely pathogenic or pathogenic variant has been identified in the proband, this information can be used in asymptomatic first-degree relatives and beyond, to identify those people who carry the gene mutation and, as importantly, those who do not. This process, called *cascade genetic testing*, is currently the primary utility of HCM genetic testing. Importantly, a negative cascade test result means the individual no longer requires ongoing clinical screening, eliminating the need for decades of expensive clinical surveillance and worry. This is the major driver for the established cost-effectiveness of genetic testing in HCM [20]. A positive cascade genetic test result means the individual carries the causative variant and is at risk of developing disease. This allows a more targeted screening approach, with the goal to prevent serious cardiac events. Just as important, a cascade genetic result can clarify the risk status of *their* first-degree relatives, including children. Importantly, a positive gene result does not imply a diagnosis of HCM, which is always based on clinical evidence of disease (i.e., left ventricular hypertrophy), and this is an important discussion point for families [21].

The group of at-risk family members with no clinical evidence of HCM but who carry a causative genetic variant is known as silent gene carriers or *genotype positive-phenotype negative.* They are the direct result of the increase in genetic testing of families with HCM [22, 23]. These patients are effectively "gene carriers," and very little is known regarding how to best manage these asymptomatic patients, e.g., participation in competitive sports. Early studies suggest those who are HCM gene carriers and reach adulthood with no clinical signs of HCM have a generally favorable outcome with a low chance of developing clinical disease [24, 25]. Nevertheless, these individuals represent a fascinating subgroup, likely to increase significantly as more genetic testing in HCM is performed, and may be an ideal subgroup to initiate preventative therapies before the development of clinical disease [26, 27].

While genetic testing in HCM does not currently guide therapy, there is growing evidence that "gene dose" may

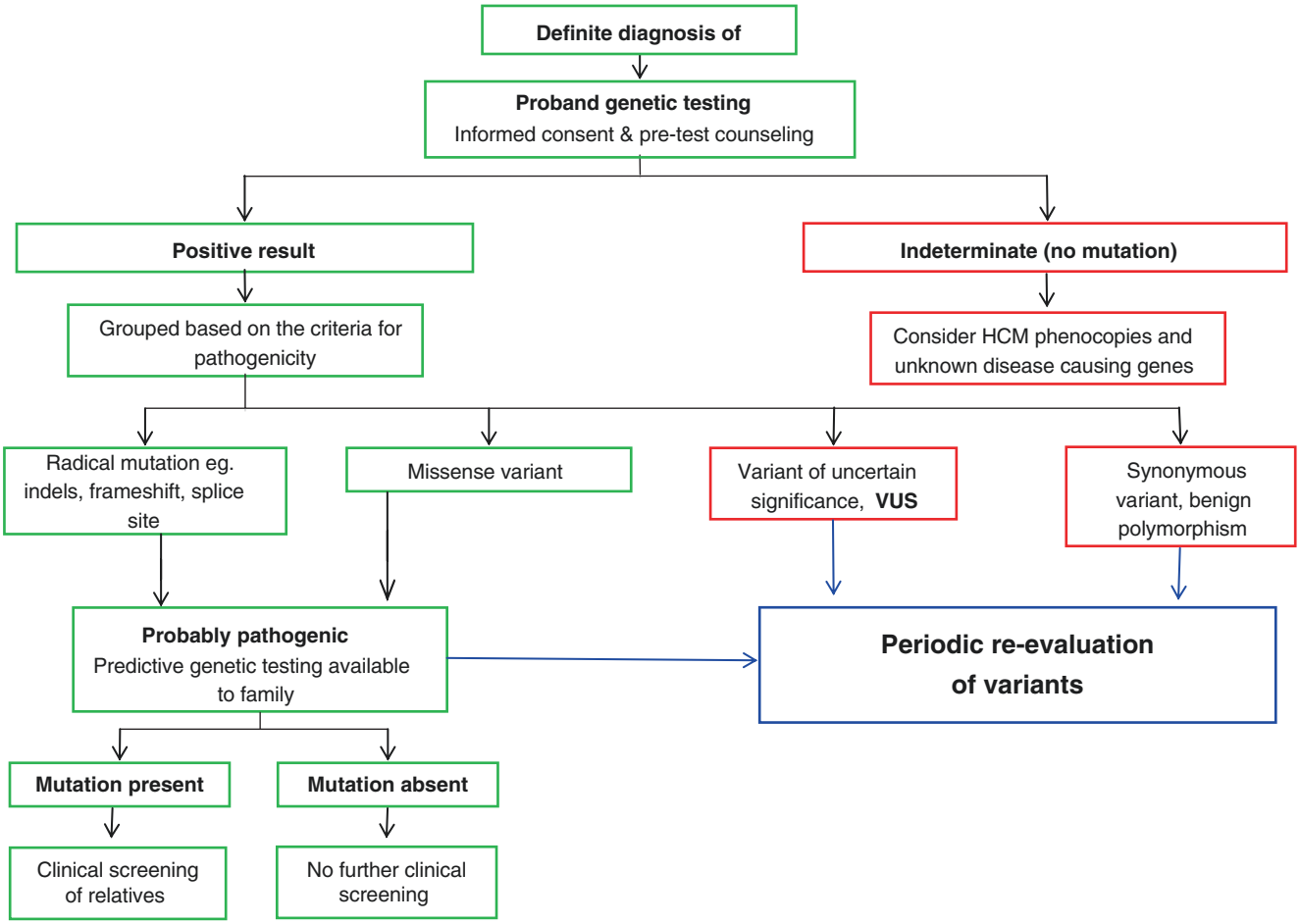

Fig. 6.3 Flow diagram for genetic testing in HCM and DNA variant classification. (Adapted from Das et al. [19])

predict those patients with more severe clinical outcomes [28]. While historically, HCM studies have shown that up to 5% of families carry two or more pathogenic HCM variants [29, 30], more recent work suggests this to be much lower, due to increased stringency of variant classification [14, 31]. A cumulative variant hypothesis has been proposed, where multiple rare variants, regardless of their classification (i.e., likely pathogenic, pathogenic or VUS), were associated with younger disease onset compared to single variant carriers [14].

Multidisciplinary Specialized Clinic Model of Care in HCM

A genetic diagnosis in the HCM proband has major implications for family relatives. In all situations where HCM is identified, appropriate clinical and genetic screening is indicated. The clear goal of both clinical and genetic screening of family members is to identify those with clinical evidence of HCM or those who may carry the same pathogenic mutation as the proband but do not express a clinical phenotype. As discussed previously, early identification of these at-risk individuals provides opportunities to initiate early therapies aimed at preventing disease complications.

The management of families with HCM is therefore complex. HCM is a challenging clinical and genetic disease. There are many different issues to consider, such as clinical evaluation and management, coordination of services including genetic counseling and testing, patient education and support, and awareness of the psychological, social, and potential legal issues. These services are offered in a sensitive environment, with the knowledge that the families may experience a range of emotions, particularly where there has been a sudden death of a loved one. As a consequence the ideal model of care is the cardiologist-led specialized multidisciplinary cardiac genetic clinic (Fig. 6.4) [13, 32]. Expertise from a number of health professionals is drawn upon, including cardiologists, genetic counselors, clinical geneticists, psychologists, as well as services such as patient support groups and research centers. This type of multidisciplinary model has been shown to improve psychosocial outcomes of patients with genetic heart diseases, specifically showing less worry and reduced levels of anxiety [33].

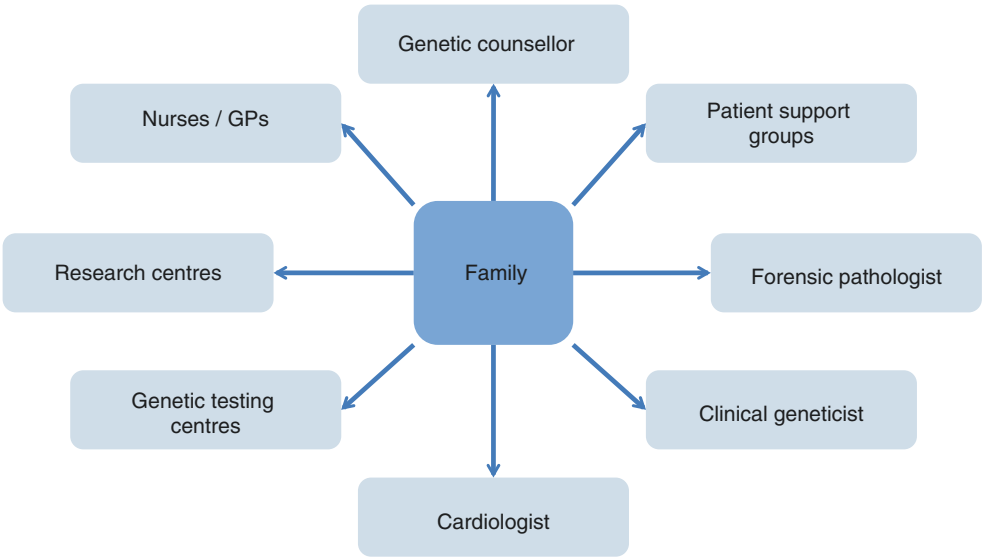

Fig. 6.4 Key role of the specialized multidisciplinary clinic in the evaluation of families with HCM. GP general practitioner. (Adapted from Ingles et al. [13])

Ethical, Legal, and Societal Implications

The ethical, legal, and societal implications of genetic testing in HCM are beyond the scope of this chapter and are influenced strongly by government regulations, societal views, and cultural considerations. There do exist some common issues, such as timing of genetic testing. Should children at risk of HCM have genetic testing? Comprehensive guidelines exist for genetic testing in children, which take into account many factors related to the child, the parents and family, and the medical circumstances of the underlying genetic heart disease. Genetic testing in HCM can be offered in both the prenatal setting (i.e., in early pregnancy) and at conception, referred to as preimplantation genetic diagnosis. Such approaches are based on identifying embryos that carry the causative variant and then implanting only those that are unaffected. While available currently, prenatal and preimplantation approaches need to be discussed extensively with families, appropriate counseling provided, and decisions made in an informed manner. The complexities of such issues, which span clinical, social, psychological, ethical, and moral boundaries, further highlight the importance of multidisciplinary teams in the care of families with HCM. If the attending cardiologist is not equipped to discuss these issues, further discussion should be offered in partnership with genetic counselors and/or clinical geneticists. Such a multidisciplinary approach will help serve the needs of the patients and their families more comprehensively and will facilitate open and informed discussion about the ethical, legal, and societal implications of genetic testing. It is therefore important that pre-genetic test counseling, genetic testing, and the interpretation of genetic test results be performed in centers experienced in the genetic evaluation and family-based management of HCM families.

Future Directions

With the emergence of newer genetic technologies coupled with a greater understanding and appreciation of the clinical complexities of HCM, the coming years will represent very exciting times. Defining the other 50% of HCM, individuals where current studies do not find a causative variant will be a focus of great importance. Whether these individuals have variants in other as yet unknown genes remains unclear. Expanding our knowledge base in terms of genotype-phenotype correlations in larger cohorts, and identifying other genetic and environmental modifiers which may influence clinical outcomes, will be instrumental as we move toward gene- or mutation-based, personalized therapies. In this respect, the greatest excitement lies in the potential to not only define the precise genetic causes of HCM but to develop specific mutation-targeted molecular therapies such as small RNA silencing molecules which may ultimately lead to development of effective curative strategies in HCM.

Most recently, a landmark study has used CRISPR-Cas9 technology, a new and powerful genome-editing tool to correct an *MYBPC3* mutation in a human embryo [34]. In this study, 12 healthy female donor eggs and 1 affected male HCM patient known to carry an *MYBPC3* pathogenic deletion were used. At early stages of zygote formation, the mutation was corrected. This proof-of-principle work provides hope that this technology may 1 day be used in the clinical setting, having significant implications not just in the setting of HCM but genetic diseases more broadly.

Conclusions

Major advances have been made in our understanding of the genetic causes of HCM. The widespread commercial availability of genetic testing has facilitated the steady introduction of genetic testing for HCM into clinical cardiology practice. Overall, the greatest utility of HCM genetic testing is in the screening and diagnosis of at-risk relatives through predictive genetic testing. Currently, there is little utility of a HCM genetic mutation in guiding therapy or prognosis.

Most exciting are the amazing advances in genetic technologies. These advances have emerged from next-generation sequencing technologies, which provide the platforms for sequencing many DNA segments, rapidly and extensively, across many genes at once. Indeed, whole exome or genome sequencing, whereby all the 22,000 genes that make up the human body can be sequenced in one test, will revolutionize our understanding of the genetic basis of many medical diseases, including HCM. Clearly having the appropriate bioinformatics strategies to identify the key DNA variants from background genetic noise, and understanding the functional consequences of these DNA changes, will all be essential as we move forward in developing more comprehensive genetic testing strategies in HCM.

Clinical Pearls

- Always take a thorough and detailed family history.
- Presence of a family history of HCM or sudden death may increase diagnostic yield of genetic testing.
- Never order a genetic test without thorough clinical evaluation of the patient.
- Always provide genetic counseling to all HCM patients both pre- and post- genetic testing.
- Don't always accept the findings of the genetic test reports for HCM – check the pathogenicity of the variant thoroughly and seek advice where needed.

Questions

1. The most common form of inheritance in HCM is:
   A. Autosomal dominant
   B. Autosomal recessive
   C. X-linked
   D. Maternal
   E. None of the above

   Answer: A
   HCM can be inherited in all the listed modes, but the majority (at least 70%) is inherited as an autosomal dominant trait. The clinical importance of this relates to the fact that in autosomal dominant inheritance, 50% of the offspring of affected HCM individuals will also be affected, hence the importance of clinical and genetic screening of first-degree relatives.

2. The most common genes implicated in HCM relate to:
   A. Calcium regulation
   B. Desmosome function
   C. Ion channel function
   D. Sarcomere function
   E. Mitochondrial energy utilization

   Answer: D
   All the established genes in which mutations cause HCM encode sarcomere or sarcomere-related proteins. The two most common genes are MYH7 and MYBPC3. Mutations in HCM sarcomere genes can influence calcium regulation, desmosome function, ion channel function, and energy utilization as part of the molecular pathogenesis of HCM.

3. Genetic testing in HCM can be useful for:
   A. Diagnosis
   B. Screening family members
   C. Diagnosing HCM "phenocopies"
   D. Reproductive decisions
   E. All of the above

   Answer: E
   Genetic testing has many benefits in HCM. While the main role relates to cascade or predictive testing in screening family members (option B), it can also assist in clarifying diagnosis (e.g., HCM vs athlete's heart), diagnosing HCM phenocopies such as Fabry or Danon disease, and can help in decisions regarding family planning.

4. Which one of the following statements is true regarding a variant of uncertain significance (VUS):
   A. VUS can be used clinically in genetic testing of family members.
   B. VUS is the cause of HCM.
   C. The clinical significance and pathogenicity of the VUS remains unknown.
   D. VUS findings are rare.
   E. None of the above.

   Answer: C
   VUS are commonly seen with genetic testing in HCM and represent findings of variants where the clinical and pathogenic significance remains unclear. Therefore VUS findings should not be used for genetic screening in the family since its pathogenic, disease-causing role is unknown.

5. Genetic testing in HCM can be useful in the setting of reproductive decisions in the following way:
   A. Preimplantation genetic diagnosis
   B. Prenatal testing
   C. Genetic testing at birth
   D. Genetic testing in childhood
   E. All of the above

   Answer: E
   Genetic testing in HCM can have clinical utility from conception through to old age. A pathogenic genetic result for HCM in a proband can be used to test embryos preimplantation by IVF to ensure a baby who does not carry the mutation. A pathogenic genetic result for HCM in a proband can also be used prenatally (by chorionic villous sampling) to see whether the fetus carries the HCM mutation. In life, genetic testing can be performed at birth, during childhood, or at any stage during adulthood. Importantly, pretest and posttest cardiac genetic counseling is essential in all instances where genetic testing in HCM is being considered.

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Assessment of Heart Failure: Invasive and Noninvasive Methods

7

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Key Points

- The symptoms of hypertrophic cardiomyopathy (HCM) result from a combination of high filling pressures ("backward" heart failure) and low cardiac output ("forward" heart failure); sudden drops in cardiac output may result in syncope.
- When present, elevated right atrial pressure and right ventricular (RV) end-diastolic pressures are often associated with RV hypertrophy, which may result from pulmonary hypertension due to left heart failure in older patients or may be a primary manifestation of HCM in the young.
- The symptoms of coronary artery disease (CAD) overlap those of HCM. The diagnosis of CAD by conventional stress testing may be inconclusive in patients with HCM. Cardiac computed tomographic angiography is a reliable means of detecting concomitant CAD in patients with HCM.
- In HCM patients with concomitant lung disease, right and left heart cardiac catheterization and/or cardiopulmonary exercise testing is useful for determining whether symptoms are due to a cardiac or pulmonary limitation.

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Heart failure is perhaps the most common manifestation of HCM in adulthood, especially for those in the middle or later years of life. The diagnosis of heart failure in these patients may be especially difficult, as diastolic dysfunction is the main finding in the vast majority and has typically been slowly progressive over years to decades. Accordingly, patients typically fail to notice acute declines in function and may attribute their insidious symptoms to a natural decline in functional status as they age or to a gradual increase in weight and associated morbidities. In addition, few patients have signs or symptoms of congestion until late in the disease process, with the majority of early symptoms being those of "forward" heart failure, or an inappropriately low cardiac output in response to exercise, resulting primarily in fatigue and dyspnea on exertion.

Once the diagnosis of HCM is firm and heart failure is clinically evident, it may be quite difficult in some cases to elucidate and prioritize the various components of a patient's heart failure syndrome, especially as patients age and accumulate multiple comorbidities. This chapter will discuss the various causes of heart failure in patients with HCM and provide insights into how to determine the main causes in individual patients and tailor therapies accordingly.

Heart Failure in HCM

"Backward" vs. "forward" manifestations of heart failure "Backward" symptoms of heart failure in HCM include dyspnea, orthopnea, PND, and, less commonly, edema, whereas "forward" symptoms include fatigue, dyspnea, and lightheadedness, and even frank syncope (Fig. 7.1). Exertional dyspnea may reflect elevation of pulmonary venous (and left atrial) pressure (a manifestation of "backward" failure) or limitation of cardiac output available to exercising muscle (a manifestation of "forward" failure); in many cases, forward and backward failure coexist. Alternatively, exertional dyspnea may be due to myocardial

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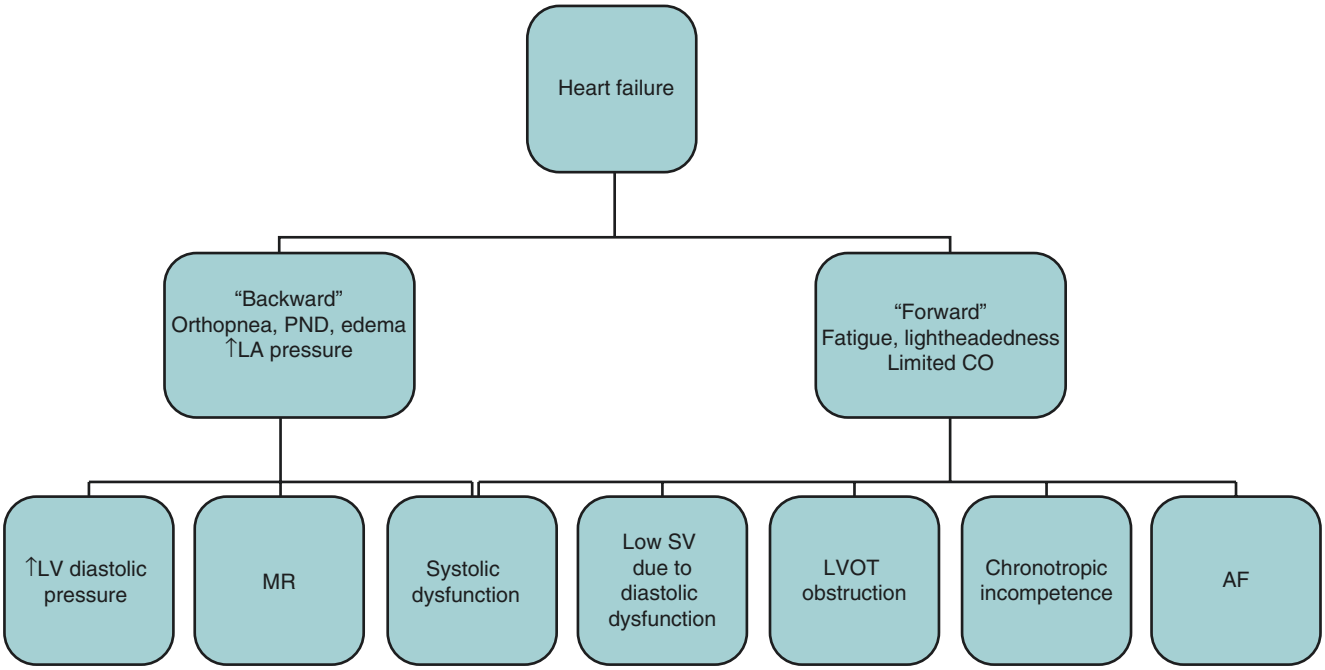


Fig. 7.1 Schematic representation of mechanisms of "backward" and "forward" manifestations of heart failure in patients with hypertrophic cardiomyopathy. AF atrial fibrillation, CO cardiac output, LA left atrial, LV left ventricular, LVOT left ventricular outflow tract, MR mitral regurgitation, PND paroxysmal nocturnal dyspnea, SV stroke volume

ischemia ("anginal equivalent") resulting from inadequacy of coronary blood flow to the hypertrophied myocardium or, in patients with LVOT obstruction, high myocardial wall stress; both forward and backward heart failure may be present in these cases.

Elevation of pulmonary venous pressure in HCM may result from (1) abnormal diastolic left ventricular (LV) function associated with hypertrophy and, in some patients, fibrosis; (2) mitral regurgitation (MR) associated with systolic anterior motion (SAM) of the mitral valve and left ventricular outflow tract (LVOT) obstruction and/or intrinsic abnormalities of the mitral valve associated with HCM; or, much less commonly, (3) abnormal systolic left ventricular LV function. Limitation of cardiac output in HCM may result from LVOT obstruction; rarely, systolic dysfunction; or, perhaps most commonly, low LV end-diastolic volume and stroke volume due to diastolic dysfunction. Low cardiac output may also result from chronotropic incompetence or, in patients with atrial fibrillation, from loss of atrial transport. Finally, low cardiac output may result from secondary pulmonary hypertension.

Exertional lightheadedness and even syncope may result from inadequate augmentation of cardiac output with exercise, particularly in the presence of volume depletion. Alternatively, these symptoms may result from autonomic dysfunction with abnormal peripheral vasodilation [1] or from exercise-induced ventricular tachyarrhythmias. Exercise-induced hypotension may occur in the presence or absence of LVOT obstruction. Patients with HCM may be particularly prone to orthostatic hypotension and to postprandial splanchnic shunting, with consequent effective intravascular volume depletion. The systemic vasodilation associated with certain systemic illnesses, such as sepsis and systemic immune response syndrome, may also bring out the hemodynamic manifestations of HCM.

Right heart failure Manifestations of right heart failure, such as jugular venous distention, ascites, and edema, are unusual in HCM. Patients with longstanding HCM and left heart failure, however, often manifest a component of pulmonary hypertension and right heart failure. When present, elevated right atrial pressure and (RV) end-diastolic pressure are often associated with RV hypertrophy, which may result from pulmonary hypertension due to left heart failure or may be a primary manifestation of HCM [2]. In the latter case, the hypertrophied septum may impinge on RV outflow, causing obstructive pathophysiology similar to that more commonly seen within the LV; this finding is more common in childhood and young adulthood in patients with massive septal hypertrophy.

Importantly, patients with HCM may have comorbidities affecting the pulmonary vasculature and RV, the most common of which are chronic obstructive pulmonary disease and sleep apnea; when present, these diseases contribute to right-sided heart congestion and reduced cardiac output.

Intrinsic mitral valve disease Posterolaterally directed MR regularly accompanies SAM of the anterior leaflet of the mitral valve in patients with LVOT obstruction. HCM may also be associated with intrinsic abnormalities of the mitral valve (in which case the regurgitant jet may not be posterolaterally directed), including papillary muscle malposition, leaflet elongation and thickening, and prolapse [3]. Finally, older patients with HCM may develop age-related mitral annular calcification, degenerative mitral valve disease, or other diseases that affect the mitral valve, contributing to mitral regurgitation or stenosis that is independent of underlying HCM. In some cases, posterior mitral annular calcification may exacerbate SAM and obstructive physiology. Such pathologies contribute to the manifestations of heart failure in some patients with HCM.

Intrinsic aortic valve disease (Table 7.1) Patients with HCM may also develop intrinsic pathology of the aortic valve, most commonly aortic stenosis due to calcific degeneration in older patients [4]. Valvular obstruction may occur concurrently or in the absence of subvalular obstruction due to HCM. When present, the valvular stenosis contributes to hypotension, diastolic dysfunction, and elevation of myocardial wall stress with associated myocardial ischemia, in turn contributing to both forward and backward manifestations of heart failure, including syncope.

Table 7.1 LVOT obstruction: differential diagnosis

	Site of gradient	Aortic regurgitation	Brockenbrough sign
Valvular AS	LV → Ao	Often present	Absent
HOCM	LV → LV	Generally absent	Present
Subaortic membrane	LV → LV	Often present	Absent

Assessment of Heart Failure in HCM

In patients with HCM, symptoms attributable to heart failure range from mild to severe. In general, the goal of management is to make patients asymptomatic or at least reduce symptoms to the level of New York Heart Association Class II. In order for the clinician to accomplish this goal, it is necessary to determine the pathophysiologic underpinning of the symptoms. After a careful history and physical examination, noninvasive and in some cases invasive testing may be necessary (Table 7.2). If edema and other overt signs of congestion are present, a cautious trial of diuretic therapy may be warranted.

Noninvasive testing (Tables 7.1 and 7.2) The mainstay of the noninvasive assessment of heart failure in patients with HCM is transthoracic echocardiography, generally with the Valsalva maneuver and sometimes with exercise to elicit an LVOT gradient. Transesophageal echocardiography is useful in selective patients for delineating intrinsic abnormalities of the mitral valve apparatus and, on occasion, for detecting a subaortic membrane (particularly in the presence of aortic regurgitation) [5]. Mitral regurgitation (MR)

Table 7.2 Investigations for heart failure symptoms in patients with HCM

Test	Data obtained
Transthoracic echocardiogram	Extent and pattern of hypertrophy Resting and provoked LVOT (and midcavity) gradient Abnormalities of mitral apparatus Estimation of RV systolic pressure Concomitant valvular and other abnormalities
Transesophageal echocardiogram	Abnormalities of mitral apparatus Subaortic membrane
Treadmill exercise test	Quantitative measure of exercise tolerance Chronotropic response Blood pressure response Exercise-induced arrhythmias
Cardiac magnetic resonance	Extent of hypertrophy Presence and extent of fibrosis
Holter, long-term cardiac monitor, or implantable loop recorder	Arrhythmias contributing to heart failure symptoms
Cardiac chest tomographic angiography	Concomitant CAD
Chest X-ray, pulmonary function tests	Pulmonary disease as alternative cause of dyspnea
Sleep study	Obstructive or central sleep apnea
Cardiac catheterization	Right heart, pulmonary arterial, and pulmonary capillary wedge pressures Resting and provoked gradients Exercise hemodynamics Concomitant CAD HCM mimics

caused by SAM is invariably associated with a posteriorly directed jet; if regurgitation is not posteriorly directed, the mitral apparatus should be examined with particular care for conditions including prolapse, excessive leaflet prolongation, calcification, and anomalous papillary muscle position or insertion.

Routine treadmill exercise testing yields a quantitative measure of exercise tolerance, data on heart rate (for chronotropic response) and blood pressure (for exercise-induced hypotension), and the occurrence of exercise-induced arrhythmias. Cardiac magnetic resonance imaging provides global visualization of the left ventricular myocardium for assessment of wall thickness and presence and extent of fibrosis.

Holter monitoring may be utilized to detect arrhythmias that contribute to or cause heart failure symptoms [6]. In select cases with more intermittent symptoms, a long-term cardiac monitor or implantable loop recorder may be considered. A chest X-ray and pulmonary function tests are useful in selected patients to elicit pulmonary rather than cardiac causes of dyspnea. Similarly, sleep studies may help determine the presence and severity of concomitant obstructive or central sleep apnea.

Detection of concomitant CAD The symptoms of CAD may mimic or contribute to those of heart failure in patients with HCM who are "old enough" to have CAD. Noninvasive diagnosis of CAD may be challenging in patients with HCM. Exercise-induced electrocardiographic changes are nonspecific in this patient population. Moreover, stress radionuclide perfusion imaging may show fixed or reversible defects in patients with HCM in the absence of CAD [7]. In addition, regional differences in wall thickness may cause apparent differences in tracer uptake that do not reflect abnormalities in perfusion. Exercise echocardiography to detect wall motion abnormalities has not been validated in patients with HCM. Cardiac computerized tomographic angiography (CTA) is a high-sensitivity test for the presence of CAD and has emerged as the most useful noninvasive test for the assessment of potentially ischemic symptoms due to CAD, especially in younger patients. In contrast, cardiac catheterization may be helpful in older patients, in whom CTA may be equivocal.

Cardiac catheterization In patients with HCM, cardiac catheterization may be useful for [1] documenting right atrial, RV, pulmonary arterial (PA), and pulmonary capillary wedge (PCW) pressures, cardiac output, and pulmonary vascular resistance (PVR); [2] determining whether a LVOT (or midcavity) gradient is present at rest or with provocation; [3] separating aortic valvular from subvalular gradients; [4] determining whether concomitant CAD is present; and [5] excluding, as indicated, other causes, such a amyloid, of thickening of the left ventricular wall. Since much of the hemodynamic data may be obtained from echocardiography, delineation of coronary anatomy has become the most common indication for cardiac catheterization in patients with HCM. In difficult cases of heart failure refractory to optimal medical management, however, invasive assessment of hemodynamics may be indispensable.

Pressures on "pullback" from PA to RV in a patient with RV outflow tract obstruction are shown in Fig. 7.2. RV and LV pressure tracings from a patient with bisided heart failure are shown in Fig. 7.3.

In the cardiac catheterization laboratory, LVOT gradients may be provoked with the Valsalva maneuver (Fig. 7.4), by inducing ventricular premature beats (VPBs, as by mechanical stimulation with a catheter in the RV; Fig. 7.5), or by the administration of nitroglycerin or isoproterenol. Production of VPBs during the Valsalva maneuver provides a particularly sensitive method of eliciting a gradient when no gradi-

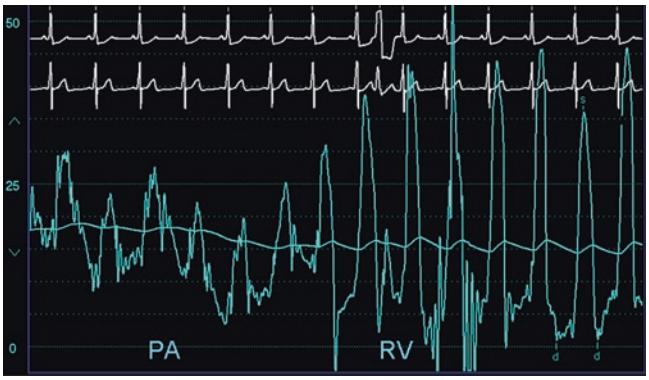


Fig. 7.2 Right heart catheter "pullback" from pulmonary artery (PA) to right ventricle (RV) in a patient with a 30 mmHg RV outflow tract gradient

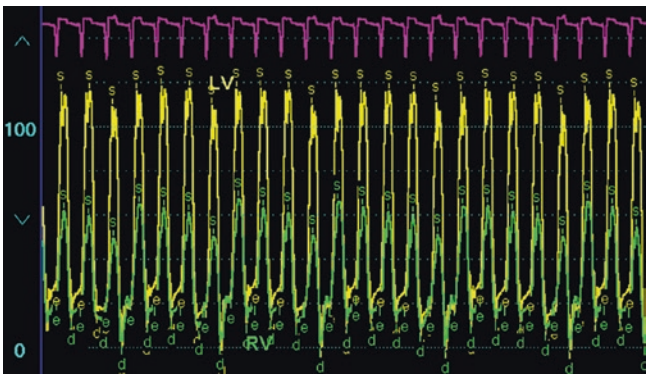


Fig. 7.3 Simultaneous right ventricular (RV) and left ventricular (LV) pressure tracings from a patient with HCM and "congestive" or "backward" heart failure symptoms and signs. Diastolic pressures are elevated in both ventricles. Systolic pressures are concordant with respect to the respiratory cycle, indicating that pericardial disease is absent

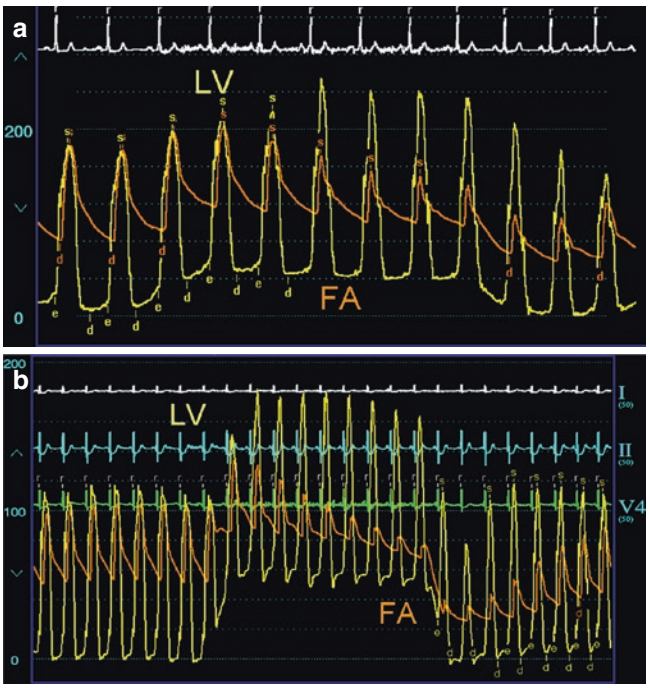


Fig. 7.4 Simultaneous left ventricular (LV) and femoral arterial (FA) pressures from two patients with HOCM. During the Valsalva maneuver, left ventricular diastolic pressure, which reflects intrathoracic pressure, increases. An LVOT gradient is absent (panel A) or present (panel B) at rest. During the Valsalva maneuver, the gradient (and, presumably, the systolic murmur) appears (panel A) or increases (panel B). In the patient whose pressures are depicted in panel B, the systolic systemic arterial pressure falls to 40 mmHg, an illustration of the importance of asking patients with HOCM to perform the maneuver only when supine

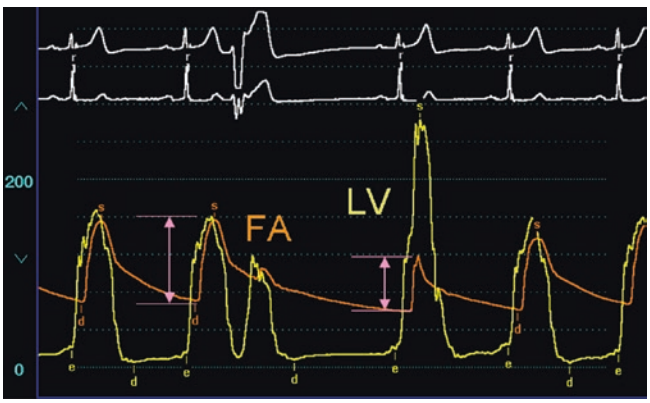


Fig. 7.5 Simultaneous left ventricular (LV) and femoral arterial (FA) pressure tracings from a patient with HOCM. There is only a small resting LVOT gradient. In the beat after a ventricular premature beat, there is a large gradient. In addition, there is a decrease in the systemic arterial pulse pressure in the postextrasystolic beat (Brockenbrough sign)

ent is found with either maneuver alone. It is critical to distinguish between LVOT and midcavity gradients. Whereas the presence or absence of an LVOT gradient determines whether, for example, treatment with disopyramide or septal reduction therapy is appropriate, the significance of a midcavity gradient is much less clear. It is possible to distinguish between the two during either transseptal or retrograde LV catheterization (Fig. 7.6). An intracavitary gradient between catheters in the LV apex and aorta (or other systemic artery) may originate from the LVOT or the midcavity (or both). An intracavitary gradient between the LV inflow region and aorta (or other systemic artery) must originate from the LVOT. The mitral inflow area may be reached via the transseptal technique or by manipulating a retrograde catheter to that region. Figure 7.6 illustrates a case in which both LVOT and midcavity gradients are present.

During cardiac catheterization, one may determine whether a Brockenbrough sign (perhaps the least well-understood sign in cardiology) is present (Fig. 7.5) [8]. A Brockenbrough sign is defined as a failure of the systemic arterial pulse pressure to increase after a ventricular premature beat (*not*, as is often mistakenly believed, an increase in the LVOT gradient), representing diminished stroke volume resulting from exacerbation of LVOT obstruction [8]. Since the gradients of valvular aortic stenosis and hypertrophic obstructive cardiomyopathy (HOCM) both increase in a postextrasystolic beat, the increase does not distinguish between the two conditions. Since the pulse pressure increases after a postextrasystolic beat in valvular aortic stenosis (Fig. 7.7), it is the decrease after a postextrasystolic beat in HOCM (the Brockenbrough sign) that distinguishes the two conditions. The fact that it is the systemic arterial pulse pressure rather than the LVOT gradient that defines the Brockenbrough sign is brought home by the point that it is actually possible to observe a Brockenbrough sign without placing a catheter in the LV (Fig. 7.8). A "spike and dome" waveform in the aortic pressure tracing (Fig. 7.8), either fixed or variable, is highly specific for outflow tract obstruction.

In patients with HOCM, left ventriculography in the cranially angulated left anterior oblique projection demonstrates the pathoanatomic features of LVOT obstruction (Fig. 7.9). A "pullback" from LV to aorta in a patient with LVOT obstruction is shown in Fig. 7.10; there is no gradient across the aortic valve. A similar finding occurs in the rare adult with a subaortic membrane (Fig. 7.11). In this case, the Brockenbrough sign is absent (consistent with fixed obstruction) and the membrane may be visualized by left ventriculography in the cranial left anterior oblique projection (Fig. 7.11).

Supine exercise testing in the cath lab may be useful for understanding exertional symptoms in patients with HCM. Exercise parameters of interest include heart rate, PA and PCW pressures, and cardiac output. Exercise testing may be accomplished with the use of a cycle or, alternatively, alternating active leg raising in patients with internal jugular or upper extremity access or with active single leg raising in patients with femoral access. Exertional dyspnea may be

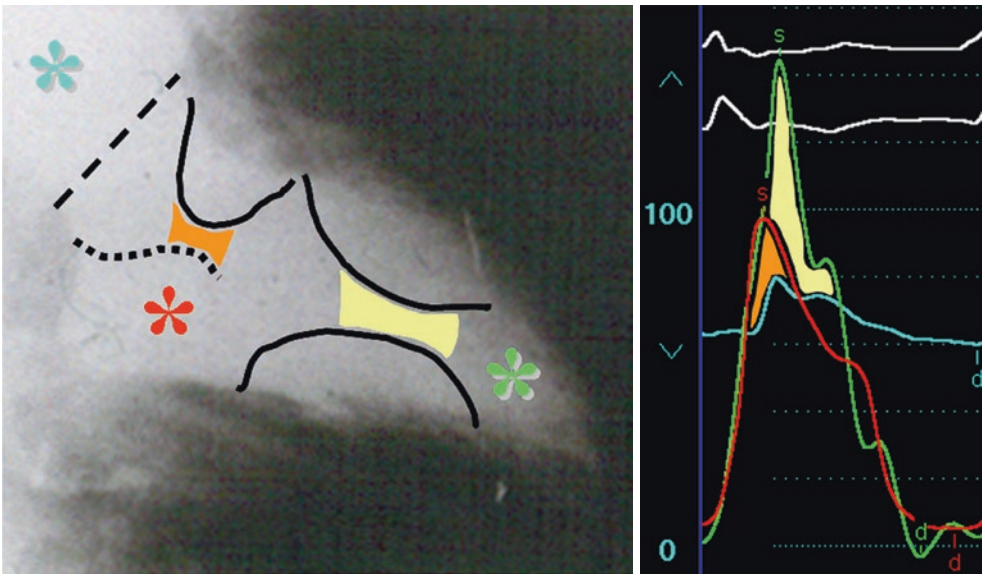


Fig. 7.6 Simultaneous left ventricular apical (green), left ventricular inflow (red), and systemic arterial (blue) pressure tracings from a patient with both LVOT (orange) and midcavity (yellow) gradients. The left ventricular inflow pressure was obtained in this case via the transseptal technique but may also be obtained via manipulation of a catheter passed in retrograde fashion through the aortic valve

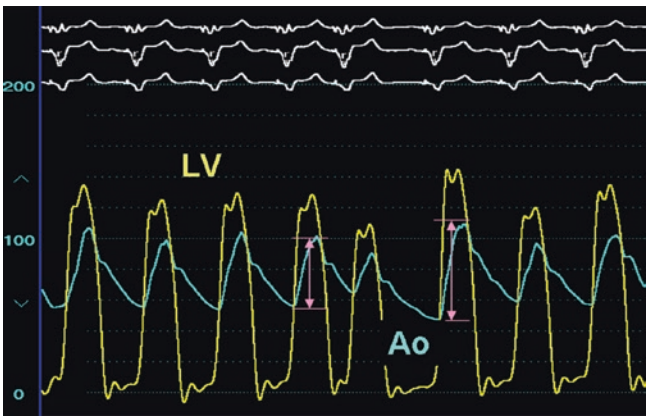


Fig. 7.7 Simultaneous left ventricular (LV) and aortic (Ao) pressure tracings from a patient with valvular aortic stenosis. In the beat following a pause, there is an increase in the transvalvular gradient *and* in the aortic pulse pressure (arrows); thus, the Brockenbrough sign is absent

Fig. 7.8 Aortic (Ao) pressure tracing from a patient with HOCM. The Brockenbrough sign (a fall in the systemic arterial pulse pressure in the postextrasystolic beat) is present. Furthermore, the "spike and dome" morphology typical of HOCM is accentuated, a sign of greater obstruction to left ventricular outflow, in the postextrasystolic beat

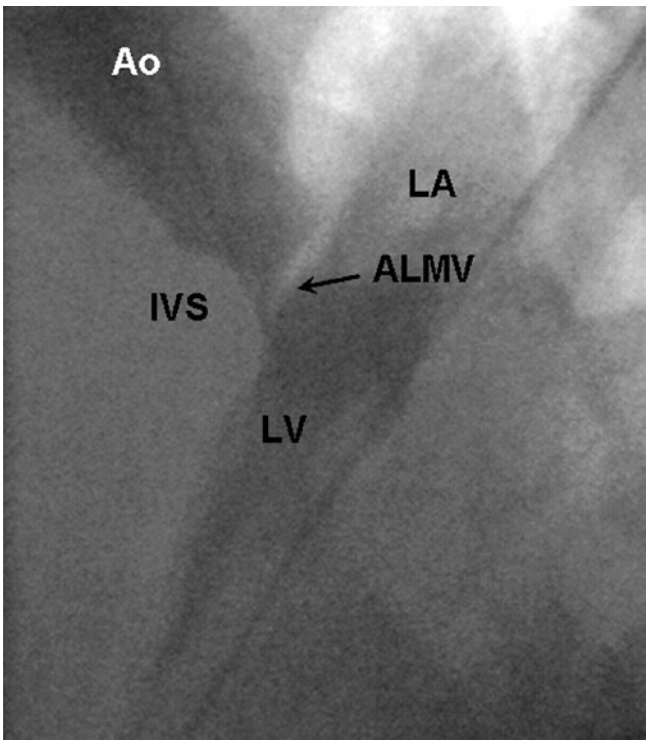


Fig. 7.9 Left ventriculogram in the cranially angulated left anterior oblique projection from a patient with HOCM. There is SAM of the anterior leaflet of the mitral valve (ALMV), which is in apposition to the interventricular septum (IVS). The LV (LV) has contracted down to a low end-systolic volume. There is contrast in the left atrium (LA), reflecting MR

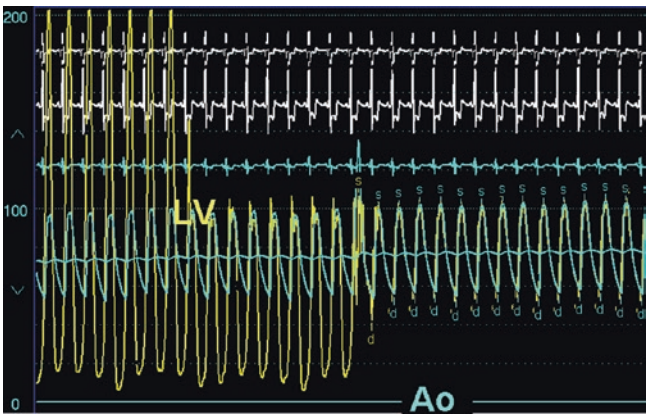


Fig. 7.10 Catheter "pullback" from LV (LV) to aorta (Ao) from a patient with HOCM. LV systolic pressure drops from approximately 200 mmHg to 100 mmHg within the LV cavity, indication that the pressure gradient is within the cavity. There is no change in systolic pressure as the catheter is withdrawn across the aortic valve, indication that valvular aortic stenosis is absent

explained, for example, by an exercise-induced increase in PCW pressure, by absence of an appropriate increase in cardiac output, or by a combination of the two. Alternatively, exercise-induced pulmonary hypertension with abnormal (or increasing) PVR implicates a separate pulmonary process as the cause of dyspnea.

On occasion, right (or left) ventricular endomyocardial biopsy may be useful for detecting the presence of Fabry disease or amyloidosis (Fig. 7.12). In the latter case, we recommend that an abdominal fat pad biopsy (which has lower sensitivity but also lower morbidity) and/or cardiac MRI be done prior to consideration of endomyocardial biopsy. And, in the former case, genetic testing with comprehensive panels including Fabry disease is available.

Cardiopulmonary exercise testing (CPET) CPET is a safe and often valuable diagnostic modality in patients with HCM. CPET, typically performed on a treadmill or upright

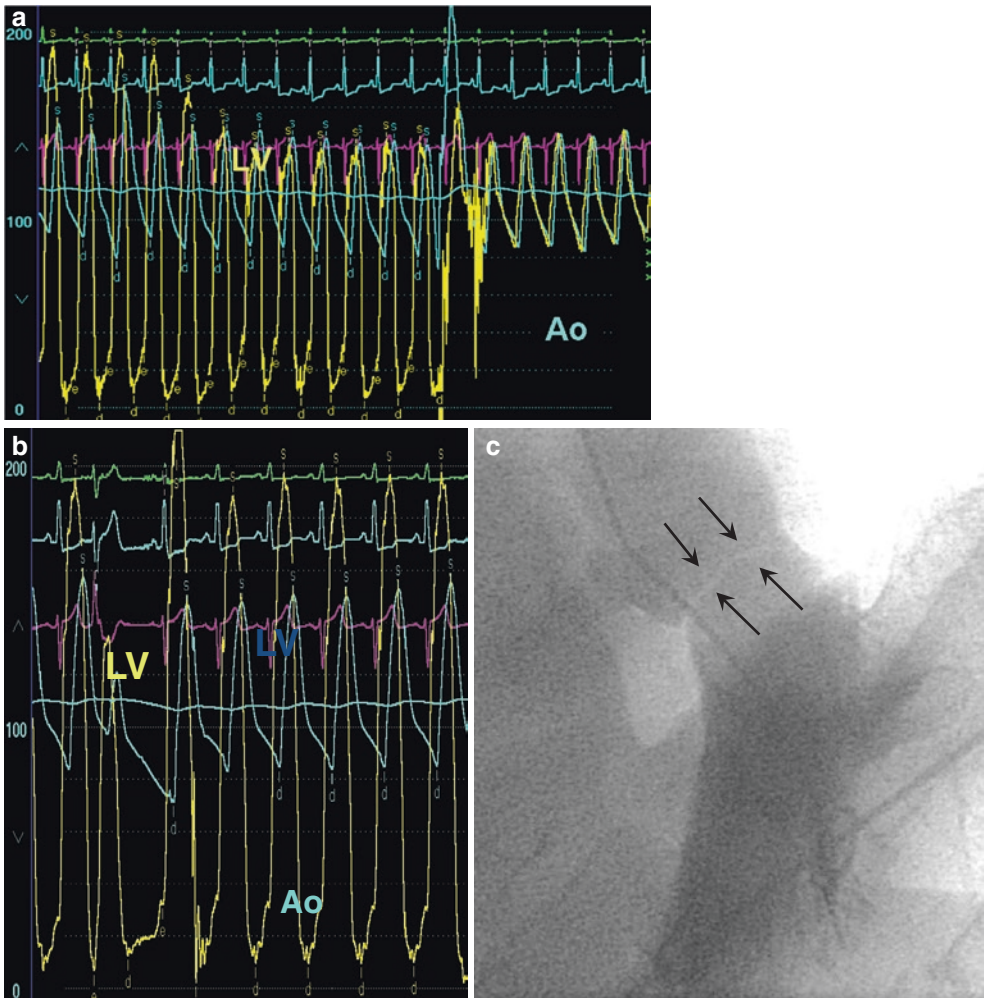


Fig. 7.11 Panel A, catheter "pullback" from LV (LV) to aorta (Ao) from a patient with a subaortic membrane. LV systolic pressure drops from approximately 180 mmHg to 140 mmHg within the LV cavity, indication that the pressure gradient is within the cavity. There is no change in systolic pressure as the catheter is withdrawn across the aortic valve, indication that valvular aortic stenosis is absent. Panel B, simultaneous LV and FA pressure tracings. The systemic arterial pulse pressure increases in the postextrasystolic beat, indicating that the Brockenbrough sign is absent. Panel C, left ventriculogram in the cranially angulated left anterior oblique projection, showing the thin subaortic membrane (arrows)

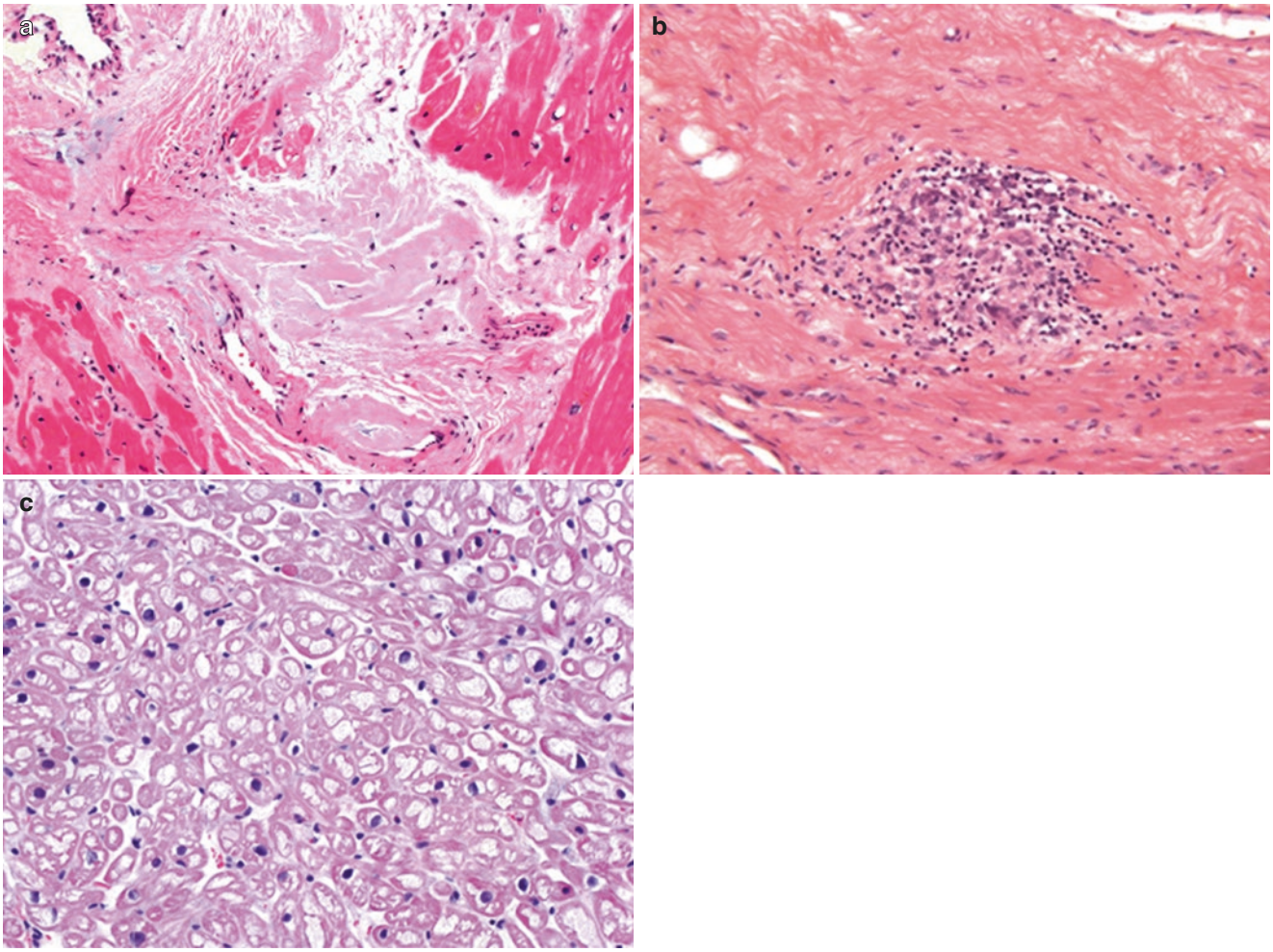


Fig. 7.12 Pathology specimens from three patients presenting with cardiac symptoms and signs indistinguishable from those of HCM. Panel A, amyloidosis; panel B, sarcoidosis; panel C, Fabry disease. The Fabry specimen was obtained by RV endomyocardial biopsy specimen, while the other two are septal myectomy specimens

cycle ergometer, integrates graded exercise to volitional peak effort or symptom limited test termination with simultaneous measurement of ventilatory gas exchange and systemic arterial oxygen saturation and continuous 12-lead electrocardiography. Comprehensive reviews of CPET technical performance and diagnostic capabilities are available for the interested reader [9, 10].

Among patients with suspected or confirmed HCM, CPET provides the most accurate and reproducible quantification of functional capacity and proves useful for establishing the diagnosis, determining the relative contributions to symptoms of cardiac and pulmonary diseases, estimating prognosis, determining suitability for heart transplantation, and assessing response to therapy. Despite theoretical concerns about the risk of intense exercise among patients with high risk cardiovascular disease, including HCM, the safety of CPET has been demonstrated, with adverse event rates among a large series of ambulatory patients of less than 0.2% [11]. The primary outcome variable obtained from CPET is peak oxygen uptake (peak VO_2). Peak VO_2 is the most accurate determinant of functional capacity and is a powerful predictor of prognosis in patients with cardiovascular disease [12].

CPET facilitates management of patients with suspected or confirmed HCM in several ways. First, peak VO_2 can be used to assist in differentiating physiologic, exercise-induced LV hypertrophy from mild forms of pathologic HCM. In a small but illustrative series, Sharma et al. demonstrated striking differences in oxygen uptake kinetics between trained athletes with LV hypertrophy and patients with phenotypically mild HCM [13]. These investigators suggested a peak VO_2 cut point of 120% of age and gender predicted maximum for differentiating athletic cardiac remodeling from HCM. An example comparing CPET results from a healthy athlete with physiologic LVH and an age-matched asymptomatic athletic patient with nonobstructive HCM is shown in Fig. 7.13.

Second, CPET is useful for determining whether symptoms such as dyspnea or subjective exercise intolerance are

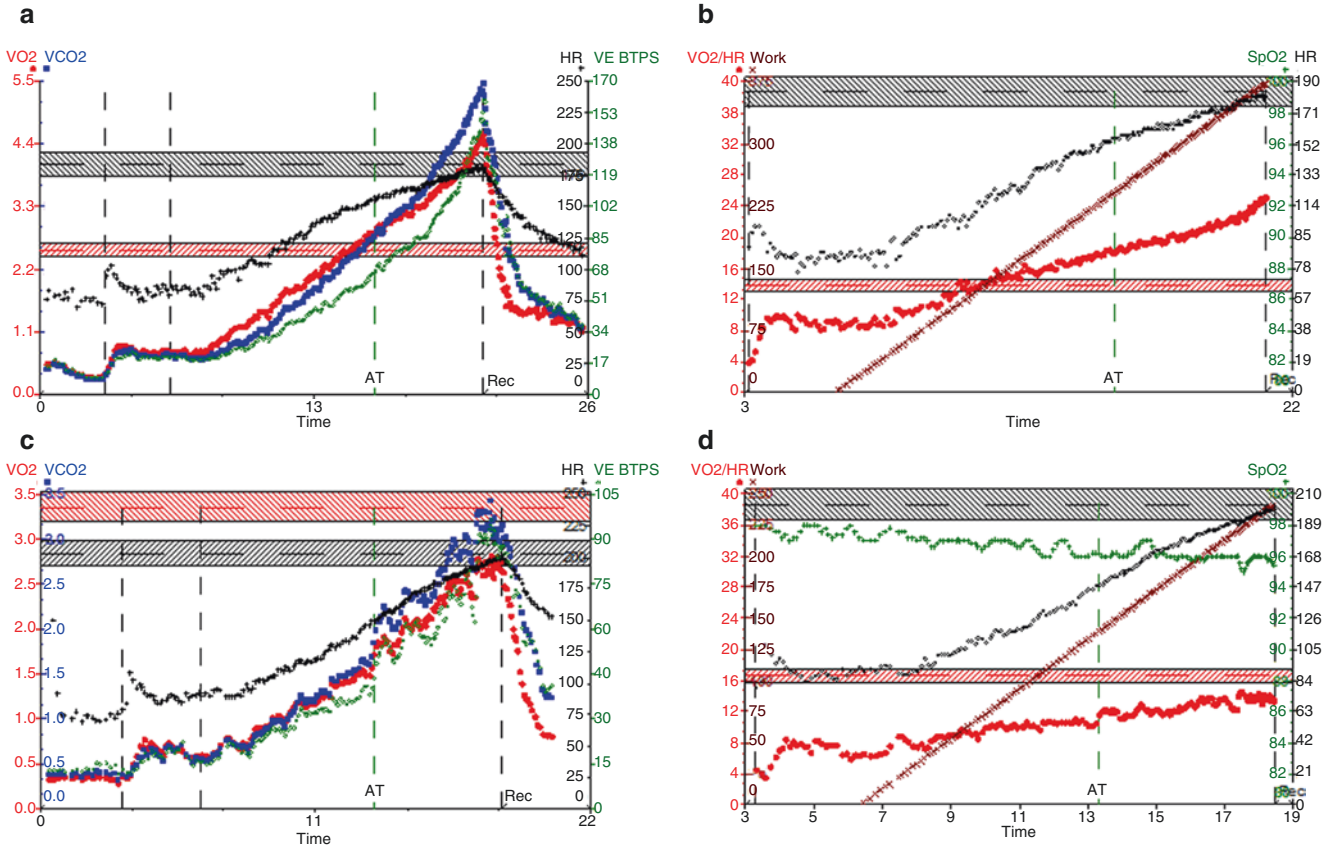


Fig. 7.13 Cardiopulmonary exercise test (CPET) data from a healthy 24-year-old rower with mild LVH detected during a research study (**a**, **b**) and a 21-year-old rower found to have phenotypically mild nonobstructive HCM during pre-participation screening (**c**, **d**). Panel A depicts a normal linear heart rate response to graded exercise (black line) coupled with normal VO_2 kinetics (red line) and a peak VO_2 of roughly 170% predicted. Panel B demonstrates a normal progressively increasing oxygen pulse (red line), reflecting normal stroke volume augmentation [O_2 pulse = stroke volume × $C(a–v)O_2$] during exercise. In contrast, (**c**) depicts blunted peak VO_2, despite reaching an appropriate peak heart rate, coupled with reduced O_2 pulse (**d**), indicating impaired exercise capacity due to a primary cardiovascular limit

attributable to a central cardiovascular limit (i.e., caused by HCM) or by a primary, perhaps underappreciated, pulmonary process. This distinction is critical in patients with HCM and concomitant lung disease, such as older patients with chronic obstructive lung disease or younger patients with asthma.

Third, CPET can be used to assess response to therapy among patients with symptomatic HCM. This evaluation is particularly useful in patients with LVOT obstruction treated with negative inotropic medications who fail to respond to therapy. In some cases, the benefits of negative inotropy afforded by beta blockers or nondihydropyridine calcium channel blockers may be outweighed by undesired reductions in achievable heart rate. Additionally, peak VO_2 is inversely related to the degree of LVOT obstruction and improves significantly with septal reduction therapy [14]. Finally, as in other heart failure populations, CPET in patients with HCM and advanced heart failure is a key determinant of eligibility for cardiac transplantation.

Conclusions

Manifestations of heart failure in HCM result from a combination of LVOT obstruction, diastolic dysfunction, and MR, as well as secondary problems including pulmonary hypertension and atrial fibrillation. The clinical presentation may be complicated by concomitant intrinsic valvular disease, CAD, or pulmonary disease. While MR regularly accompanies LVOT obstruction and SAM in patients with HOCM, careful echocardiographic assessment of the mitral valve for intrinsic pathology is essential. Whereas the results of conventional exercise testing may be ambiguous, coronary CTA and cardiac catheterization are reliable means of detecting concomitant CAD. CPET is often useful for the distinction between HCM and pulmonary disease as the cause of dyspnea. While not a component of the routine evaluation of patients with HCM, cardiac catheterization often provides critical additional information.

Clinical Pearls

- Patients with HCM may be particularly prone to orthostatic hypotension and to postprandial splanchnic shunting and may experience symptoms only after meals.
- The Valsalva maneuver may result in hypotension. Therefore, the patients should be placed in the supine position before the maneuver is elicited.
- When MR results from LVOT obstruction with SAM of the anterior leaflet, the jet is directed posterolaterally. The presence of a jet oriented in another director should prompt a search for an intrinsic abnormality of the valve.
- The Brockenbrough sign is a decrease in the systemic arterial pulse pressure *(not an increase in LVOT gradient)* in the beat following a ventricular premature beat.
- Left ventricular outflow tract (LVOT) gradients may be distinguished from midcavity gradients by careful manipulation of the catheter within the LV but may on occasion require transseptal puncture.
- The presence of aortic regurgitation should lead to careful evaluation for a subaortic membrane as a mimic of HOCM.

Questions

1. In which position should the patient be placed while Valsalva maneuver is performed?
   A. Left lateral decubitus
   B. Right lateral decubitus
   C. Standing
   D. Sitting up at 90 degrees
   E. Supine

2. Which of the following correctly describes the Brockenbrough sign?
   A. Decrease in systolic blood pressure in the beat following a VPB
   B. Decrease in diastolic blood pressure in the beat following a VPB
   C. Decrease in pulse pressure in the beat following a VPB
   D. Increase in LVOT gradient in the beat following a VPB
   E. Decrease in LVOT gradient in the beat following a VPB

3. A 52-year-old woman with apical HCM presents with exertional chest heaviness which has progressed over the last 6–12 months. Heart rate is 55 and blood pressure is 104/68. Electrocardiogram (ECG) shows normal sinus rhythm, left atrial enlargement, and deep T wave inversion in leads $V_{4–6}$. Holter monitor shows sinus rhythm during her symptoms. Echocardiography demonstrates apical hypertrophy up to 18 mm and no LVOT gradient at rest or with the Valsalva maneuver. Which of the following is the best next diagnostic step to further investigate the cause of her exertional chest symptoms?
   A. Radionuclide exercise stress testing
   B. Coronary arteriography
   C. Exercise stress echocardiography
   D. Dobutamine stress echocardiography
   E. Cardiac CT angiography

4. A 48-year-old man with HOCM and COPD presents with worsening exertional dyspnea over the past 1–2 years. Heart rate is 65 and blood pressure is 124/78. Physical examination revealed a grade III systolic ejection murmur which is augmented by the Valsalva maneuver. Electrocardiogram (ECG) shows normal sinus rhythm, left atrial enlargement, and T wave inversion in leads I, II, III, $_{a}V_{F}$, and $V_{2–6}$. Echocardiography demonstrates septal hypertrophy up to 19 mm and an LVOT gradient of 34 mmHg at rest and 54 mmHg with the Valsalva maneuver. Cardiac catheterization shows right atrial pressure 14 mmHg, pulmonary arterial systolic pressure 54 mmHg and mean pressure 40 mmHg, pulmonary capillary wedge pressure 12 mmHg, cardiac output 4.4 liter/min, cardiac index 1.6 liter/min/m^2, and 50% stenosis of the right coronary artery. Which of the following is the most likely cause of his exertional dyspnea?
   A. Left-sided heart failure due to LVOT obstruction
   B. Left-sided heart failure due to undiagnosed valvular heart disease
   C. Intrinsic pulmonary or pulmonary vascular disease
   D. Coronary artery disease
   E. Deconditioning

5. A 48-year-old man is referred to the HCM program for suspected HCM. He is asymptomatic and actively participated in recreational sports. He has no family history of HCM. ECG shows normal sinus rhythm and left ventricular hypertrophy with nonspecific ST-T changes. Echocardiography shows mild aortic regurgitation, septal thickness 15 mm, posterior wall thickness 13 mm, ejection fraction 0.65, LVOT gradient 35 mmHg at rest without augmentation with Valsalva maneuver, trace mitral regurgitation, and estimated RV systolic pressure 28 mmHg. Which of the following is the best next diagnostic modality?
   A. Cardiac MRI
   B. Transesophageal echocardiography
   C. Coronary arteriography
   D. Cardiac CT angiogram
   E. Exercise stress echocardiography

6. A 62-year-old woman is referred to our HCM program with exertional dyspnea, chest pain, and lightheadedness. She has been treated with metoprolol 100 mg PO daily, with partial improvement. Heart rate is 51 and blood pressure 105/80. There is a grade II systolic ejection murmur which is louder with the Valsalva maneuver. There is no jugular venous distension, rales, or edema. Electrocardiogram (ECG) shows normal sinus rhythm, left atrial enlargement, and T wave inversion in leads I, II, III, $_aV_F$, and V_{2-6}. Echocardiography demonstrates an LVOT gradient of 34 mmHg at rest and 84 mmHg with the Valsalva maneuver. Coronary arteriography shows no coronary atherosclerosis. She declines invasive treatment, including catheter-based and surgical interventions. Which of the following pharmacologic interventions is the best option to treat her symptoms?
   A. Increase the dosage of metoprolol
   B. Add verapamil
   C. Add disopyramide
   D. Add losartan
   E. Add furosemide

7. A 58-year-old man with history of benign prostatic hyperplasia is referred to our HCM program with exertional dyspnea. Heart rate is 52 and blood pressure 120/55 while taking metoprolol 100 mg daily. He has jugular venous distention to the earlobe, bilateral rales, no murmur, and bilateral 2+ edema up to the knee. ECG shows normal sinus rhythm and deep apical T wave inversions. Echocardiography shows septal thickness 11 mm, posterior wall thickness 9 mm, apical wall thickness 18 mm, ejection fraction 0.55, no LVOT gradient at rest or during the Valsalva maneuver, biatrial enlargement, and estimated RV systolic pressure 48 mmHg. Cardiac catheterization shows right atrial pressure 14 mmHg, pulmonary arterial systolic pressure 54 mmHg and mean pressure 40 mmHg, pulmonary capillary wedge pressure 33 mmHg, cardiac output 4.4 liter/min, cardiac index 1.6 liter/min/m^2, and minimal coronary atherosclerosis. There is no LVOT gradient with exercise or pharmacologic provocation. Which of the following is the best treatment option to relieve his symptoms?
   A. Furosemide
   B. Verapamil
   C. Disopyramide
   D. Alcohol septal ablation
   E. Septal myectomy

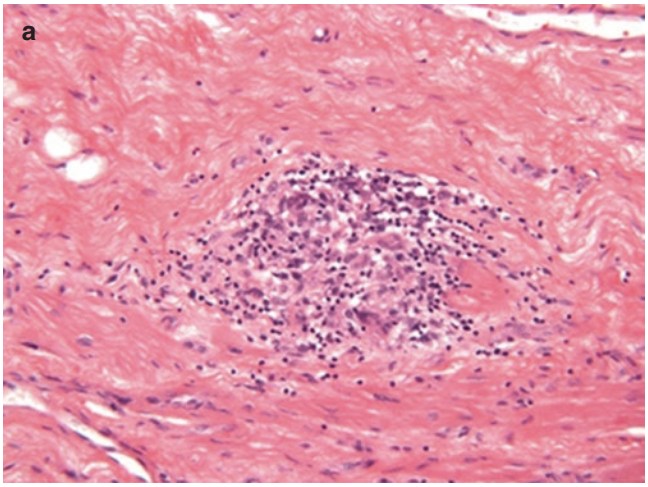
8. A 56-year-old man returns to the HCM program for follow-up. He has had worsening exertional dyspnea over the past few months. There is a grade III systolic murmur with wide radiation, including to the axilla; with Valsalva maneuver, it becomes harsher in quality. ECG shows sinus rhythm and left atrial enlargement. Echocardiography shows septal thickness 15 mm, posterior wall 12 mm, left ventricular end-diastolic dimension 56 mm, ejection fraction 0.75, LVOT gradient 18 mmHg at rest and 47 mmHg with the Valsalva maneuver, SAM, prolapse of the posterior mitral leaflet with moderate to severe regurgitation, left atrial enlargement, RV systolic pressure 48 mmHg, mild tricuspid regurgitation, and right atrial enlargement. There are two jets of MR, one posteriorly directed and one anteriorly directed, with the latter predominating. Coronary arteriography shows 50% stenosis of the left circumflex artery with normal fractional flow reserve. Which of the following intervention is most likely to relieve his exertional dyspnea?
   A. Alcohol septal ablation
   B. Percutaneous coronary intervention
   C. Alcohol septal ablation and percutaneous coronary intervention
   D. Septal myectomy and possible coronary artery bypass grafting
   E. Mitral valve repair/replacement, septal myectomy, and possible coronary artery bypass grafting

9. Connect diseases 1–3 in the table below with the corresponding cardiac disease in the following list:
   A. HCM
   B. Valvular AS
   C. Subaortic membrane

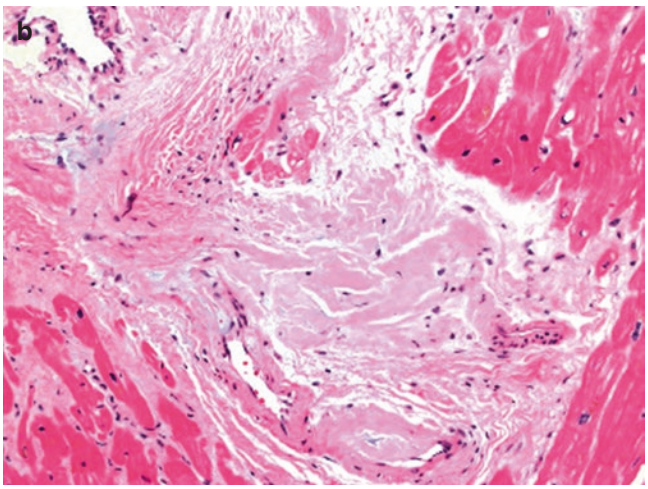
	Site of gradient	Brockenbrough sign
Disease 1	LV → Ao	Absent
Disease 2	LV → LV	Present
Disease 3	LV → LV	Absent

10. Connect myocardial pathology specimens 1–4 below with the corresponding cardiac disease in the following list:
   A. Amyloidosis
   B. Fabry disease
   C. HCM
   D. Sarcoidosis

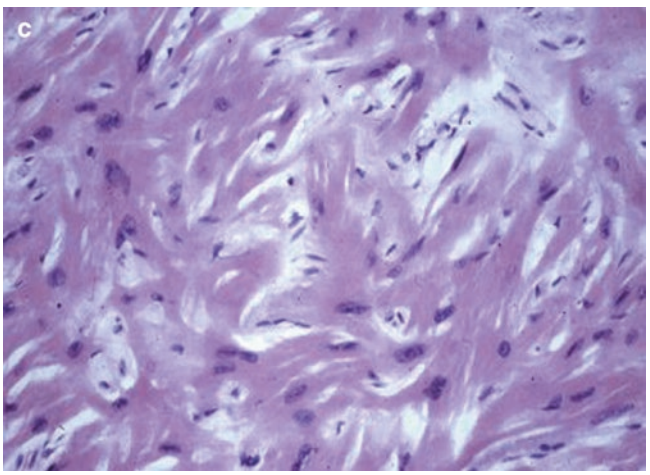
Disease 1:



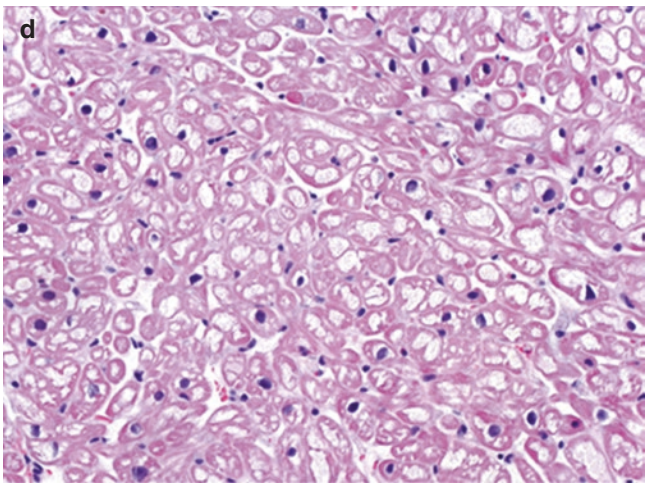
Disease 2:



Disease 3:



Disease 4:



Answers

1. E

In patients with HOCM, the Valsalva maneuver may result in symptomatic hypotension, sometimes causing presyncope or frank syncope. Therefore, the patients should be placed in the supine position before the maneuver is elicited.

2. C

The Brockenbrough sign is a decrease in the systemic arterial pulse pressure *(not an increase in LVOT gradient)* in the beat following a ventricular premature beat.

3. E

Exercise-induced electrocardiographic changes are nonspecific in patients with HCM. Moreover, stress radionuclide perfusion imaging may show fixed or reversible defects in patients with HCM in the absence of CAD [7]. In addition, regional differences in wall thickness may cause apparent differences in tracer uptake that do not reflect abnormalities in perfusion. The diagnostic accuracy of exercise echocardiography to detect wall motion abnormalities has not been validated in patients with HCM. Coronary CT angiography is a highly sensitive test for the presence of CAD and has emerged as the most useful noninvasive test for the assessment of potentially

ischemic symptoms in due to CAD, especially in younger patients. In contrast, cardiac catheterization may be helpful in older patients, in whom CTA may be equivocal due to coronary calcification.

4. C

This patient has a high transpulmonary pressure gradient (40–12 = 28 mmHg), with high pulmonary vascular resistance as well as normal pulmonary capillary wedge pressure (28/4.4 = 6.4 wood units = 509 dyn·s·cm^{-5}), suggesting that his COPD is the cause of his dyspnea.

5. B

The presence of aortic regurgitation should prompt a careful evaluation for a subaortic membrane as a mimic of HOCM. Among the listed items, transesophageal echocardopgraphy is the best diagnostic modality for detection of a subaortic membrane.

6. C

Metoprolol cannot be increased and verapamil cannot be added because her heart rate is already low at 51. Losartan is relatively contraindicated in patients with LVOT obstruction and is at any rate note likely to be of benefit to this patient. Furosemide is typically reserved for patients with overt volume overload and may worsen LVOT obstruction. Disopyramide is a good medical option for symptomatic patients with HOCM who have no contraindications for disopyramide (e.g., closed-angle glaucoma, benign prostatic hyperplasia, QT prolongation, or uncontrolled hypertension).

7. A

Verapamil cannot be added to this patient's medical regimen because his heart rate is already low. Disopyramide is reserved for HOCM (this patient has a nonobstructive form of HCM). Additionally, disopyramide is relatively contraindicated in patients with benign prostate hyperplasia because its anticholinergic effects may cause urinary retention. Septal reduction therapy such as alcohol septal ablation and septal myectomy is reserved for patients with HOCM. Diuretics must be used with caution in patients with HCM, particularly if obstruction is present, but may be useful for relieving symptoms in patients with overt volume overload.

8. E

This patient has intrinsic mitral valve disease concurrent with SAM provoked by LVOT obstruction. Therefore, pure septal reduction therapy (e.g., alcohol septal ablation, septal myectomy) would be insufficient to relieve his symptoms, since it would only treat the latter. Percutaneous coronary intervention would not change his symptoms given the nonobstructive nature of his coronary artery disease. Symptomatic relief of this patient requires repair/replacement of the mitral valve as well as septal reduction therapy.

9. Disease 1 = b, Disease 2 = a, Disease 3 = c

Please refer to Table 7.1 in the main text.

10. Disease 1 = d, Disease 2 = a, Disease 3 = b

Please refer to Fig. 7.12 in the main text.

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Assessment of Syncope

8

Nickolaos Michelakis and Todd J. Cohen

Key Points

- Hypertrophic cardiomyopathy is associated with syncope via three major mechanisms: arrhythmias, left ventricular outflow tract obstruction, and autonomic dysfunction.
- Major risk factors for sudden cardiac arrest in hypertrophic cardiomyopathy include an area of thickened myocardium exceeding 3 cm, sustained ventricular tachycardia, a family history of sudden cardiac arrest in someone <50 years of age with a known diagnosis of hypertrophic cardiomyopathy, a history of recurrent, unexplained syncope, and finally a history of cardiac arrest.
- Workup of syncope includes a history, a physical exam, a baseline ECG, and a noninvasive testing; invasive testing may be necessary in a subset of patients.
- Mainstay of therapy includes beta-1-selective blockade for those with obstructive physiology, implantable cardioverter-defibrillator implantation for high-risk SCD candidates or those with documented malignant arrhythmias, and cardiac catheter ablation for those with recurrent and refractory, symptomatic ventricular tachycardia.

Introduction

Syncope (from the Greek: "syn," thoroughly, and "koptein," to cut.) can be defined as a complete loss of consciousness. It is not an infrequent condition in hypertrophic cardiomyopathy, and indeed the anatomic structure, function, and geometry of the heart in patients with hypertrophic cardiomyopathy may result in the propensity to syncopize. In particular, myocardial disarray in hypertrophic cardiomyopathy, neurologic innervation of the myocardium, and/or anatomy of left ventricular outflow tract obstruction may all contribute to the development of syncope and should be fully evaluated.

This chapter reviews three distinct, and potentially interrelated, etiologies of syncope in patients with hypertrophic cardiomyopathy: arrhythmogenic causes (bradycardia and tachycardia), left ventricular outflow tract obstruction, and neurocardiogenic causes, including autonomic dysfunction. The chapter discusses the etiology, presentation, and pathophysiology of these etiologies, focusing on the first two as they are the most common. The chapter also reviews an approach to the workup and recommended treatment of syncope in the affected population.

Arrhythmogenic Causes

Arrhythmogenic causes of syncope in patients with hypertrophic cardiomyopathy may be the most life-threatening but fortunately the most amenable to therapy. The presentation of this type of syncope may be either without warning signs or with premonitory symptoms of lightheadedness and dizziness (pre-syncope), syncope, and/or palpitations. Occasionally, patients may feel other hemodynamic effects of arrhythmia and complain of chest pressure and shortness of breath. Table 8.1 lists the arrhythmias which may be potential causes of syncope in hypertrophic cardiomyopathy: (1) bradycardias, such as sinus node, AV nodal disease, and other forms of conduction disorders (including disease in the His-Purkinje system), and (2) tachycardias, including supraventricular and ventricular forms. Supraventricular tachycardia (such as atrial fibrillation) may be highly symptomatic and, in those with significant left ventricular outflow tract obstruction, may result in syncope either from a rapid ventricular response or a loss of atrial kick. Non-sustained ventricular tachycardia in and of itself may be a marker for sudden death but is oftentimes asymptomatic in this

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Table 8.1 Arrhythmias contributing to syncope

1. Bradycardia
(a) Conduction disease
(b) Sinus node dysfunction
(c) Tachy-Brady syndrome
2. Tachycardias
(a) Atrial fibrillation or other supraventricular tachycardia
(b) Ventricular tachycardia
(c) Ventricular fibrillation

Table 8.2 Traditional major risk factors for sudden cardiac death

1. Thickened myocardium >3 cm in any location
2. Family with history of sudden death in HCM patient <40–50 years of age
3. Sustained ventricular tachycardia
4. Ventricular fibrillation/cardiac arrest
5. History of recurrent, unexplained, and recent syncope

population. Non-sustained ventricular tachyarrhythmias might also be symptomatic and result in lightheadedness and dizziness (pre-syncope), especially when prolonged or when there is profound diastolic dysfunction.

When identified, non-sustained ventricular tachycardia and/or ventricular tachycardia may be harbingers of subsequent sudden cardiac death ("SCD"), especially when combined with other SCD risk factors. Sustained ventricular tachycardia in particular may be poorly tolerated due to an elevated rate and the associated loss of atrial component to late diastolic filling and also may degenerate to ventricular fibrillation and sudden cardiac death. Fortunately, once ventricular tachycardia and/or a confluence of associated risk factors are identified, device-based treatment with an implantable defibrillator can effectively prevent sudden death.

The micro- and macroscopic anatomic substrate, together with the superimposed stress and strain of the hypertrophied myocardium's contraction, may predispose the affected population to arrhythmia and syncope. On a microscopic level, the substrate's inherent myocardial disarray may create the amount of differential electrical conduction (anisotropy) needed for bidirectional conduction and unidirectional block (a prerequisite for reentrant tachycardia). This anisotropy may be a basic requirement for a circus rhythm tachycardia or reentry in patients with hypertrophic cardiomyopathy. Reentry is a principal mechanism in both ventricular and supraventricular tachyarrhythmias.

Spirito and colleagues [1] have shown that the thicker myocardium in patients with hypertrophic cardiomyopathy, in particular left ventricular septal thickness of greater than 3 cm, places patients at a higher risk for sudden death, whether the thickness is a surrogate for the extent of disarray and potential for reentrant arrhythmias remains unknown, but scar density appears to track with thickness at least in some. In addition, several other markers may lead to an increased propensity to sudden death, including the presence of outflow tract obstruction. Thus, at a macroscopic level, the outflow tract obstruction makes a patient more susceptible to the hemodynamic consequences of arrhythmias that may be better tolerated in those with more normal hearts, while at the microscopic level both diastolic dysfunction and the propensity to reentrant arrhythmias are evident. Jensen et al. [2] and Orme et al. [3] have found that the treatment of hypertrophic cardiomyopathy with alcohol septal ablation and/or surgical septal myectomy may result in a reduction in either sudden death (in the former) or syncope (in the latter). This shows the interrelationship between myocardial disarray, left ventricular outflow tract gradient, and arrhythmogenic causes of sudden death. Table 8.2 lists the traditional risk factors for sudden death in patients with hypertrophic cardiomyopathy.

Spirito and colleagues [4] investigated syncope and sudden death in over 1500 patients with hypertrophic cardiomyopathy. In this patient population, 40% had experienced syncope. The relative risk of sudden death in the population was 1.78. Importantly, a recent syncopal event occurring within 6 months was associated with a fivefold increased risk of sudden death as compared to those who did not experience syncope. Moreover, patients with distant syncopal episodes did not show an increased risk of sudden death. Importantly, syncope in and of itself is not a major risk factor; rather, refractory and unexplained syncope is a harbinger of sudden cardiac death. If the syncope cannot be explained by bradycardia, autonomic dysfunction, or outflow tract gradient, then malignant arrhythmia is the most likely etiology by exclusion and warrants implantable cardioverter-defibrillator placement.

Bradycardia as an etiology of syncope in patients with hypertrophic cardiomyopathy is relatively rare. Bradycardia may be due to excessive beta-blocker or other AV nodal blocking agents, particularly in elderly patients with some degree of degenerative conduction disease or in patients with atrial fibrillation with slow ventricular response; alternatively, conduction disease for any number of reasons is also possible, although it is a rare occurrence in this disease. Nonetheless, such bradyarrhythmias can potentiate syncope and necessitate treatment with a permanent pacemaker. In some patients, prior surgical myectomy or alcohol septal ablation may mitigate the occurrence of syncope from outflow tract obstruction but result in intermittent or permanent conduction disease and bradycardia-induced syncope instead. Such patients also benefit from permanent pacemaker placement, with resolution of syncope.

Left Ventricular Outflow Obstruction

Left ventricular outflow obstruction is a major cause of syncope in hypertrophic cardiomyopathy patients. The dynamic nature of obstruction may cause dizziness and syncope in

patients who are dehydrated or who are under physical stress. Physical stressors may include climbing stairs, rising from a seated position, or even walking briskly or running briefly from a standing position. Obese patients may complain of lightheadedness upon rapidly assuming an upright position. Certain medications may precipitate syncope in hypertrophic cardiomyopathy patients, especially those that either reduce preload and/or afterload. Angiotensin converting enzyme inhibitors, angiotensin-receptor inhibitors, and systemic vasodilators in particular can reduce the afterload. Drugs that vasodilate the systemic periphery include phosphodiesterase-5 inhibitors used for either erectile dysfunction or pulmonary hypertension, such as sildenafil and tadalafil. Drugs that reduce the preload include venodilators such as nitroglycerin and loop diuretics such as furosemide.

Patients can also develop pre-syncopal or syncopal episodes in postprandial states. Splanchnic blood flow is augmented and may be greater after large meals. Blood is shunted to the gut to increase absorption of food content. This reduces available blood for left ventricular preload, effectively "dehydrating" the hypertrophic cardiomyopathy patient and promoting the development of syncope. Accordingly, postprandial exacerbation of dyspnea and/or syncope is a commonplace complaint among symptomatic obstructive patients with HCM.

The syncope related to a significant outflow tract gradient may be abrupt, without warning signs, similar to that traditionally ascribed to arrhythmogenic syncope. Although most patients notice premonitory symptoms, including a flushed sensation or lightheadedness, traumatic syncope can and does occur in the absence of an arrhythmia and should not automatically implicate an arrhythmogenic etiology.

Autonomic Dysfunction and Neurocardiogenic Syncope

The autonomic nervous system consists of myelinated parasympathetic and unmyelinated sympathetic nerve fibers innervating the myocardium. Stretch receptors present in the carotid bodies and aortic arch sense fluctuations in blood pressure on a beat-to-beat basis, and the response to these fluctuations leads to the regulation of the heart rate and peripheral vascular resistance, known as the baroreceptor reflex [5]. Delicate control of blood pressure and heart rate are dependent on the baroreceptor reflex function. The baroreceptor reflex mechanisms involve the integration of afferent signals from the carotid baroreceptors (via the glossopharyngeal nerve) and the aortic arch baroreceptors, as well as the left ventricular mechanoreceptors (via the vagus nerve), which sense changes in preload [6]. The central nervous system integrates the afferent mechanical stretch information and then responds with efferent flow to the heart and peripheral vessels [7]. These relationships are depicted in Fig. 8.1.

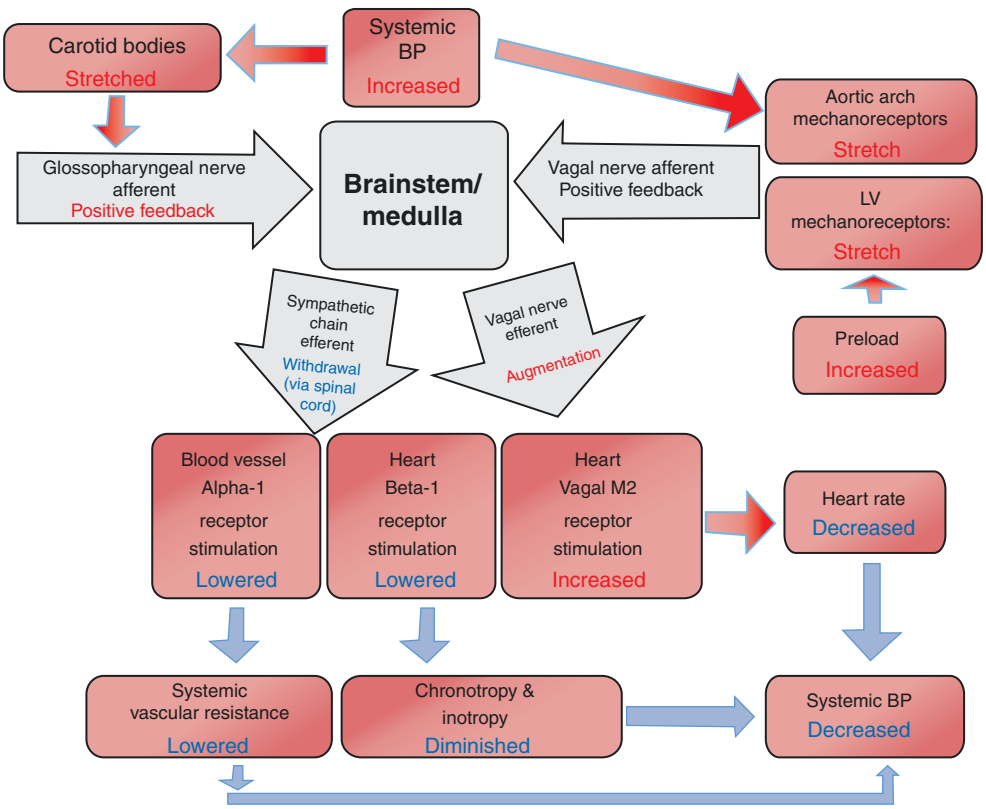

Fig. 8.1 Normal individual profile

These efferent signals flow along the vagus and sympathetic nerves, innervating the SA and AV nodes, as well as the atrial and ventricular myocardium. The sympathetic efferent flow to the arterial resistance and venous capacitance vessels adjusts the peripheral vascular tone according to the prevailing extent of baroreceptor stretch. For example, with increased carotid baroreceptor and left ventricular mechanoreceptor stretch, there is decreased peripheral vascular tone, thereby maintaining hemodynamic homeostasis.

In general, activation of the baroreceptor reflex leads to withdrawal of sympathetic tone and prolongs ventricular repolarization and refractoriness [8]. There is decreased sympathetic efferent flow to the peripheral vascular smooth muscle (alpha-mediated vasoconstriction) and cardiac tissue (beta-1-mediated tachycardia), thereby exerting a negative feedback effect on the hemodynamic status, i.e., decrease in systemic vascular resistance and decrease in heart rate [9].

The distribution of autonomic fibers highlights the heterogeneity of autonomic tone in the heart, both from apex-to-base and transmurally, from epicardium to endocardium. When viewed from base to apex, the sympathetic fibers run along the subepicardial surface of the left ventricle. The parasympathetic fibers, however, start subepicardially at the left ventricular base, course toward the subendocardial surface at the left ventricular base, and then continue along the subendocardial surface to terminate in the left ventricular apex [10]. This autonomic nervous system distribution underscores the importance of vagal tone in the subendocardial region of the left ventricular outflow tract, located at the septal base of the left ventricle.

In hypertrophic cardiomyopathy patients, the afferent limb of the baroreflex mechanism may be defective, as evidenced by a dampened forearm vascular resistance, which measures the dampened alpha-mediated vasoconstriction response to reduced left ventricular preload [6] (see Fig. 8.2). The impaired afferent flow from the left ventricular mechanoreceptors to the brainstem may be secondary to the disorganized myocyte arrangement characteristic of patients with hypertrophic cardiomyopathy. With increased left ventricular preload and left ventricular outflow tract obstruction, the left ventricular mechanoreceptors are stimulated, but they do not send vagal afferent signals to the brain stem. Concurrently, the aortic arch and carotid bodies are not stretched due to the overall reduced stroke volume from the left ventricular outflow tract obstruction. This leads to an overall sustained sympathetic tone to the vascular alpha-1 and cardiac beta-1 receptors, along with a lack of vagal tone augmentation to the left ventricular basal septal subepicardial and subendocardial surfaces. The overall effect is heightened sympathetic tone to the left ventricular myocardium, causing an augmented inotropic and chronotropic left ventricular response. This

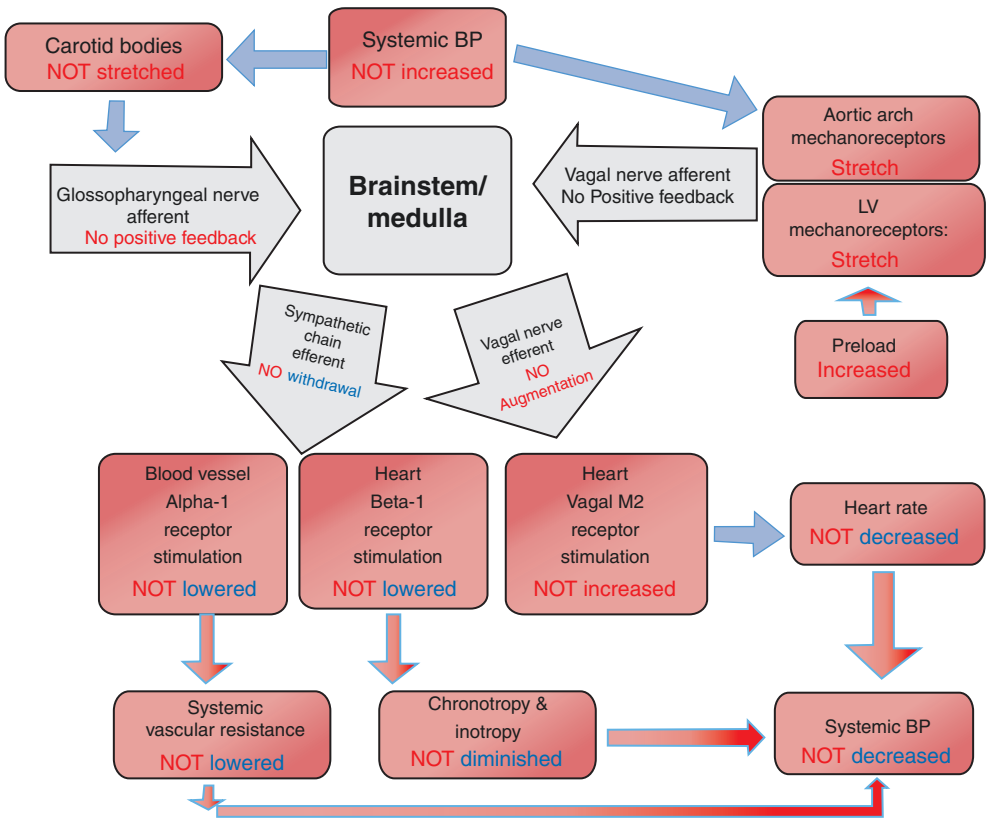

Fig. 8.2 HCM patient profile

leads to an exacerbation of the left ventricular outflow tract obstruction and perpetuation of the fall in cardiac output characteristically seen in hypertrophic cardiomyopathy patients.

Prasad and colleagues [11] have shown that approximately a third of patients with hypertrophic cardiomyopathy have an abnormal blood pressure response during peak exercise. This has been attributed to an exaggerated decrease in the systemic vascular resistance as well as the development of outflow tract obstruction in some. They attributed the former to an abnormality in the activation of mechanoreceptor C-fibers found in the left ventricle. More recently, they have implicated this mechanism as a potential cause for syncope in patients with hypertrophic cardiomyopathy and a risk factor for sudden cardiac death in some patients. They examined a total of 29 patients and found vascular instability as a cause of syncope or pre-syncope in 8 of the 18 patients who reported symptomatic impairment of consciousness (syncope or pre-syncope).

Syncope Workup in Hypertrophic Cardiomyopathy

The workup of syncope in hypertrophic cardiomyopathy is very similar to that of syncope in general (see Table 8.3). It begins with a history, paying attention to the type of presentation, the presence of premonitory symptoms, and the abruptness of the presentation. Patients with hypertrophic cardiomyopathy may have abrupt syncope, frequently leading to trauma, regardless of the underlying etiology, and presumably because of the interplay and potentiation of multiple potential mechanisms once the cycle begins. This is unlike the presentation in the general population, where traumatic syncope is almost always due to brady- or tachyarrhythmias. Palpitations and their association to lightheadedness or dizziness (pre-syncope) may still indicate an arrhythmogenic cause, however. In contrast, a more gradual, somewhat posturally related syncopal presentation may tend more toward neurocardiogenic syncope and/or autonomic dysfunction. Syncope related to dehydration, non-compliance with medications, or new medications (especially vasodilators) may lead to exacerbation of the pre-existing left ventricular outflow obstruction physiology as the causative mechanism. And, finally, syncope on exertion may be due to any of the three mechanisms, outflow tract obstruction, arrhythmia, or autonomic dysfunction.

Table 8.3 Syncope workup

1. History
2. Physical exam
3. ECG
4. Noninvasive tests
(a) Holter monitor
(b) Event/loop recorder
(c) Echocardiogram
(d) Exercise stress test
5. Other imaging studies, i.e., cardiac MRI, coronary CT angiography
6. Invasive testing
(a) Cardiac catheterization
(b) Electrophysiology testing
(c) Implantable loop recorder (ILR)

After a thorough history, a complete physical examination should be performed. Patients may often have the typical physiologic findings of hypertrophic cardiomyopathy, and examination with and without Valsalva is often useful to elicit the outflow tract physiology. An S4 gallop may further implicate diastolic dysfunction. An electrocardiogram may be helpful with specific attention to a long rhythm strip, looking for evidence of heart block and/or supraventricular/ventricular arrhythmias.

A noninvasive workup of syncope asks whether LVOT obstruction is present. Evaluation of the cardiac substrate by two-dimensional echocardiography includes assessment of the degree of myocardial thickness, the left ventricular cavity dimensions, and the presence of outflow tract obstruction. The degree of provoked outflow tract obstruction could also be identified before and after the Valsalva maneuver, while 2D echocardiography images are obtained. Alternatively, stress echocardiography may be utilized to elicit obstruction. Cardiac MRI imaging may be useful in evaluating the scar location/burden and thickness of the myocardium, as well as look for other potential anatomic causes of obstruction, such as supravalvar and valvar aortic stenosis (or membranes). Coronary angiography may be useful in confirming the absence of coronary artery disease and the level or severity of outflow tract obstruction. The Brockenbrough-Braunwald-Morrow sign is elicited by provoking a premature ventricular contraction to produce a diminished pulse pressure in the next contraction, thereby assessing if the LVOT obstruction exceeds 30 mmHg or is severe.

When LVOT obstruction is absent and electrocardiographic monitoring for arrhythmias has not yielded any cause for the syncope, then stress testing is indicated to both further rule out obstructive physiology and help determine an abnormal blood pressure response that might indicate a primary autonomic dysfunction issue. Assessment of the potential for LVOT obstruction with activity can be done utilizing exercise/treadmill stress echocardiography. Symptoms may not be present at rest, so elicitation of the obstructive symptoms with treadmill stress testing can help elicit these symptoms. Treadmill testing is well suited to determine the exertional LVOT gradients as well as any occurrence of

abnormal blood pressure response (due to underlying autonomic dysfunction or potentiated obstruction) during exercise. Arrhythmogenic causes can also be evaluated during exercise and/or immediately in recovery. A myocardial perfusion exercise stress test may also be useful in defining the presentation of syncope as it is helpful to rule out ischemia in this population, which although a rare cause of syncope may be the culprit in some. Of note, perfusion defects in the absence of epicardial coronary disease is also seen in hypertrophic cardiomyopathy, and therefore CT angiography or cardiac catheterization may be preferred if coronary disease is suspected.

If the LVOT obstructs, then the appropriate therapy should be implemented. This includes hydration and lifestyle modification to prevent abrupt drops in preload, which can worsen the LVOT obstruction. Use of long-acting beta-1-selective blockers as first-line agents is indicated. Second- and third-tier choices for medical therapy include non-dihydropyridine calcium-channel blockers and disopyramide. Finally, surgical myectomy or alcohol septal ablation should be considered in severely symptomatic patients. Importantly, patients with recurrent, refractory syncope due to left ventricular outflow tract obstruction may be candidates for invasive therapies, either surgical myectomy or alcohol septal ablation, even when they do not meet NYHA Class 3 or 4 symptoms of heart failure. Elderly patients may also be candidates for a trial of dual-chamber pacing to reduce outflow tract obstruction, especially when the use of such devices will allow higher doses of beta-blocker therapy.

In parallel with asking the question whether LVOT obstruction is present, loop recorder monitoring for arrhythmias should be undertaken. If a bradyarrhythmia is present, which is determined to be a contributing factor to syncope, then a pacemaker is indicated. If risk factors for sudden cardiac arrest are present in such a patient, especially if NSVT is also found, then an ICD should be implanted instead. If a tachyarrhythmia is present, its chamber origin should be determined first. SVTs and AF warrant rate control, anticoagulation (for AF or Aflutter), and rhythm control if rate control does not ensure adequate diastolic filling time of the LV. VT warrants ICD implantation, although recurrent VT episodes necessitate anti-arrhythmic therapy and/or possibly catheter-based ablation of the VT foci in addition to ICD implantation.

An implantable loop recorder (ILR) is a subcutaneously implanted version of an external loop recorder. It is a leadless device, with a durable battery life that can approach 3 years [12]. These devices can detect bradyarrhythmias, as well as detect tachyarrhythmias based on the QRS morphology and coupling interval between the sinus beat and the subsequent premature beat. HCM patients can experience a high incidence of atrial fibrillation (AF), which can be subclinical if overt symptoms are not apparent or the arrhythmia is not detected objectively [13]. The ILRs may be able to detect AF in HCM patients, which provide an attractive option to screen asymptomatic individuals at risk for rapid ventricular response and resultant syncope. The ILR can also be used to assess the AF recurrence rate following AF ablation [14].

A downside to the use of ILRs is their limited storage potential, which can lead to overwriting of valuable recordings and, thus, missed diagnostic information [15]. This sequela can be mitigated by interrogating the ILR on a frequent basis, either remotely or during an office visit.

Nevertheless, implantation of an ILR in an HCM patient with unexplained syncope can offer a reasonable diagnostic tool for the clinician to determine under what activity and circadian circumstances the individual experiences tachy- and bradyarrhythmias, as well as discern the type of tachyarrhythmias present that can precipitate a rapid ventricular response with syncope.

If no arrhythmia is found during routine 30-day external loop recorder or implantable loop recorder monitoring, and the patient continues to have syncope refractory to medications, then the LVOT should be reassessed for obstruction if none has been previously determined to be present. This may warrant invasive testing such as right and left heart catheterization in the awake patient (no sedation). If obstruction is finally determined, the above-described approach for managing LVOT obstruction should be pursued. If there is no LVOT obstruction, then a tilt-table test and/or repeat exercise stress testing with the patient off of their medications may help in determining the presence (or absence) of autonomic dysfunction. With exercise and tilt-table testing, the periphery vasodilates, so maintenance of blood pressure depends on an adequate preload, augmented contractility (without obstruction), and heart rate response.

Adequate hydration and lifestyle modification are necessary to prevent autonomic dysfunction-mediated and LVOT obstruction-mediated syncope. Medications such as beta-blockers with intrinsic sympathomimetic activity may help prevent systemic vasodilatation during tachycardic episodes. Midodrine may also be useful to expand volume and increase blood pressure. If syncope recurs despite adequate hydration, lifestyle modification, and appropriate medication administration, an ICD is indicated. Although this does not treat autonomic dysfunction, the theory is that an arrhythmic focus may still be at play in such patients and simply not uncovered. Given the high risk of SCD in such patients with refractory recurrent syncope and a negative workup, ICD implantation is indicated by consensus opinion. A systematic process to syncope evaluation and treatment in HCM patients is shown in Fig. 8.3a, b.

The Role of Electrophysiology Testing

The role for invasive electrophysiology testing in hypertrophic cardiomyopathy is not entirely clear. In particular, the finding of inducible ventricular arrhythmias may be nonspecific in this population and does not automatically warrant ICD implantation. However, electrophysiologic testing is useful in confirming the presence or absence of significant conduction disease. It can also be helpful at ruling out supraventricular etiologies that may be treatable via catheter ablation. This includes a variety of paroxysmal supraventricular tachycardias such as atrioventricular reentry (i.e., Wolff-Parkinson-White syndrome) or atrioventricular nodal reentry. In addition, atrial tachycardia and atrial flutter might be highly symptomatic in this population but also curative via catheter ablation. The presence or absence of inducible ventricular tachyarrhythmias is not as helpful in this population as in other populations with ischemic cardiomyopathy/coronary artery diseases. In addition, a Holter monitor may be useful, but the implantation of an implantable cardiac monitor and/or implantable loop recorder may be particularly helpful by providing long-term monitoring in order to elucidate the true etiology of syncope.

Treatment

The treatment of syncope depends on the reported etiology (see Table 8.4). It is critical to identify cardiac arrhythmogenic causes in order to treat them accordingly. If the patient presents with cardiac arrest and/or documented sustained ventricular tachycardia and ventricular fibrillation, the treatment must include an implantable cardioverter-defibrillator. If the patient has risk factors placing the patient at high risk for sudden death, such as recurrent, unexplained syncope after a thorough evaluation or severe thickness >3 cm, an implantable cardioverter-defibrillator must also be considered. The utility of the electrophysiology study in determining and ruling in or out inducible sustained ventricular arrhythmias is less useful in this population and therefore given a Class 3 indication in the 2011 ACC/AHA Guidelines for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy [16]. If the patient has the risk factors outlined in Table 8.2, an implantable cardioverter-defibrillator may be useful. However, its implantation might not prevent the exact etiology of syncope which brought the patient to the physician's attention in the first place. However, recurrent syncope with an ICD showing no arrhythmias is a

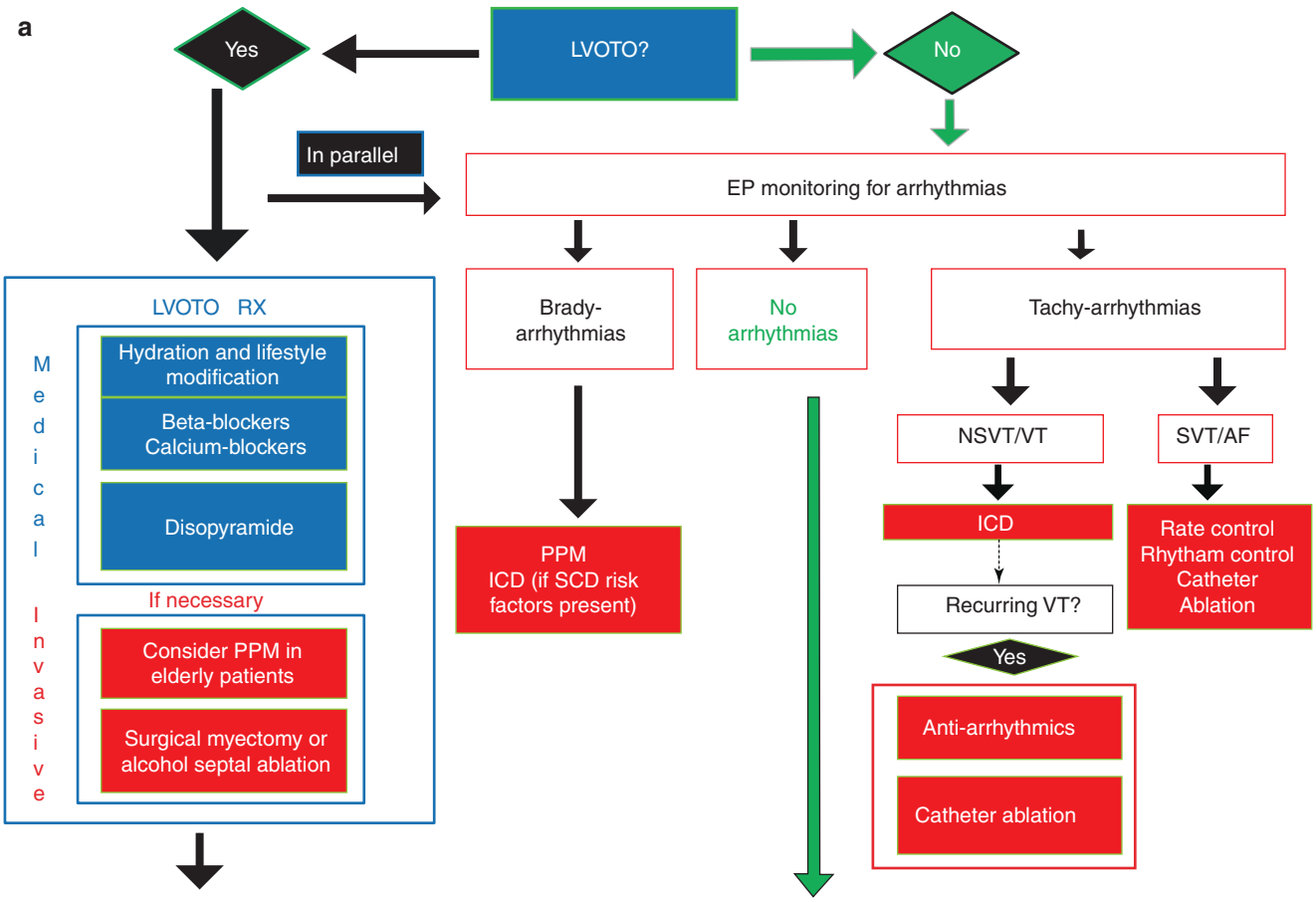

Fig. 8.3 (**a**, **b**) Syncope treatment

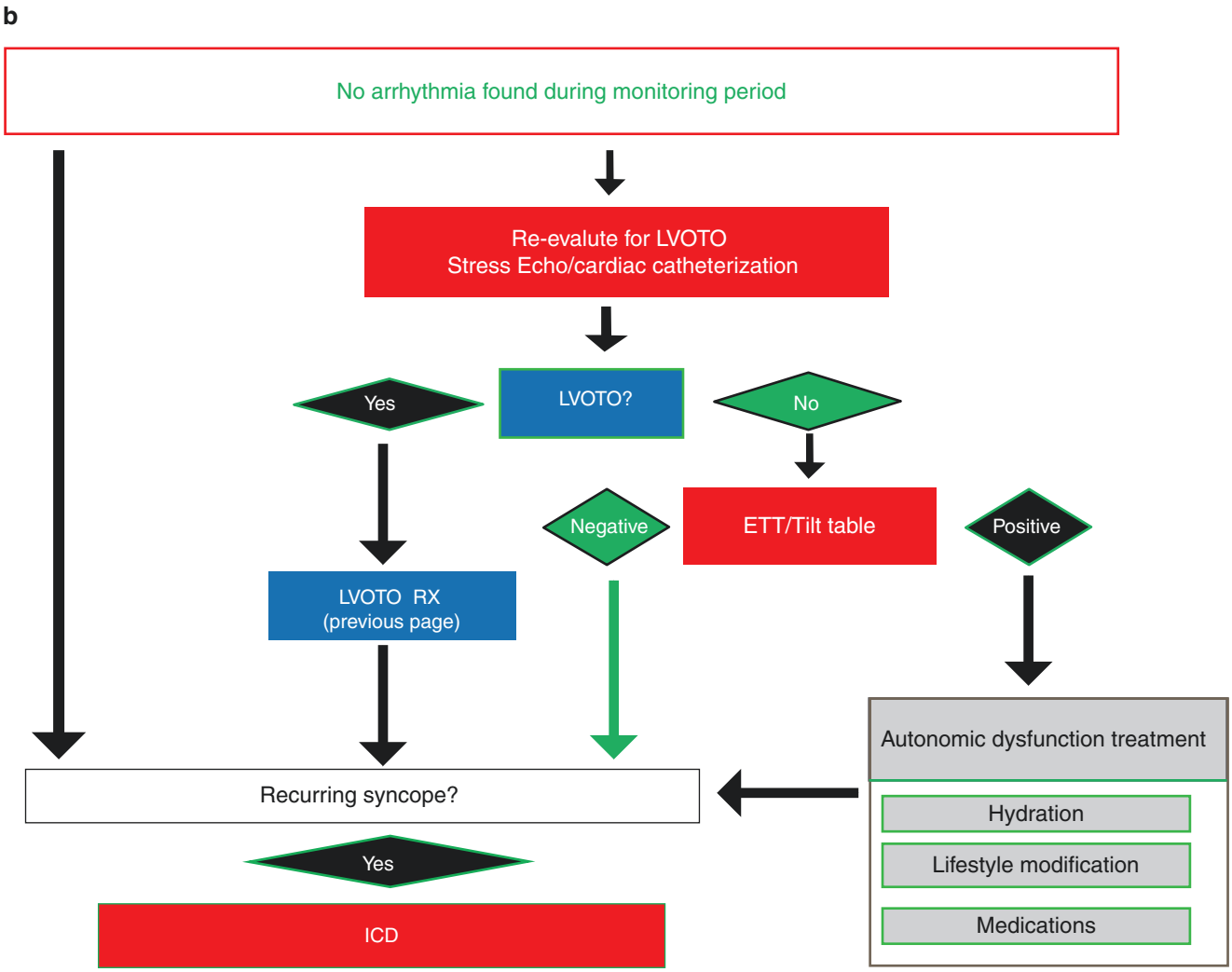

Fig. 8.3 (Continued)

Table 8.4 Treatments

1. Lifestyle modification
2. Pharmacologic
3. Cardiac electrophysiologic ablation
4. Coronary revascularization
5. Invasive therapies for outflow tract obstruction
(a) Surgical myectomy
(b) Alcohol septal ablation
6. Implantable devices
(a) Dual-chamber pacing
(b) Antitachycardiac devices (ICDs)
(c) Subcutaneous ICDs

powerful sign that outflow tract gradient or autonomic dysfunction is the etiology. Certain patients who have symptomatic supraventricular arrhythmia such as atrial fibrillation and/or atrial flutter may benefit from pharmacologic therapy, such as amiodarone, disopyramide, or metoprolol succinate. In addition, atrial fibrillation ablation therapy or general cardiac ablation therapy may be useful in treating the supraventricular arrhythmias in this population.

With respect to neurocardiogenic syncope and/or autonomic dysfunction, treating the patient with significant hydration and support/compression stockings may be useful. These are useful measures in all patients with hypertrophic cardiomyopathy who are euvolemic and especially those with outflow tract obstructive physiology. Use of metoprolol succinate twice daily prolongs the diastolic filling time and increases the left ventricular preload, while midodrine may be useful in a subset of patients. An implantable loop recorder can be useful in patients who are not at high risk for sudden death and in whom the etiology of recurrent syncope remains a mystery. This relatively innocuous subcutaneous implantable device can be left in place for up to 3 years and can help rule out cardiac arrhythmias as an etiology for the syncope.

The treatment of left ventricular outflow obstruction is twofold: medical and invasive. Lifestyle modification to

limit dehydration is important: decreased alcohol intake and decreased caffeine consumption. Beta-1 selective blockers can mitigate the left ventricular outflow obstruction by prolonging the diastolic filling time and reducing contractility and are the first-line pharmacotherapy. Drugs such as dihydropyridine calcium-channel blockers should be avoided as they can reduce the afterload. Verapamil, a non-dihydropyridine calcium-channel blocker, has been used for its negative inotropic, negative chronotropic, and negative dromotropic effects. At high doses, however, systemic afterload reduction may negate the beneficial effect of reduced heart rate and reduced contractility of the left ventricle.

Disopyramide has been used with variable efficacy in reducing the left ventricular outflow obstruction. It is not considered a first-line agent in hypertrophic cardiomyopathy patients with left ventricular outflow obstruction, however, and must be combined with other AV nodal blocking agents. Importantly, however, disopyramide may reduce both resting and provocable gradients in a subset of patients and thus may be useful. More information on the treatment of outflow tract obstruction is found in the Medical Therapy chapter.

When medical therapy does not successfully improve the left ventricular outflow obstruction and recurrent syncope remains, and when the left ventricular outflow obstruction exceeds 50 mmHg at rest or on provocation, surgical or percutaneous alleviation of the obstruction may be considered regardless of the NYHA heart failure class. This is especially important for patients who continue to pass out despite the absence of significant atrial or ventricular arrhythmias which could explain the syncopal episodes. This subset of patients often demonstrates the interplay between left ventricular outflow obstruction and neurocardiogenic causes. Elimination of the left ventricular outflow obstruction gradient effectively mitigates the interplay between obstruction and the neurocardiogenic-mediated mechanisms for syncope.

Therefore, recurrent non-arrhythmic (due to outflow tract obstruction) syncope despite medical therapy in patients with hypertrophic cardiomyopathy is an indication for advanced invasive therapies despite lack of significant NYHA Class 3 or 4 heart failure symptoms.

The efficacy of dual-chamber pacing has been a controversial topic in the treatment of hypertrophic cardiomyopathy. Studies have shown disparate results regarding the efficacy in consistently reducing the left ventricular outflow tract obstruction gradient and improving symptoms. In theory, pacing the right ventricle alone with its associated abnormal myocardial depolarization can result in less isotropy and a decrease in gradient. The entire impact of dual-chamber pacing is at best controversial but may be helpful on a case-by-case basis. Most recently, Yue-Cheng and colleagues [17] presented the results of their long-term follow-up study of dual-chamber pacing in those with hypertrophic obstructive cardiomyopathy. They closely followed 37 patients for up to 4 years and specifically found a benefit from this kind of therapy which translated into what they called improved "cardiac structural reconstruction." However, it is important to note that dual-chamber pacing parameters needed to be adjusted (i.e., AV delay and pacing rate) in order to achieve a very high rate of ventricular pacing in this study. If pacing is to be employed, every opportunity should be taken to ensure that the ventricular pacing feature is utilized almost all of the time.

The subcutaneous ICD was developed to alleviate the safety concerns inherent in transvenous ICDs, such as tricuspid regurgitation, bacterial infection, and venous thromboembolism [18, 19]. The unique features of the subcutaneous ICDs are its parasternal position and absence of transvenous indwelling leads. Considering its unique alternative to help prevent sudden cardiac arrest in hypertrophic cardiomyopathy patients, the subcutaneous ICD requires higher defibrillation energy versus conventional transvenous ICDs [20]. It also can shock inappropriately in the setting of T wave oversensing and supraventricular tachycardias with rapid ventricular response [21].

Therapies are limited to shocking with subcutaneous ICDs, as antitachycardia pacing cannot be employed with this type of device. Considering the heightened frequency of non-sustained ventricular tachycardia in HCM patients [22], as well as the potential for complete heart block in patients with pre-existing bundle branch block who undergo an alcohol septal ablation or septal myectomy [23], subcutaneous ICDs may not provide the optimal solution for prevention of sudden cardiac arrest in these vulnerable patients.

The decision to proceed with advanced invasive therapy to alleviate the left ventricular outflow obstruction has to involve a detailed discussion of the advantages and disadvantages of both surgical and percutaneous approaches to therapy. Factors such as degree of septal hypertrophy, anterior displacement of the anterior mitral valve papillary muscle, chordal tendon, and anterior mitral valve leaflet redundancy extent will be taken into consideration in the joint decision between patient and clinician in determining the optimal course of advanced therapy. The significant experience of the operator with surgical myectomy or alcohol septal ablation plays an obvious role in determining the safer choice of therapy for the patient. The patient's age and comorbid conditions will also determine the patient's suitability for either surgical myectomy or alcohol septal ablation. Finally, the patient's preference for advanced invasive therapy may trump all other considerations for alleviating the patient's left ventricular outflow obstruction. More information on the choice of invasive therapy for outflow tract obstruction may be found in the chapter on "Indications for and Individualization of Septal Reduction Therapy."

Conclusions

Arrhythmogenic, neurocardiogenic syncope/autonomic dysfunction and left ventricular outflow tract obstruction etiologies for syncope in hypertrophic cardiomyopathy have been described. In reality, there is interplay between all three of these etiologies, with one or two dominating in any given hypertrophic cardiomyopathy patient with syncope. Arrhythmogenic causes tend to be associated with a worse prognosis, especially if left untreated. Metoprolol succinate may attenuate the risk for ventricular arrhythmias, although this has not been proven, but does prolong the diastolic filling time, reduce contractility, and re-upregulate the postsynaptic myocardial beta-1 adrenoceptor density. Medications also reduce left ventricular outflow tract obstruction and thus improve syncope in patients with significant recurrent obstructive physiology.

Treatment with implantable devices is reserved for patients with documented ventricular arrhythmias, those who meet high-risk SCD criteria, and those with recurrent syncope despite optimal control of outflow tract obstruction. When obstruction is felt to be the dominating lesion, augmented medications, permanent pacemaker implantation, and/or other invasive therapies may be required, with pacemaker therapy typically reserved for elderly patients. There is no specific treatment for neurocardiogenic syncope, which is the rarest of the three etiologies for syncope to exist in isolation; thus, patients with autonomic dysfunction may be best treated by hydration and elimination of outflow tract obstruction. When no defined etiology can be found, and recurrent syncope occurs despite optimal medical management, patients should proceed to defibrillator for primary prevention.

Clinical Pearls

- Patients with left ventricular outflow tract obstruction gradients exceeding 30 mmHg at rest or with provocation should be kept hydrated, unless signs of hypervolemia are present, and avoid dehydrating agents as well as agents that increase contractility.
- Preload- and afterload-reducing drugs should be avoided whenever possible in hypertrophic cardiomyopathy patients with outflow tract obstruction physiology.
- Patients should be screened for high-risk features predisposing them to sudden cardiac arrest and referred early for ICD implantation; syncope is a major risk factor for sudden cardiac death if recurrent and unexplained, despite optimal medical therapy.
- Those with symptomatic left ventricular outflow tract obstruction and recurrent syncope should be considered for alleviation of the obstruction, either with alcohol septal ablation or with septal myectomy, if optimal medical therapy does not control symptoms.
- Syncope in hypertrophic cardiomyopathy is frequently traumatic and does not in and of itself implicate an arrhythmogenic cause; outflow tract obstruction may lead to traumatic syncope in a subset of patients.

Questions

1. The etiology of syncope in patients with hypertrophic cardiomyopathy is:
   A. Arrhythmogenic causes (bradycardia, tachycardia)
   B. Left ventricular outflow tract obstruction
   C. Neurocardiogenic causes
   D. All of the above
   E. None of the above

Answer: D. Arrhythmias, both bradycardic and tachycardic, and originating either in the atria or ventricle, oftentimes contribute to syncope. Outflow tract obstruction is also a common cause of syncope and may be traumatic. Neurocardiogenic syncope, while rarest of the three, is also seen in HCM and usually interacts with obstructive physiology.

2. Bradycardic arrhythmia(s) that can contribute to syncope include:
   A. Conduction disease
   B. Sinus node dysfunction
   C. Tachy-brady syndrome
   D. All of the above
   E. None of the above

Answer: D. Conduction disease, sinus node dysfunction, and tachy-brady syndrome are all seen as potential contributors to syncope. Relative bradycardia due to medication-induced chronotropic incompetence may also contribute.

3. Tachycardic arrhythmia(s) that can contribute to syncope include:
   A. Atrial fibrillation
   B. Ventricular tachycardia
   C. Ventricular fibrillation
   D. All of the above
   E. None of the above

Answer: D. Atrial fibrillation and VT are common causes of syncope in patients with HCM. Primary VF is also seen. Ventricular arrhythmias are often post-exercise but also may be seen under resting conditions.

4. Major risk factor(s) for sudden cardiac death in HCM patients is:
   A. Thickened myocardium >3 cm in any location
   B. Family with history of sudden death in HCM patient <40–50 years of age
   C. Sustained ventricular tachycardia, ventricular fibrillation, and/or cardiac arrest
   D. History of recurrent, unexplained, and recent syncope
   E. All of the above

Answer: E. All of these are traditional risk factors for sudden cardiac death, which warrant ICD placement. In addition, NSVT and abnormal blood pressure response were previously considered major risk factors but have since been downgraded to risk modifiers.

5. Left ventricular outflow tract obstruction can be caused by:
   A. Dehydration and sudden orthostasis
   B. Systemic vasodilators, including ACE inhibitors and angiotensin-receptor blockers
   C. Phosphodiesterase-5 inhibitors
   D. Venodilators, including nitroglycerin and loop diuretics
   E. All of the above

Answer: E. Medications or maneuvers that reduce preload or afterload augment obstruction. In addition, increased contractility through adrenergic tone can augment obstruction, prompting significant lifestyle adjustment in patients with HCM and obstructive physiology.

6. The baroreceptor reflex regulates:
   A. Peripheral vascular resistance
   B. Blood pressure
   C. Heart rate
   D. All of the above
   E. None of the above

Answer: D. All of the above are regulated by the baroreceptor reflex.

7. What does activation of the baroreceptor reflex cause?
   A. Activation of the sympathetic tone and shortening of the ventricular repolarization and refractoriness.
   B. Withdrawal of the sympathetic tone and prolongation of the ventricular repolarization and refractoriness.
   C. Increased sympathetic efferent flow to the peripheral vascular smooth muscle and cardiac tissue.
   D. Increase in systemic vascular resistance
   E. Increase in heart rate.

Answer: B. The baroreceptor reflex

results in withdrawal of the sympathetic tone and prolongation of the ventricular repolarization and refractoriness (Fig. 8.1).

8. In HCM, which of the following alterations in the baroreceptor mechanism occur(s):
   A. Defective afferent limb of the baroreflex mechanism
   B. Dampened forearm vascular resistance
   C. Impaired afferent flow from LV mechanoreceptors due to disorganized myocyte arrangement
   D. Reduced stretching of the aortic arch and carotid bodies mechanoreceptors
   E. All of the above

Answer: E. All of the above can be seen in HCM patients.

9. Syncope workup in HCM entails:
   A. History, physical, and ECG
   B. Holter monitor, event or loop recorder
   C. Echocardiogram
   D. Exercise stress test
   E. All of the above

Answer: E. Syncope workup in patients with HCM is complex and entails a focused history and physical examination; EKG and echocardiography; extended electrocardiographic monitoring for arrhythmias, which might include an internal loopr recorder; and exercise stress test to rule out ischemia and obstructive physiology. Tilt table testing and invasive hemodynamics may be needed in a subset of patients, as well as advanced imaging.

10. Echocardiography of the HCM patient can see:
    A. The degree of myocardial thickness
    B. The LV cavity dimensions
    C. The LVOT gradients at rest/baseline
    D. The LVOT gradients following Valsalva maneuver
    E. All of the above

Answer: E. Echocardiography is the main imaging modality in HCM and can assess all of these features. The assessment of maximal wall thickness and the presence or absence of obstruction are key factors in the assessment of syncope.

11. The maneuver that elicits a diminished pulse pressure following a PVC is known as:
    A. Bezold-Jarisch reflex
    B. Bainbridge reflex
    C. Ergoreflex
    D. Brockenbrough-Braunwald-morrow sign
    E. None of the above

Answer: D. This maneuver increases obstruction through heightened contractility in the post-PVC beat, resulting in a drop in stroke volume recorded as a diminished pulse pressure.

12. Significant obstruction across the LVOT at rest is defined as:
    A. >20 mmHg
    B. >30 mmHg
    C. >50 mmHg
    D. >100 mmHg
    E. >200 mmHg

Answer: B. 30 mmHg is the threshold for the diagnosis of obstructive HCM. Gradients less than 30 mmHg can be seen normal in hearts under states of dehydration and/or hypercontractility.

13. If significant LVOT obstruction is present at rest, the first medication that should be prescribed to reduce the resting obstruction is:
    A. Amiodarone
    B. Dipyridamole
    C. Long-acting beta-1-selective blocker
    D. Hydralazine
    E. Isosorbide

Answer: C. Beta Blockers are the mainstay therapy and first-line agents to relieve obstruction in patients with HCM. When these fail to control symptoms and obstruction optimally, disopyramide or non-dihidropyridine calcium-channel blockers may be added, with careful attention to the QTc in the former. Hydralazine and nitrates are contraindicated in obstructive physiology, while amiodarone has no role.

14. Pacemaker implantation causes the following effect on the LVOT gradient:
    A. Decreases at rest and with exercise
    B. Increases at rest and with exercise
    C. No change at rest nor with exercise
    D. No change at rest but decreases with exercise
    E. No change at rest but increases with exercise

Answer: A. On average, PPM placement with apical pacing of the RV causes a reduction in the LVOT gradient. However, randomized controlled trials did not produce objective improvements, and therefore PPM placement is not indicated routinely in patients with obstructive HCM. In rare patients, especially the elderly, PPM may be a good option to allow increased beta-blocker therapy or to avoid invasive septal reduction therapy.

15. An implantable loop recorder can be used to detect:
    A. Atrial fibrillation with rapid ventricular response
    B. Ventricular arrhythmias
    C. Bradyarrhythmias
    D. Asystole
    E. All of the above

Answer: E. ILRs can be used to detect any arrhythmias. Frequent interrogations can avoid overwriting of older information with newer information, due to limited device storage capacity.

16. The battery life of a ILR is:
    A. 1 year
    B. 2 years
    C. 3 years
    D. 4 years
    E. 5 years

Answer: C. ILRs usually last 3 years and then are explanted.

17. If LVOT obstruction is not present and no arrhythmias are present during the monitoring period, what test can be performed to re-evaluate for LVOT obstruction?
    A. Exercise stress echo, to assess for exertional LVOT obstruction and induction of exertion-related arrhythmias.
    B. Cardiac catheterization, to assess for inducible LVOT obstruction with the Brockenbrough-Braunwald-morrow maneuver.
    C. Cardiac MRI
    D. Both A. and B. options
    E. None of the above options

Answer: D. LVOT obstruction can be assessed via exercise echocardiography or via invasive hemodynamic testing. Both may be required in the patient in whom obstruction is highly suspected. Cardiac MRI, while it can indirectly suggest obstruction through visualization of turbulence in the outflow tract, cannot assess pressure gradients and therefore cannot confirm significant obstruction.

18. In addition to beta-1-selective blocker and disopyramide, what invasive options are available to treat HCM patients with syncope?
    A. Surgical myectomy
    B. Alcohol septal ablation
    C. Dual-chamber pacing with a permanent pacemaker
    D. Antitachycardia pacing of ventricular arrhythmias with an ICD
    E. All of the above

Answer: E. Depending on the etiology of syncope, all of these may be considerations.

19. At what LVOT obstruction gradient cutoff at rest or with provocation, are surgical or percutaneous alleviation options considered?
    A. >30 mmHg
    B. >50 mmHg
    C. >70 mmHg
    D. >100 mmHg
    E. >120 mmHg

Answer: B. LVOT obstruction of at least 50 mm hg is required prior to contemplation of septal reduction therapy.

20. Which safety concerns that are present in transvenous ICDs do subcutaneous ICDs alleviate?:
    A. Tricuspid regurgitation
    B. Bacterial infection
    C. Venous thromboembolism
    D. All of the above
    E. None of the above

Answer: D. There are several potential advantages to subcutaneous ICDs, including no interaction with the tricuspid valve, a markedly reduced infection rate, and avoidance of venous problems including thrombus formation. There are as well several weaknesses, including the inability to pace, potential for inappropriate shocks, and the larger current of energy required for defibrillation.

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Pediatric Diagnosis and Management

9

Steven D. Colan and Christa Miliaresis

Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
AED	Automated external defibrillator
CMR	Cardiac magnetic resonance
CPET	Cardiopulmonary exercise test
CPR	Cardiopulmonary resuscitation
DHE-MRI	Delayed hyper-enhancement on CMR
ECG	Electrocardiogram
ESC	European Society of Cardiology
FHCM	Familial hypertrophic cardiomyopathy
G + P–	Genotype positive, phenotype negative
HCM	Hypertrophic cardiomyopathy
ICD	Implantable cardioverter defibrillator
LV	Left ventricle
LVH	Left ventricular hypertrophy
NSVT	Non-sustained ventricular tachycardia
SCD	Sudden cardiac death
TDI	Tissue Doppler imaging
VCO_2	CO_2 output
VE	Minute ventilation
VO_2	Oxygen consumption

Key Points

- Hypertrophic cardiomyopathy is a very rare disorder in children that frequently has dramatic impact and covert manifestations.
- Outcome and management are highly dependent on establishing an etiologic diagnosis.
- Available data in pediatrics are few because of the rarity of the disorder and decisions are often based on the adult experience in related disorders.
- The risk profile for medications, defibrillators, and surgery is substantially different in children compared to adults.
- The psychological profile of the adolescent creates specific issues with regard to denial, risky behavior, and potential for depression that must be factored into the risk-to-benefit calculations.

Introduction

Cardiomyopathy is a rare (about 1/100,000 children) but serious condition in infants and children [1]. Hypertrophic cardiomyopathy accounts for about 40% of cardiomyopathy cases in children and is an unusually heterogeneous group of disorders during childhood. Pediatric hypertrophic cardiomyopathy encompasses conditions with diverse genetic origins and clinical phenotypes, including associations with inborn errors of metabolism, mitochondrial defects, neuromuscular disorders, and malformation syndromes. Few data are available to predict which patients with pediatric hypertrophic cardiomyopathy will experience congestive heart failure or sudden cardiac death (SCD). Morbidity and mortality are higher in the first year of life by a factor of ten compared with the remainder of childhood. This discussion will focus primarily on issues related to diagnosis and management of these children.

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Diagnosis of Hypertrophic Cardiomyopathy in Children

Hypertrophic cardiomyopathy (HCM) is defined as the presence of a hypertrophied, non-dilated ventricle in the absence of a hemodynamic disturbance that is capable of producing the existent magnitude of wall thickening, such as hypertension, aortic valve stenosis, catecholamine-secreting tumors, hyperthyroidism, and other disorders. Physiologic hypertrophy secondary to intense athletic participation is also excluded from this definition. In contrast to the practice in adult cardiology, the criteria for the magnitude of wall thickness that can be considered diagnostic of HCM in children require adjustment for body size. A left ventricular (LV) wall thickness of 14–15 mm is considered diagnostic of HCM in adults [2], corresponding to a value that is 5–6 standard deviations above the normal adult mean. In contrast, z-scores relative to body surface area are used to adjust the size of cardiovascular structures for body size in children, where the z-score is the number of standard deviations from the mean [3]. The adult criteria therefore correspond to a z-score range of 5–6, while typically a wall thickness z-score >4–5 is used as the diagnostic criterion in children. It is important to note that the American Heart Association (AHA) [2] and European Society of Echocardiography (ESC) [4] current guidelines mistakenly state that the criteria for HCM in children are a z-score >2. This is clearly incorrect for two reasons. First, statistically, a z-score >2 by definition includes 2.3% of the population, whereas the frequency of pathogenic sarcomeric genes in the general population is 1 in 500 (0.2%), and the actual incidence of expressed disease is 0.001%. Application of this criterion would therefore result in a rate of overdiagnosis somewhere between 10- and 200-fold. Secondly, the diagnosis would need to be rescinded in the vast majority of individuals when they reach age 18 since they would no longer meet adult criteria. A graph of the normal range and the four z-score cutoff value for diastolic septal thickness using data from our echocardiographic laboratory are provided in Fig. 9.1 [5]. Substantial isolated regional variation in wall thickness (asymmetry), typically defined as delimited areas with >1.5 times the prevailing wall thickness, is often accepted as a diagnostic criterion. It should be noted that a progressive fall in wall thickness from base to apex is normal. Similar to diagnostic criteria based on wall thickness alone, this discriminating value for magnitude of asymmetric hypertrophy may overlap with changes seen in physically active individuals [6].

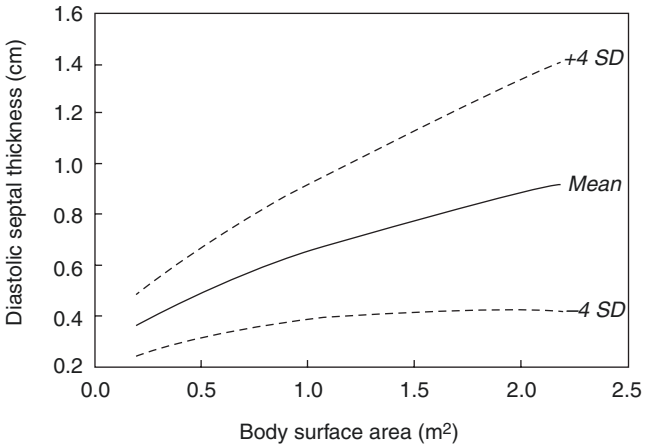

Fig. 9.1 Graph of normal end-diastolic interventricular septal thickness (cm) as a function of body surface area (m^2) with the z-score values of +/−4 standard deviations (SD) indicated with interrupted lines

Nomenclature Issues in Hypertrophic Cardiomyopathy It should be noted that the foregoing definition, which is based on the presence of a phenotype characterized by non-hemodynamically induced hypertrophy and does not specify etiology, is derived from the original World Health Organization recommendations on the nomenclature of the cardiomyopathies, is preferentially used in the pediatric cardiology community, and forms the basis for the terminology used in this chapter (Table 9.1) [7, 8]. This nomenclature and classification scheme are also in alignment with the position paper published by the European Society of Cardiology (ESC) [9, 10]. However, the advent of genetic characterization of the disease has resulted in an effort to include the genetic basis of the disease in the definition. The ACCF/AHA guidelines, although specifically specifying the same phenotypically based definition provided here, have recommended a narrower use of the term "hypertrophic cardiomyopathy," restricting it to patients with (1) left ventricular hypertrophy (LVH), (2) overt disease restricted to the heart, and (3) either a sarcomeric mutation or unknown mutation (2). Notably, the ACCF/AHA guidelines mark as hypertrophic cardiomyopathy only those disorders that fit these criteria, whereas within the pediatric population, multiple disease states may present with the broader definition of hypertrophic cardiomyopathy, the presence of non-hemodynamically induced hypertrophy from any cause. Alternative terms that have been used for this subset of patients with HCM are familial HCM (FHCM) and sarcomeric HCM. In contrast to this recommendation to narrow the definition beyond the original phenotypically based terminology, some groups favor a broader definition of the disease that includes carriers of HCM-associated sarcomeric gene mutations, even if LVH is absent. These genotype positive, phenotype negative (G + P−) individuals have also been labeled as preclinical HCM, subclinical HCM, presymptomatic HCM, HCM mutation carriers, and HCM without hypertrophy [11]. Equating the presence of the gene with the presence of the disease is quite controversial, particularly in children, since an increased risk of SCD or other adverse outcomes has not been identified when LVH is absent. There is also a substantial experience indicating incomplete penetrance for these mutations, making the use of the term problematic since some of these patients may never experience clinical manifestations. The pediatric cardiology community has been resistant to expanding the definition of HCM to

Table 9.1 Classification of hypertrophic cardiomyopathy

Primary (isolated) hypertrophic cardiomyopathy
Familial hypertrophic cardiomyopathy
Sarcomeric hypertrophic cardiomyopathy
Maternally inherited hypertrophic cardiomyopathy syndromes
Idiopathic isolated hypertrophic cardiomyopathy
Secondary (systemic, syndromic) hypertrophic cardiomyopathy
Syndromic hypertrophic cardiomyopathy
Noonan syndrome
Noonan syndrome with multiple lentigines
Costello syndrome
Cardiofaciocutaneous syndrome
Beckwith-Wiedemann syndrome
Swyer syndrome
Leprechaunism (Donohue syndrome)
Hypertrophic cardiomyopathy in glycogen storage disease
Pompe disease
Protein kinase AMP-activated non-catalytic subunit gamma 2 (PRKAG2)
Glycogenosis type III (Forbes disease)
Lysosomal-associated membrane protein 2 (LAMP2, Danon) disease
AMP-activated protein kinase (AMPK)
Hypertrophic cardiomyopathy in lysosomal storage disease
Anderson-Fabry disease
Hurler disease (MPS I)
Fucosidosis type 1 (I-cell disease)
Mucolipidosis II
Mannosidosis
Mucopolysaccharidosis type I H (hurler syndrome)
Mucopolysaccharidosis type I S (Scheie syndrome)
Mucopolysaccharidosis type II (hunter syndrome)
Hypertrophic cardiomyopathy in mitochondrial disorder
Friedreich's ataxia
MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes)
MERFF (myoclonic epilepsy with ragged-red fibers)
NADH-coenzyme Q reductase
Cytochrome b deficiency
Hypertrophic cardiomyopathy in disorder of fatty acid metabolism
Carnitine palmitoyl transferase II deficiency
Carnitine-acylcarnitine translocase deficiency
Carnitine deficiency
Hypertrophic cardiomyopathy in amyloidosis
Hypertrophic cardiomyopathy in congenital generalized lipodystrophy
Hypertrophic cardiomyopathy in infant of diabetic mother
Hypertrophic cardiomyopathy in anabolic steroid therapy and abuse

include gene carriers without hypertrophy, in this case a position that is in agreement with the ACCF/AHA guidelines [2]. The purpose of this nomenclature discussion is not to attempt to assert which is the "correct" nomenclature but to clarify for the purposes of the ensuing discussion that in this chapter: (1) the term HCM is used to encompass the full spectrum of non-hemodynamically induced hypertrophy represented in Table 9.1) the presence of other clinically detectable manifestations of gene carriage, collectively referred to as biomarkers for genetic predisposition, are not taken to represent "cardiac disease" in the absence of cardiac hypertrophy.

Diagnostic Testing for Hypertrophic Cardiomyopathy in Children

The electrocardiogram (ECG) is abnormal in approximately 90% of patients with HCM. These abnormalities include voltage criteria for LVH with or without strain, left atrial enlargement, and deep Q waves [12]. There is no ECG pattern that is specific for HCM, although pediatric criteria have been put forth as more sensitive and specific when the R wave in aVL and the S wave in V2 are greater than 23 mm [13]. Although the ECG is at times used as a screening tool, ultimately the diagnosis of HCM in children is nearly always based on echocardiography due to the excellent images that can typically be obtained in this age group. Cardiac magnetic resonance (CMR) imaging is occasionally required in patients with poor echocardiographic access or when apical HCM is suspected based on family history or failure to image the left ventricular apex on echocardiography. In general, the same wall thickness criteria are used for both the echocardiographic and CMR diagnosis of HCM.

A variety of other morphologic, electrophysiologic [14], and hemodynamic manifestations of the disease have been described in children with the HCM phenotype that are similar to the findings in adult populations, including dynamic LV outflow tract obstruction, elongation of the mitral valve leaflets [15], mitral regurgitation, abnormal tissue Doppler velocities, elevated end-diastolic pressure, and left atrial dilation. Assessment of diastolic dysfunction with the use of left ventricular tissue Doppler and the mitral inflow velocities has been linked to adverse outcomes in children [16] although the adequacy of current criteria for diastolic dysfunction in pediatrics is uncertain [17]. In adults, abnormal diastolic tissue Doppler imaging (TDI) parameters (s', systolic peak velocity; e', early diastolic peak velocity; and a', late diastolic peak velocity) have been identified in sarcomeric mutation carriers even in the absence of LV hypertrophy (the so-called "preclinical" HCM) [18]. Similarly, in children with sarcomeric mutations, an increased E/e' can be seen prior to other echocardiographic manifestations of HCM. Children with HCM were noted to have no increase in TDI s' with stress echocardiography, leading the authors to speculate that decreased contractile reserve might contribute to the diminished exercise capacity associated with HCM [19]. The clinical utility of stress echocardiography imaging in pediatrics has not been extensively evaluated in children with HCM [20], but a recent report using an adult protocol for stress echocardiography in ten pediatric patients with nonobstructive HCM found that

30% developed LV outflow tract gradients with exercise [21]. Although uncommon in older patients, infants often have biventricular outflow tract obstruction secondary to septal protrusion into both ventricles. Although these additional findings may have important implications for management and prognosis, ultimately the diagnosis of HCM remains dependent on the finding of hypertrophy. For example, dynamic LV outflow tract obstruction can be seen in morphologically variant mitral valves and even in normal hearts in the absence of HCM [14]. Myocardial crypts (narrow, deep, blood-filled invaginations within LV myocardium) have been noted on CMR (Fig. 9.2) [22]. Although not unique to HCM, these appear to be seen more frequently in HCM than in other diseases. Nevertheless, the presence and severity of myocardial hypertrophy remain the fundamental diagnostic criterion and are an important predictor of outcome.

A helpful but underutilized tool in the management of patients with HCM is the cardiopulmonary exercise stress test (CPET). It is used to evaluate the functional capacity of patients with HCM as well as to identify the factors that cause or exacerbate exercise limitations. Patients with diastolic dysfunction may be unable to augment their stroke volume due to limited preload reserve. A blunted blood pressure response to exercise (inability to increase systolic blood pressure at least 20 mmHg over baseline) or an actual blood pressure fall is one of a handful of conventional risk factors for SCD (Table 9.2). Exercise testing can be useful in the identification of patients with chronotropic incompetence

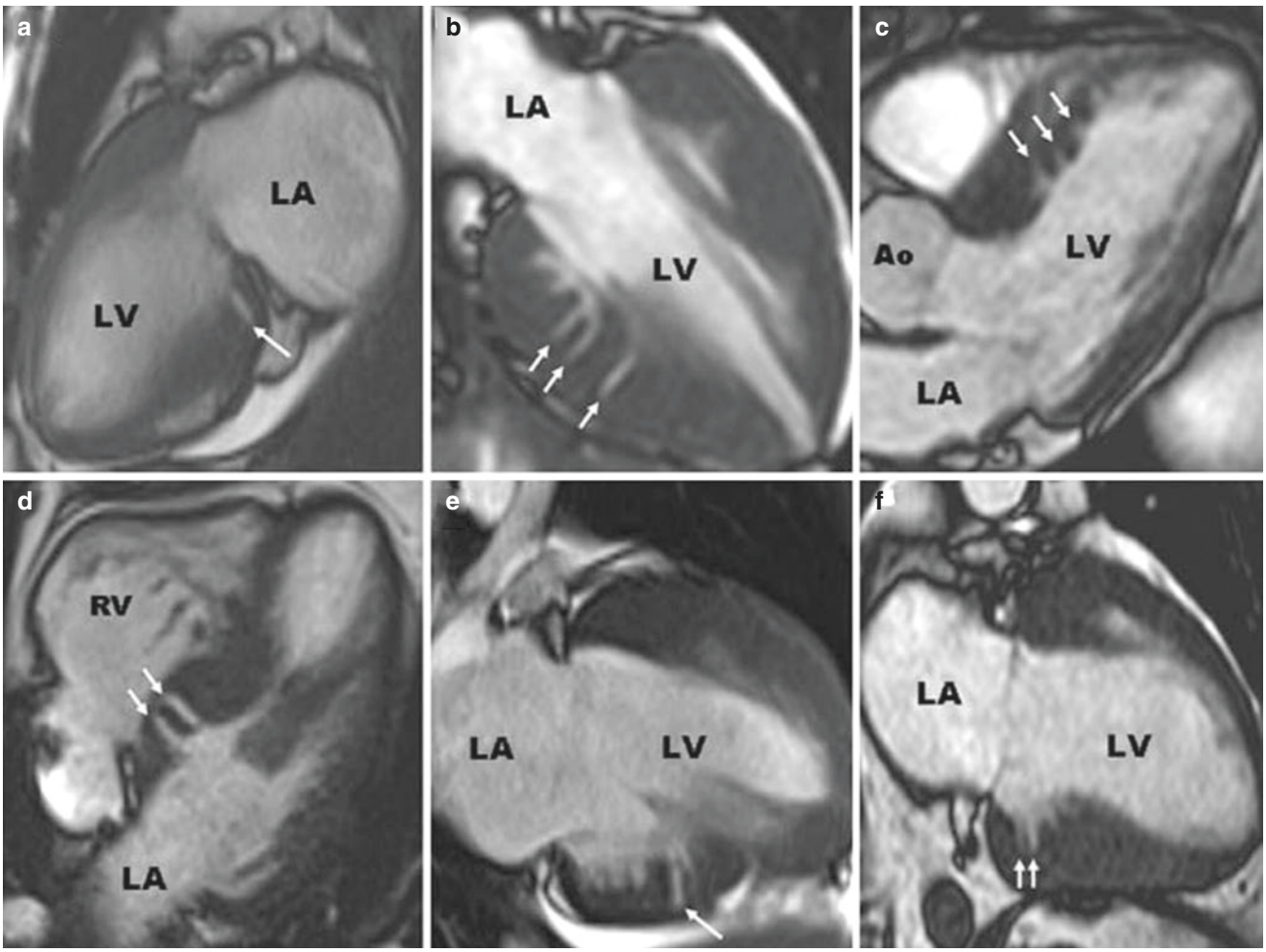

Fig. 9.2 Diverse spectrum of myocardial crypts in patients with HCM with LV hypertrophy. Shown in end-diastolic long-axis CMR images. (**a**) Single crypt (arrow) penetrating almost the entire thickness of the basal posterior (inferior) wall; the LA is greatly enlarged; (**b**) three deep crypts (arrows) involving the posterior (inferior) free wall in basal and mid-LV levels in a patient with massive LV hypertrophy (maximal wall thickness, 32 mm); (**c**) three crypts (arrows) in the basal anterior septum; (**d**) two deep crypts (arrows) penetrating virtually the entire thickness of the basal posterior septum in a patient also with LV apical aneurysm; (**e**) single crypt (arrow) in the posterior (inferior) free wall at mid-LV level; (**f**) two crypts (arrows) in the basal posterior free wall. HCM indicates hypertrophic cardiomyopathy, LV left ventricle, CMR cardiovascular MR, Ao aorta, LA left atrium, LV left ventricle, RA right atrium, RV right ventricle. Survival rates from diagnosis of cardiomyopathy to (a) death (logrank $P < 0.001$) and (b) death or transplant (logrank $P < 0.001$) in the combined prospective and retrospective cohorts ($N = 855$) by age at diagnosis (<1 year, 1 to <6 years, 6 to <12 years, and 12 to <18 years) [22]

which occurs in half of HCM patients [23, 24]. The CPET can also help differentiate the athlete with LVH from one with HCM. Those patients with exercise-induced hypertrophy typically have a peak oxygen uptake (VO_2) >50 ml/kg/min or more than 110% of the sex- and age-predicted value [25, 26]. The O_2 pulse (oxygen uptake per heartbeat), a surrogate for stroke volume, is calculated as VO_2/heart rate. Unlike athletes, patients with HCM often have an early flattening of the O2-pulse curve with a compensatory increase in heart rate, presumably related to relatively non-compliant ventricles. There is a direct correlation between when the curve begins to flatten and the severity of cardiomyopathy (Fig. 9.3) [26, 27]. The VE/VCO_2 slope (the relationship between minute ventilation and CO_2 output, a measure of ventilatory efficiency) was identified as an independent prognostic marker for morbidity and mortality in a study of 83 patients with nonobstructive HCM by Arena et al. [28], with a VE/VCO_2 slope >32 associated with an increased risk for SCD. Additional studies have emerged in recent years that also identify the CPET as a useful tool for management and prognosis in HCM in adults, but the applicability of these observations to children remains unclear. For example, Coats et al. [29] found CPET to be predictive of all-cause mortality or heart transplant in adults who had transitioned to the dilated, hypocontractile form of HCM, but these results are of limited applicability in pediatrics given the rarity of the dilated form of HCM during childhood.

Table 9.2 Potential risk factors for sudden death in hypertrophic cardiomyopathy

History of cardiac arrest[a]
Sustained ventricular tachycardia[a]
Left ventricular maximum wall thickness >30 mm
Family history of sudden cardiac death in first-degree relative
Unexplained syncope
Blood pressure fall during exercise
Delayed hyper-enhancement on cardiac magnetic resonance
Non-sustained ventricular tachycardia

[a]Independent risk factors for SCD warranting an ICD

Morphologic Variants of Hypertrophic Cardiomyopathy in Children Several patterns of myocardial and ventricular morphology are encountered in HCM. The majority of children have reduced cavity volume that is near or below the normal range for body size in conjunction with hyperdynamic systolic function, similar to the pattern that is characteristic of adult populations, a pattern that can be referred to as typical or "pure HCM." There are subsets of children with mixed phenotype disease who, in addition to ventricular hypertrophy, have marked ventricular dysfunction (hypokinetic HCM) or severe restrictive physiology (restrictive HCM), patterns found in 6% and 5% of cases, respectively [30]. These patterns are of importance as they tend to be associated with specific etiologies and outcomes. In contrast to the transition to dilated cardiomyopathy that is seen as an end-stage manifestation of HCM in adult populations and is only rarely encountered in children, the hypokinetic HCM phenotype is seen in infants as a primary manifestation (i.e., no preceding phase of hyperdynamic HCM) and is not characterized by wall thinning and ventricular dilation. Finally, the mixed phenotype of HCM with noncompaction can be encountered, but the frequency of this pattern is less well characterized, in part because of its rarity but also related to the uncertainty associated with making the diagnosis of noncompaction [31].

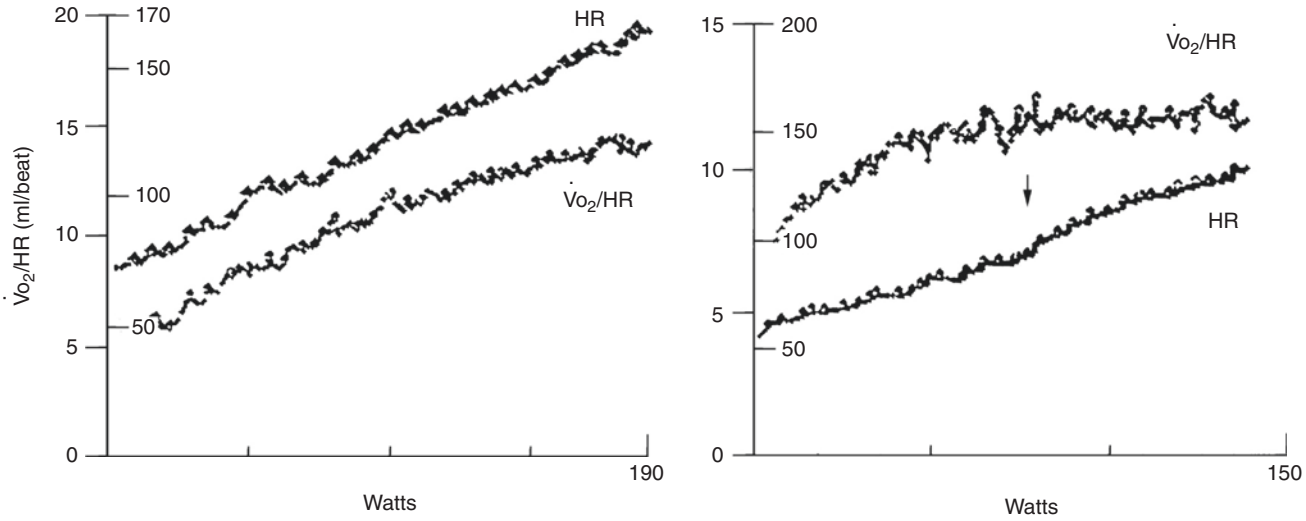

Fig. 9.3 Profile of response of heart rate and oxygen pulse to progressively increasing work rate to limit of tolerance in a control subject (left panel) and in a patient with hypertrophic cardiomyopathy (HCM) (right panel). Note that the oxygen pulse continues to increase throughout the work rate in the control subject, whereas it reaches a plateau at some 60% of the maximum work rate in a patient with HCM. Note also the clearly discernible increase in the heart rate response at the work rate at which the oxygen pulse begins to plateau [27]

Diagnosis of Hypertrophic Cardiomyopathy in Pediatric Athletes The challenge related to differentiation of HCM from physiologic hypertrophy in young adults who participate in high level athletics and in enlisted military personnel has been well documented. The issue rarely arises prior to puberty but should be considered in any adolescent with the combination of relatively mild hypertrophy and high levels of exercise participation. The potential consequences of the diagnosis or at times even the suspicion of the diagnosis can have a marked impact on the educational, career, and financial opportunities for these athletes, escalating the gravity of the decision [32]. Specific activities (wrestling, weight lifting, football, basketball) are more often represented in these athletes, and anabolic steroid use may further confound the situation. Generally, wall thickness up to a z-score of 5 or 6 can occasionally be encountered, and this is the area of overlap that creates the greatest diagnostic uncertainty. A number of characteristics of the phenotype can help differentiate pathologic from physiologic hypertrophy. Findings such as a family history of HCM or SCD increase the probability of HCM. Symptoms such as diminished exercise tolerance are uncommon in athletes. Syncope is very common in the general population, including athletes, and should not be presumed to tilt the balance toward HCM without findings to suggest an arrhythmic basis. Generally, syncope following exercise is more likely to be related to hyperthermia, hypovolemia, or neurally mediated syncope, whereas patients with hypertrophy who experience syncope during exercise must generally be presumed to have HCM until proven otherwise. Extensive effort has been devoted to testing electrocardiographic methods for screening for hypertrophic cardiomyopathy, but it is clear that there is broad overlap with the changes induced by intense training and this is not a reliable method for discriminating the two [33]. Physiologic remodeling is more frequently associated with symmetric hypertrophy, larger LV chamber size, normally ellipsoidal LV shape, left atrial dilation proportional to left ventricular dilation, normal diastolic function indices, and absence of outflow track obstruction and delayed enhancement on CMR. When all these parameters are normal, HCM is quite unlikely, but ultimately some cases will remain ambiguous. The strongest evidence of physiologic hypertrophy is significant reduction in hypertrophy in response to detraining, a process that often requires 6–12 months of relative inactivity. Some of these individuals have great difficulty adequately restricting their level of exertion, but functionally this activity restriction is equivalent to presuming HCM is present until proven otherwise. Therefore, exclusion from competitive sports participation is required and is likely the only intervention that would be undertaken for asymptomatic HCM with mild hypertrophy.

Diagnosis of Hypertrophic Cardiomyopathy in Children with Structural Congenital Heart Disease The coexistence of HCM in the setting of structural congenital heart disease is sometimes suspected, particularly in infants, and can present a particularly difficult dilemma. The presence of asymmetric septal hypertrophy is commonly seen in right ventricular outflow tract obstruction, such as valvar pulmonary stenosis, tetralogy of Fallot, or double-chambered right ventricle [34], and is not uncommonly observed in complete atrioventricular septal defects. In addition, there are patients who manifest ventricular hypertrophy that appears excessive for the severity of the hemodynamic disturbance. This represents a diagnostic dilemma insofar as the coincidence of both diseases may complicate management. There is generally no satisfactory method for untangling the two other than eliminating the hemodynamic overload and seeing if regression of hypertrophy takes place, similar to the approach in suspected athletic heart syndrome. Complete elimination of the hemodynamic burden related to the congenital heart disease is often not possible, resulting in a persistent diagnostic dilemma. Efforts to differentiate on the basis of histopathology have also not been successful [35]. Identification of a known pathogenic mutation via genetic testing will heighten the probability of HCM and aid in exclusion of other genetic syndromes with cardiac manifestations but cannot be considered definitive due to the variable age of onset of gene expression.

Diagnosis of Etiology in Hypertrophic Cardiomyopathy In contrast to the relatively homogeneous etiologic profile seen in adults, where the overwhelming majority of patients have FHCM, with the responsible gene mutation typically in a sarcomeric protein, the HCM phenotype in children is etiologically diverse, and outcomes tend to be highly dependent on etiology. A classification is presented in Table 9.1 [8] where the fundamental differentiation is division into primary and secondary forms, and the primary form is devoid of findings outside of the heart. Secondary forms include diseases, such as Friedreich's ataxia [36] where ventricular hypertrophy is common but is not the dominant clinical manifestation, and others, such as glycogen storage disease type IX [37], in which a systemic disorder has primary or exclusive cardiac manifestations.

The importance of etiologic diagnosis relates to the fact that management and outcome in pediatric HCM are highly dependent on etiology. The Pediatric Cardiomyopathy Registry, a multicenter observational study of pediatric cardiomyopathies, was initiated in 1995. A 2003 report is notable for the following: HCM was found to account for 42% of childhood cardiomyopathy, had an incidence of 0.5/100,000 children, is significantly more common in male subjects, occurs in subjects <1 year of age at rates ten times the rate in older children, and is significantly more common in blacks than in whites or Hispanics. Subsequently, the distribution of etiologies and the etiology-specific HCM survival in 849

children was reported [38]. We found a nearly equal distribution between inborn errors of metabolism (9%), malformation syndromes (9%), and neuromuscular disorders (8%), with idiopathic and FHCM comprising the remaining 75%. Patients in the inborn errors of metabolism and malformation syndrome groups were diagnosed at a mean age <6 months with a significantly older age at diagnosis in the other groups. This explains why, by the time subjects reach adulthood, the familial/idiopathic group is the dominant form, and genetic testing or a search for alternate etiologies is less productive. Survival was also found to be etiology- and age-specific, as illustrated in Fig. 9.4 [38] and Fig. 9.5 [30]. For patients with FHCM, the survival rate is similar to contemporary reports in adults. Both survival and management are highly etiology-specific. In 2007 we found that based on data from the preceding 15 years, about 50% of HCM cases under age 1 year remained idiopathic [38]. This study excluded infants with HCM secondary to maternal diabetes, who are generally more readily diagnosed and are characterized by spontaneous resolution of the HCM. More recent data of this type are not available, but the pace of advances in genetic and metabolic diagnostics has quickened, and the expectation that a specific diagnosis can be achieved has improved substantially in recent years. Many states have expanded the range of disorders screened on the neonatal blood spot screening as well, and consequently the underlying metabolic disorder may be known prior to the recognition of cardiomyopathy.

Children presenting with the HCM phenotype in the presence of a family history of HCM are typically presumed to have FHCM, a diagnosis that can be confirmed by testing for a familial mutation if this is identifiable. Presentation in infancy is rare, and further evaluation is justified to ensure the absence of multiple causes, which includes both multiple pathogenic sarcomeric mutations and coexistent syndromic HCM such as Noonan syndrome, both of which have been reported. The presence of multiple pathogenic sarcomeric gene mutations in infants has resulted in the hypothesis of a genetic "dosage" effect accounting for the early presentation.

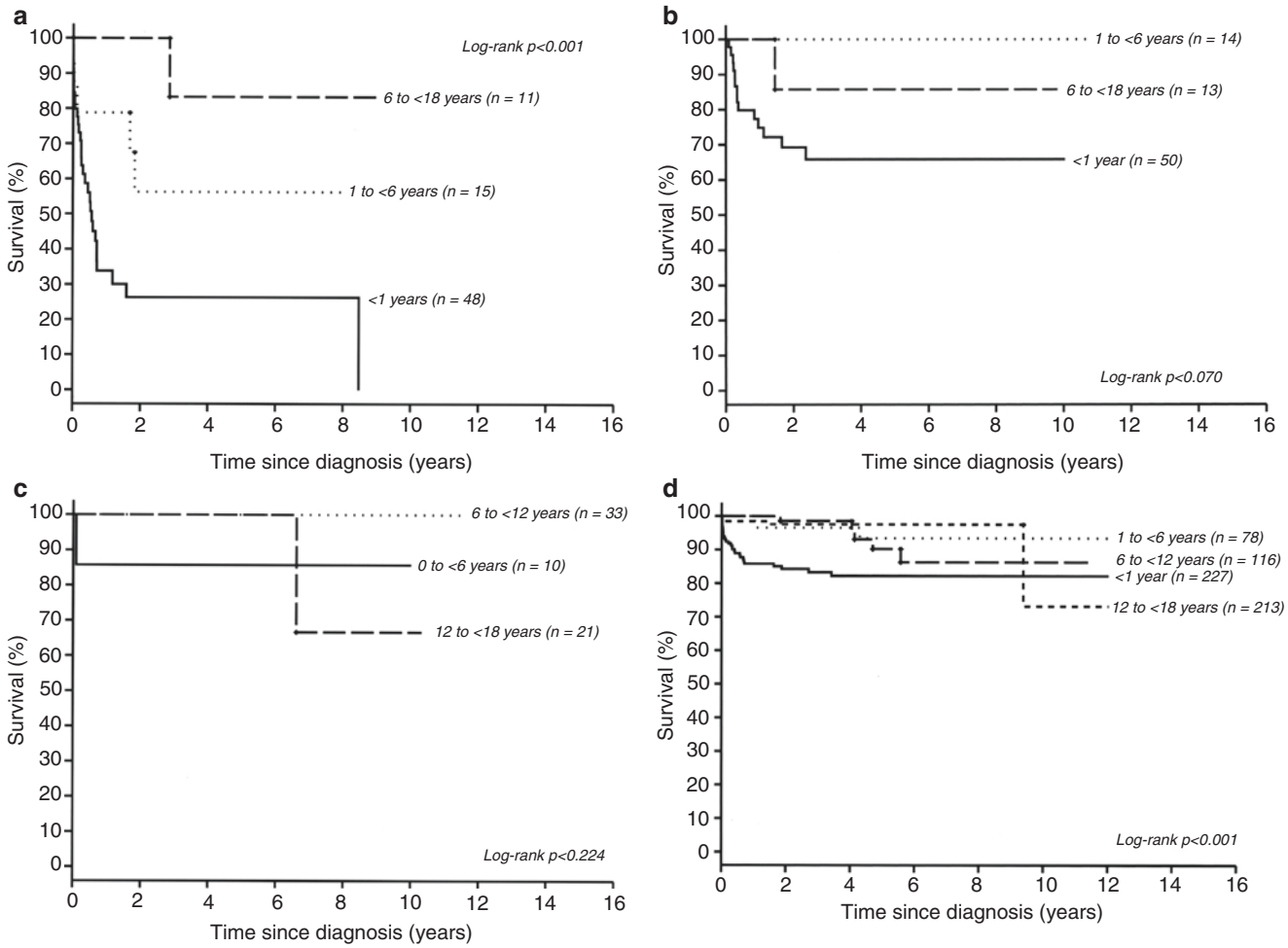

Fig. 9.4 Kaplan-Meyer survival rates from diagnosis of cardiomyopathy in inborn errors of metabolism (**a**; $n = 74$; log-rank $P < 0.001$), malformation syndromes (**b**; $n = 77$; log-rank $P < 0.070$), neuromuscular disorders (**c**; $n = 64$; log-rank $P < 0.224$), and idiopathic hypertrophic cardiomyopathy (**d**; $n = 634$; log-rank $P < 0.001$) by age at diagnosis [38]

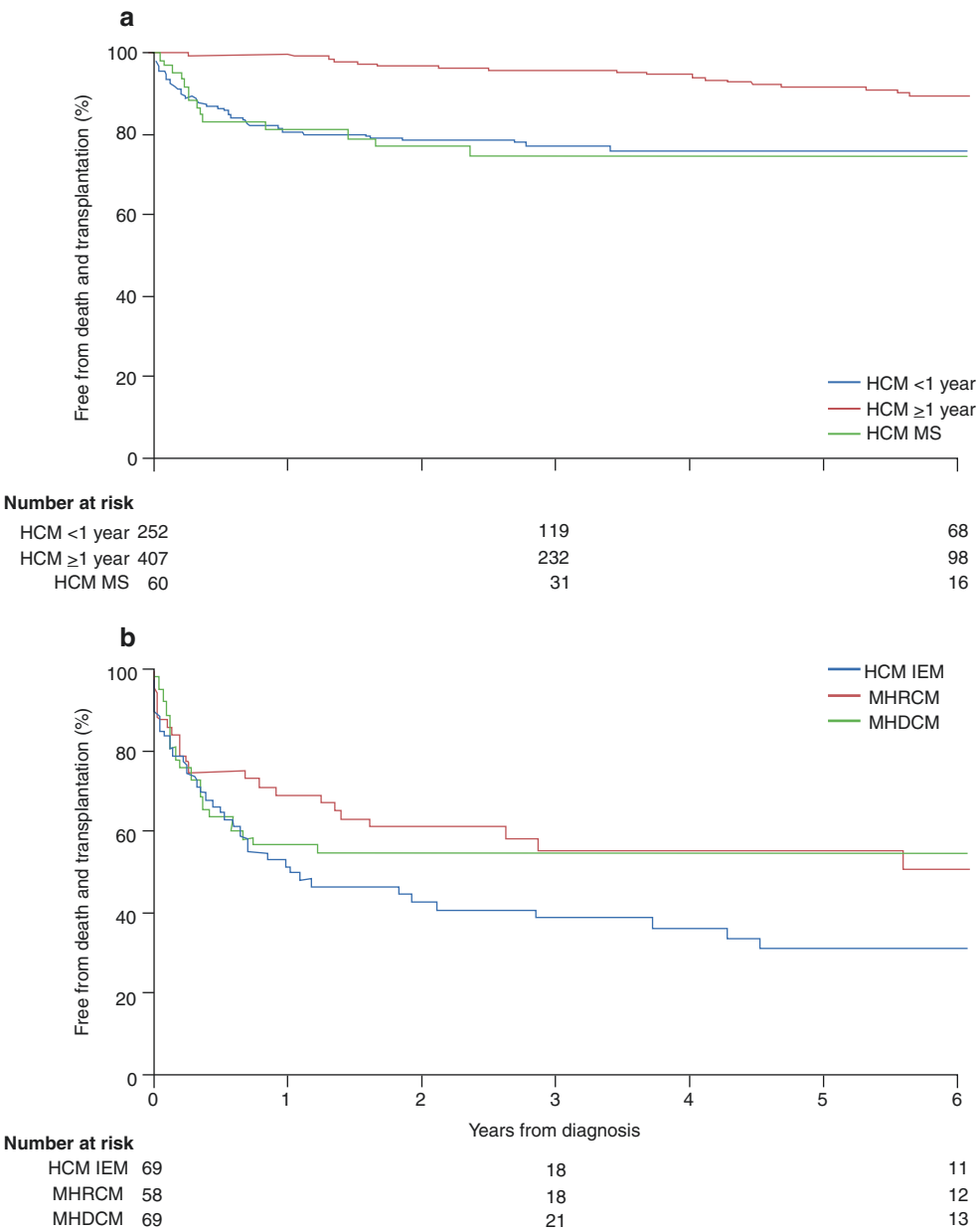

Fig. 9.5 Kaplan-Meyer survival rates from diagnosis of cardiomyopathy to death or cardiac transplantation of subgroups of children based on age at diagnosis, cause, or phenotype (**a**) Rates for 252 patients with pure hypertrophic cardiomyopathy diagnosed at younger than 1 year of age (HCM <1 year), 407 patients with pure hypertrophic cardiomyopathy diagnosed at age 1 year or older (HCM ≥1 year), and 60 patients with pure hypertrophic cardiomyopathy with malformation syndromes (HCM MS). (**b**) Rates for 69 patients with pure hypertrophic cardiomyopathy with inborn errors of metabolism (HCM IEM), 58 patients with mixed hypertrophic and restrictive or other cardiomyopathies (MHRCM), and 69 patients with mixed hypertrophic and dilated cardiomyopathy (MHDCM) [30]

The presence of a coexistent syndromic or metabolic disorder may be clinically occult during infancy, impeding early diagnosis and appropriate management, justifying a more extensive and comprehensive diagnostic evaluation of the newborn with HCM.

Children presenting with the HCM phenotype in the absence of a family history of HCM require consideration of the associated metabolic, syndromic, and neuromuscular disorders presented in Table 9.1. Depending on age, they may require a wide ranging diagnostic evaluation to assure absence of an underlying disorder. Although the finding of sarcomeric HCM in children who do not have a family history of HCM may represent a new mutation, there is also a well-documented incidence of incomplete penetrance in sarcomeric HCM, and therefore gene testing in these children is recommended for the reasons discussed in detail below, followed by cascade gene testing of the parents and other family members when appropriate; clinical correlation with cardiac (echocardiographic) testing of gene-positive individuals may reveal a familial disease.

Association of HCM with numerous disorders other than FHCM has been described, and in many instances these case reports actually represent coincidence, but there are several for which HCM is seen with sufficient frequency to indicate that it is an intrinsic element of the disease (Table 9.1). Patients with Friedreich's ataxia have a >50% incidence of HCM, and they rarely present prior to the onset of neurologic symptoms, tend to manifest symmetric hypertrophy

without outflow obstruction, and do not appear to be at significant risk for SCD [38]. HCM is seen in up to 20–30% of patients with Noonan syndrome [39] and other developmental syndromes of Ras/MAPK pathway dysregulation, the so-called RASopathies (Noonan syndrome, Costello syndrome, cardiofaciocutaneous syndrome, Noonan with multiple lentigines syndrome, and neurofibromatosis type 1) [40]. The cardiac findings in the RASopathies are similar to FHCM with myocardial disarray, asymmetric hypertrophy, dynamic LV outflow obstruction, and risk of SCD. However, these patients have a higher percentage of associated congenital heart disease such as pulmonary stenosis and more frequently experience biventricular outflow tract obstruction. RASopathy patients may present with congestive heart failure, and recognition of the associated syndrome is often delayed due to incomplete phenotypic expression in infancy. In infants, the risk of congestive heart failure with HCM associated with Noonan syndrome is more common than in infants with FHCM, and those who experience heart failure at <6 months of age have only a 33% 1-year survival, with nearly all of the childhood deaths being secondary to congestive heart failure and occurring within the first 2 years of life [41]. Infants of diabetic mothers and neonates exposed to corticosteroids often have transient biventricular hypertrophy, sometimes with outflow tract obstruction, and occasionally causing symptoms or even death, but invariably survivors experience spontaneous resolution of hypertrophy over a period of weeks.

Generally, HCM in infants presents unique problems in differential diagnosis. In various series, diseases other than FHCM have accounted for 30–70% of HCM cases in patients <2 years of age [42]. Among those patients for whom a defined etiology is identified, a few disorders (Pompe disease, Noonan syndrome, and FHCM) account for the majority of cases with the remainder caused by a broad range of rare disorders. From the cardiac perspective, the association of particular patterns of the cardiac phenotype with specific etiologies has been an area of considerable interest because of the potential to guide the evaluation and management. For example, the finding of a hypertrophic, hypokinetic LV is rare in FHCM but has been frequently associated with mitochondrial defects [43] and inborn errors of metabolism, as has severe concentric hypertrophy in patients under 2 years of age. Myocardial biopsy is often necessary to distinguish among these disorders, is recommended in all patients under the age of 2 years if a diagnosis cannot be achieved by other means, and can be particularly helpful in children with symmetric hypertrophy or depressed function who have no family history of HCM [43, 44]. Biventricular outflow tract obstruction is more common in Noonan syndrome than in other forms of infantile HCM. Asymmetric patterns of hypertrophy are more commonly seen in syndromic and familial HCM than in inborn errors of metabolism. Knowledge of the etiology can lead to early treatment strategies. For example, recent reports have demonstrated efficacy of enzyme replacement therapy in Pompe disease with regression of hypertrophy [45]. Although these observations can provide some guidance, for most infants with HCM, early referral for multispecialty evaluation including specialists in cardiology, neurology, genetics, and metabolism is warranted. Finally, differentiation between physiologic hypertrophy secondary to athletic participation and pathologic hypertrophy in FHCM is a frequent and an important problem in adolescents and young adults and is dealt with separately in this volume.

Genetic Diagnosis of Hypertrophic Cardiomyopathy in Children The routine use of genetic testing in the HCM population remains controversial, and many insurers deny coverage, in part related to a perceived lack of clinical utility because management of the index case is generally not affected by the results. However, this view is shortsighted because it fails to recognize the benefits to other family members, particularly for children, who face the highest probability of new-onset HCM. Because development of the phenotype can be noted at any age, current practice is to periodically undertake echocardiographic screening of first- and second-degree relatives of individuals with familial or idiopathic HCM because of the associated risk of gene carriage of 50% and 25%, respectively. If a pathogenic gene can be identified in phenotypically positive family member(s), the remainder of the pedigree can be screened, and family members who prove to be genotype negative can avoid the need for longitudinal screening. This results in a reduction in the overall cost of care, mitigation of anxiety, and elimination of potential exercise restriction. Phenotype-negative relatives who prove to be genotype positive are appropriately evaluated periodically for development of disease, gain the possibility of preventing gene transmission through embryo preselection, and become eligible for trials of interventions to prevent or attenuate the phenotype.

The potential to prevent the onset of hypertrophy remains an unproven hypothesis in humans although animal models have provided proof of concept for this theory. A mouse model of myosin heavy chain HCM treated prior to the onset of hypertrophy with diltiazem had less hypertrophy, fibrosis, and myocyte disarray than placebo-treated mice [46], and rapamycin has been reported to reverse the cardiac hypertrophy in a mouse model of multiple lentigines syndrome associated with a PTPN11 mutation [47]. To this end, a randomized clinical trial of valsartan in G+/P– children and young adults is currently underway evaluating whether the phenotype can be prevented or reduced [48].

Nongenetic Detection of Genotype-Positive Status A definitive genetic diagnosis cannot be achieved through currently available commercial genetic testing in about 40% of HCM phenotype-positive individuals. As discussed above, accurate identification of which of these relatives has a genetic predisposition permits targeted screening of only susceptible individuals. There has consequently been considerable interest in identification of serum or imaging biomarkers that might be detectable prior to the onset of pathologic hypertrophy. The availability of genotyped pedigrees has permitted evaluation of whether gene-positive individuals can be distinguished from gene-negative individuals based on standard electrocardiographic and echocardiographic testing, with early studies [49] demonstrating reasonable specificity but poor sensitivity to genotype-positive status [50]. More recently, a variety of potential biomarkers for genetic predisposition have been reported. Reduced early diastolic tissue Doppler velocities were found to correlate with gene carriage by several different groups [11, 18, 51, 52]. The specific velocity value that has had optimal positive predictive value for at-risk individuals has varied but has generally been <10 cm/sec in several studies, corresponding to the lower limits of normal in adults <40 years old [53]. However, early diastolic velocities are age-dependent [5, 53], as illustrated in Fig. 9.6, and consequently the discriminatory power is improved by the use of age-adjusted z-scores. Findings on CMR that have been reported as potentially useful in the detection of G + P− individuals include late gadolinium enhancement [54], increased extracellular myocardial volume [55], and myocardial crypts [22]. Left atrial and LV dimensions, torsion, strain, and strain rate have been reported to have different mean values in G + P− individuals compared to a control population [56, 57]. Thus far, similar to the electrocardiographic patterns in this population, although many of these biomarkers have a higher prevalence in gene carriers, they fail to definitively segregate gene-positive from gene-negative individuals, even in combinations [57].

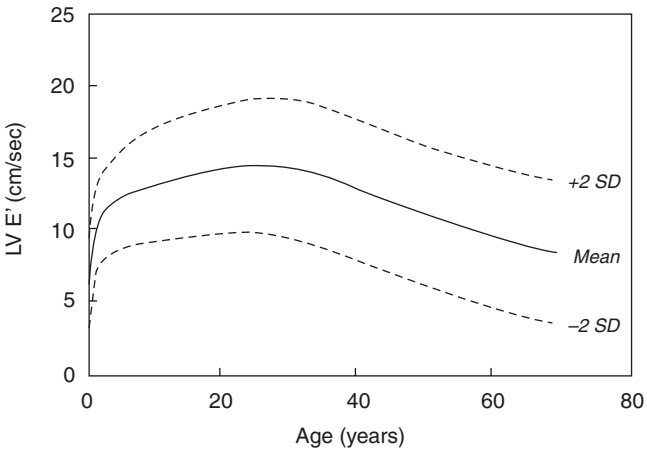

Fig. 9.6 Composite graph of the normal values for septal peak early diastolic tissue Doppler values as a function of age based on data from Boston Children's Hospital in children aged 18 years and younger [5] and adult values from Dalen et al. [53]. The male and female values from Dalen et al. were averaged, and the mid-position of the age range was used for each data point

The exploration of these biomarkers was initially performed primarily to enable the detection of genotype-positive status because genetic testing was both expensive and not widely available, a situation that is gradually improving. Identification of biomarkers in G+P− has interesting potential implications for pathogenesis of the disease, but ultimately the ability of these methods to identify the genotype-negative subjects (i.e., the negative predictive value) is likely of equal or more value than the positive predictive value. Management of phenotype-negative first- and second-degree relatives who are genotype positive is not different from those with unknown gene status in terms of the need for longitudinal evaluation for new-onset hypertrophy. However, those who can be proved to be genotype negative can be dismissed from further evaluation. If clinical testing with electrocardiography, imaging, biomarkers, or other nongenetic testing could reliably identify which members of the pedigree do not carry a familial HCM genetic mutation, they would benefit from being excluded from longitudinal evaluation, whereas the individuals for whom this clinical testing was either ambiguous or predicted presence of the mutation would have no change in management. Work to date has centered primarily on positive predictive value, and it is likely that some biomarkers that perform poorly in this regard would nevertheless have strong negative predictive value. Similar to disease expression (i.e., onset of hypertrophy), there is potential for age dependence of these biomarkers, a factor that has not been investigated. The accuracy of negative predictive capacity that is required to exclude family members from longitudinal assessment would only need to achieve 90% to exceed the value of the current practice of evaluating only first- and second-degree relatives (third-degree relatives remain at 12.5% risk of mutation carriage).

In theory, the issues concerning optimal methods for biomarker-based identification of genotype-negative individuals can be addressed in future studies, but ultimately there is an important issue that may render these efforts futile. Development of these methods of genetic stratification has been based on studies performed on populations with known genotypes. However, these potential biomarkers of G+P− status can be mutation specific, as has been noted for abnormal tissue Doppler velocities [52]. Extrapolation of the predictive capacity of these biomarkers to individuals with an unknown genetic predisposition could fail because association between mutation carriage and any specific biomarker may not be generalizable.

Management of HCM in Children

The goals of therapy in this disorder are to improve quality of life and prolong survival, goals that at times may conflict. Management of the symptoms associated with HCM is commonly an issue in infants and occasionally in other age groups and is discussed in this section, but the majority of children are symptom-free. Implantable cardioverter-defibrillator (ICD) therapy remains the only therapeutic option that is unequivocally accepted as effective for improved survival in high-risk groups by reducing the incidence of SCD. The issues concerning ICD implantation in children are discussed in more detail below.

Management of Symptoms Related to Hypertrophic Cardiomyopathy in Children Similar to management in adult patients, digitalis is not helpful and is usually contraindicated in the absence of ventricular systolic dysfunction or atrial fibrillation, both of which are quite rare in pediatrics. In patients with HCM and preserved ventricular function, diuretic therapy is usually not helpful in alleviating dyspnea and may increase symptoms by reducing cardiac output and increasing the outflow gradient due to reductions in both arterial pressure and ventricular volumes. Outflow tract obstruction and mitral regurgitation are frequently seen together and play an important role with regard to symptom status in HCM. The clinical importance of outflow obstruction has been highly controversial over the years, as recently recounted in some detail [58]. Patients with outflow tract obstruction are at greater risk for symptoms and progression to heart failure and death [59], but the impact on the risk of SCD remains controversial.

Some reports have found that relief of outflow tract obstruction, in addition to symptomatic relief and potentially averting progression to congestive heart failure, may indeed reduce the incidence of SCD in adults [60, 61]. However, a recent large study in adults found that although invasively managed, LV outflow tract obstruction had improved survival compared with medically managed patients, the difference related to death from noncardiac causes with no significant improvement in HCM-related mortality [62]. The variability of these results accounts for the continued controversy as to whether pharmacologic or interventional reduction of LV outflow tract obstruction should be considered in the absence of symptoms [2]. In contrast to the adult patients enrolled in these reports, children with HCM have a low burden of comorbidities. Although there are no independent data in children to contribute to this decision, pharmacologic therapy of outflow obstruction is nearly universal in infants and young children, related to both the difficulty in early detection of symptom such as growth failure and the excellent safety profile of beta-blockers and calcium channel blockers.

Exercise-induced or exacerbated outflow tract obstruction is both common and associated with a higher risk of symptoms [63]. Reduction in outflow tract obstruction is one of the primary targets of therapy for symptomatic patients. In some patients outflow obstruction is present only with provocation, such as inotropic stimulation, vasodilation, or exercise, and often demonstrates marked spontaneous lability [64]. Although provocation of latent outflow obstruction with maneuvers such as amyl nitrate and Valsalva maneuver has been recommended, the clinical significance of gradients elicited in this fashion remains uncertain, in part due to the difficulty in standardization, and is typically not performed in children.

In general, HCM-related symptoms have been considered the primary indication for other medical or surgical interventions in children. Similar to management of adults with HCM [65], a stepwise approach is taken, first using medical therapy (beta-blocker, calcium channel blocker, and/or disopyramide), reserving surgical myectomy for patients with symptomatic LV outflow obstruction unresponsive to medical therapy. In general, alcohol septal ablation has not been considered a reasonable alternative to myectomy in children due to the technical issues concerning coronary access in smaller children and concerns about the adverse lifetime risk associated with the large myocardial scar that is created. Data have now accumulated indicating that, although the risk of SCD may not be higher in the presence of outflow tract obstruction, overall survival is nonetheless reduced by the presence of outflow obstruction due to an increased risk of congestive heart failure. Evidence that improved overall survival can be achieved from interventions to reduce LV outflow tract obstruction have begun to accumulate [62]. The sudden death mortality rate in HCM is sufficiently low (1–2% in most series) that large cohorts and substantial length of follow-up are needed to detect such a benefit, and pediatric-specific data are not available. Heart failure in children with HCM is quite rare after the first year of life, making it unlikely that any sort of benefit from presymptomatic intervention for outflow obstruction will be detectable during childhood. At present, interventions specifically targeted to relief of outflow tract obstruction in children are generally reserved for symptomatic patients. However, any cumulative contribution of the pressure overload associated with outflow tract obstruction to the progressive diastolic dysfunction in HCM could render this approach shortsighted. Indeed, an argument can be made that a more aggressive approach to gradient reduction might improve long-term outcomes. As for most issues related to late outcomes in children, such questions are very difficult to address because of the extended time horizons, low disease incidence, and continuous evolution of disease management. It is therefore almost certain that management of outflow tract obstruction will continue to be based on physiologic principles and extrapolation of data from adult studies.

Management of Symptoms in Children with HCM

Beta-blockers Beta-adrenergic blockaders are the most common form of pharmacologic therapy in FHCM. Symptom improvement is related to an increase in lusitropy and alleviation of LV outflow tract obstruction. Although chest pain and dyspnea are often reduced, improved exercise capacity is less common. The response appears to be dose dependent and very high dosage levels have been tested. The use of these agents in children has been associated with a high incidence of side effects such as fatigue, depression, sleep disorders, and impaired school performance. Despite early improvement, symptoms often recur and may not respond to dose escalation. Studies of the impact of beta-blocker therapy on survival in adults and children have invariably been uncontrolled but generally have not identified a measurable effect on survival. In a report of an uncontrolled observational study in children, a small number of pediatric patients in each of two geographically distinct areas were compared, with only one of the centers treating all HCM patients with high-dose propranolol. Unusually high mortality (52% 10 year survival) was found in the untreated cohort compared with no mortality in the treated cohort [66]. These findings stand in stark contrast with many prior, larger studies that failed to identify a survival benefit from propranolol although dosage as large as was used in this cohort (>4.5 mg/kg/day) has not generally been used. Additionally, the high mortality in the untreated group is difficult to reconcile with large pediatric studies that have found a 10-year survival of >80% in unselected HCM populations [38]. The results of this report may be in part related to the well-known confounder that stratification based on geographic location is often associated with genetic stratification, particularly for autosomal dominant diseases where multiple family members of individual pedigrees segregate to the same cohort.

Calcium channel blockers Calcium channel blockers in general and verapamil in particular have been used extensively in patients with FHCM. Sustained improvement in diastolic relaxation is generally noted in response to verapamil administration with secondary reduction in diastolic pressure and mean left atrial pressure [67, 68], resulting in a reduction in dyspnea and increase in exercise capacity. Improved distribution of subendocardial blood flow and diminished inducible ischemia have been noted as well [69]. Although verapamil may exacerbate congestive heart failure in older patients, pediatric tolerance has been excellent, even in neonates [42]. In contrast to the beta-blockers, adverse effects of calcium channel blockers in children are rarely encountered.

Disopyramide Disopyramide is a type Ia antiarrhythmic agent with negative inotropic properties that has been advocated to be used in combination for patients with FHCM unresponsive to beta-blocker or verapamil. The potent negative inotropic effect of disopyramide diminishes LV outflow obstruction and mitral regurgitation and has been associated with variable results, with clinical improvement in some but not all patients. Several uncontrolled case series have found reduced obstruction at both rest and provocation and symptomatic improvement in up to 2/3 of patients who remained symptomatic on standard therapy [70, 71]. The experience in adults has not identified a significant incidence of proarrhythmic effects, and the vagolytic side effects can be managed with concomitant cholinesterase inhibitor therapy when needed [72]. The published experience in pediatrics consists primarily of case reports, although the safety profile appears acceptable based on the experience in adults and on the pediatric experience using this drug for neurocardiogenic syncope [73]. Symptomatic LV outflow obstruction can be a particularly difficult issue in the first 2 years of life, a time period when recurrence of obstruction after effective myectomy is particularly common. Dosing in small children may require monitoring of plasma concentrations as therapeutic levels often require much higher dosing than in older patients [74].

Angiotensin-converting enzyme inhibitors (ACEi) Inhibition of the renin-angiotensin system has a favorable impact on LVH and diastolic function in secondary hypertrophy but has rarely been used in FHCM. Patients with dynamic LV outflow tract obstruction respond negatively to ACEi with a fall in cavity size and increase in outflow gradient, as well as impaired LV relaxation and compliance [75]. The potential for exacerbation of outflow obstruction has generally led to the conclusion that these as well as other systemic vasodilators are contraindicated in HCM. However, more recent data have noted a significant role for aldosterone [76] and the renin-angiotensin system in general [77] in modulating the phenotypic manifestations of HCM, and it is possible that blocking this system might reduce hypertrophy and fibrosis in patients with HCM [78]. Conclusive data are not available, and there is no reported experience in children with HCM.

Asynchronous pacemaker therapy Asynchronous ventricular pacing for treatment of symptoms in patients with LV outflow tract obstruction has largely fallen into disfavor. Results in small cohorts of children with outflow obstruction described symptomatic improvement, reduced outflow obstruction, reduced LVH, and improved exercise tolerance [79–81]. However, subsequent controlled studies found that only about 60% of subjects improved, and in two-thirds of these, the benefit appeared to reflect placebo effect with an

adverse response in 5% [82]. The significant placebo effect has been seen in other studies [83], providing a plausible explanation for persistent symptom relief after pacing termination [84], an effect not confirmed in later studies [85]. We consider surgical or (rarely) transcatheter septal reduction as first-line therapy in patients with obstructive FHCM who are symptomatic despite maximum medical therapy and would only consider asynchronous pacing if other interventions are not possible.

Alcohol septal ablation Septal infarction following transcatheter infusion of absolute alcohol directly into septal coronary perforators can result in a reduction in septal thickness and relief of LV outflow tract obstruction, with symptomatic improvement and increased exercise tolerance. Procedural complications are higher than for surgical myectomy, primarily related to a tenfold higher incidence of permanent complete heart block [86–88]. Success is highest when obstruction is related to basilar septal hypertrophy, whereas patients with intrinsic mitral valve abnormalities or obstruction that is more apical are poor candidates, limiting the number of patients that are candidates for this intervention. Results to date indicate septal ablation may represent a reasonable alternative to surgery for relief of outflow tract obstruction in selected patients [89]. Coil occlusion of these vessels has been reported as an alternative method of inducing controlled infarction [90]. There is almost no reported experience with these techniques in children, in part related to the smaller coronary vessels in younger children and concerns about the lifetime consequences of a large septal infarction. Accordingly, the ACCF/AHA guidelines currently advise against routine utilization of alcohol septal ablation in childhood and young adulthood [1].

Surgical myectomy In symptomatic subaortic stenosis, septal myotomy-myectomy results in symptomatic improvement in nearly all patients, and most contemporary studies have documented a high success rate, near-zero mortality, and few complications with the procedure in adults, when performed by high-volume, experienced HCM surgeons [91–94]. Results in children have been similar to those reported in adults [95, 96] with survival rates as high as 98.6% at 5 years [97]. Mitral regurgitation often improves in response to myectomy due to improved intraventricular flow patterns, and surgery permits concomitant mitral valve repair in patients with underlying mitral valve abnormalities. Although recurrence of obstruction is rare in older patients (2% [98]), it is common in neonates and infants, likely due to continued growth as well as associated disease states, when present, in these age groups. In our experience, despite complete relief of LV outflow tract obstruction, recurrence to pre-intervention gradients is seen within a year in up to 50% of children under age 2, in particular.

Management of SCD Risk in Children with HCM

Exercise restriction Avoidance of high-intensity exercise is generally recommended for patients with FHCM. The rationale for this restriction is based on the observation that even though SCD in HCM occurs less frequently during exercise, when adjusted for the amount of time spent exercising, SCD has a higher than expected association with exercise [99]. Nevertheless, the basis for this recommendation has several serious weaknesses [100]. The true incidence of FHCM in athletes who experience SCD is uncertain since genetic confirmation is rarely available and diagnosis is based on morphologic criteria that may not unequivocally differentiate FHCM from physiologic hypertrophy. It is clear that some patients with FHCM tolerate intense, competitive athletic participation without symptoms or SCD [101]. Population studies have documented the apparent paradox that although there is a transient increase in the risk for SCD during intense exercise in patients with coronary artery disease who regularly participate in low- and high-level exertion, these individuals experience an overall reduction in the risk for SCD [102, 103]. Additionally, individuals who do not exercise regularly have an exaggerated risk of SCD during exercise [104]. In fact, it is precisely those individuals with cardiovascular risk factors who derive the largest risk reduction from regular participation in moderate to intense exercise [104]. There are no data to substantiate improved survival in HCM related to either exercise exclusion or inclusion, and indeed this is an experiment that is almost impossible to perform.

In view of the fact that the risk versus benefit ratio of exercise restriction is unknown, the adverse impact of exclusion from exercise participation should be considered when making recommendations to young patients with FHCM. Several population studies have now documented that exercise and sports participation during childhood are predictive of activity level in adults [105]. Detraining and social stigmatization are particularly difficult problems for the adolescent who is excluded from the usual school activities and peer interactions. It is common for the adolescent athlete who is abruptly excluded from sports participation to experience significant adverse psychological reactions resulting in social withdrawal, impaired school performance, and depression that may in some cases require hospitalization. Balancing the potential risks and benefits of exercise restriction is one of the most challenging aspects of providing care to the adolescent newly diagnosed with FHCM. Competitive team sports elicit an emotional overlay that appears to increase the risk associated with participation, in addition to demanding more intense exercise, and can therefore be justifiably proscribed. Certain activities, such as weight lifting, are associated with high levels of circulating catecholamines that can predispose to

arrhythmias and elicit a marked stimulus to eccentric cardiac hypertrophy. However, in patients who do not manifest high-grade arrhythmias or exercise-induced arrhythmias or hypotension, there is little evidence to indicate that moderate aerobic-type exercise represents a significant risk and it does provide measurable hemodynamic and psychological benefits. Although it would be highly desirable to define an unequivocal line demarcating the level of exercise participation that provides the optimum division between risk and benefit, this is a decision that must be individualized and is associated with huge uncertainties. The shortage of applicable data have resulted in recommendations for exercise participation that is limited to activities deemed "low static" and "low dynamic" (Fig. 9.7) [106]. These activities classified as "1A sports" are the only ones currently recommended in patients with HCM by the AHA/ACC Task Force [106]. Those patients who are genotype positive but phenotype negative are not subject to exercise restrictions by this task force report.

Antiarrhythmics Although most instances of SCD in FHCM are arrhythmic events, prophylactic antiarrhythmic therapy has not been proven effective [107]. Amiodarone was initially reported to reduce the incidence of SCD in certain high-risk subgroups, but subsequent studies indicated an increased risk of SCD [108]. Furthermore, the pediatric experience with amiodarone therapy for FHCM is very limited due to the toxicity associated with chronic therapy. The promising experience with ICDs has resulted in a shift to recommending an ICD for patients with ventricular tachycardia on Holter monitor or resuscitated cardiac arrest [109].

ICD Implantation Implantation of an ICD in a child is a difficult decision because the incidence of SCD in HCM is <1% per year in both adults and children, and ICDs are not without hazard [110], including depression, anxiety, inappropriate discharges, and overall reduced quality of life. Even in adults, the annualized frequency of inappropriate ICD intervention rate exceeds the appropriate discharge rate (4.8% versus 3.3%). "Appropriate discharges" occur at a much higher rate than the expected rate of SCD by at least twofold, supporting the interpretation that not all of the arrhythmias that trigger ICD discharge would be otherwise fatal and suggesting that less than 25% of discharges are actually lifesaving. Nonetheless, the data concerning efficacy of ICDs in HCM derive primarily from studies reporting the frequency with which "appropriate discharges" take place, an event that is used as a surrogate for aborted SCD [60]. In general, the minimum requirement for consideration of ICD implantation is the potential for a reduced risk of SCD, which generally means identification of subpopulations at higher risk for SCD.

For purposes of risk stratification, a number of risk factors for SCD in adults with FHCM have been proposed, as presented in Table 9.2. The 2011 ACCF/AHA guidelines [2] recognized aborted SCD and sustained ventricular tachycardia as established, independent risk factors for SCD warranting an ICD. Several other potential risk factors are of less certain significance, including family history of SCD in a first-degree relative, recent unexplained syncope, nonsustained ventricular tachycardia, extreme hypertrophy (LV maximum wall thickness >3 cm), and abnormal blood

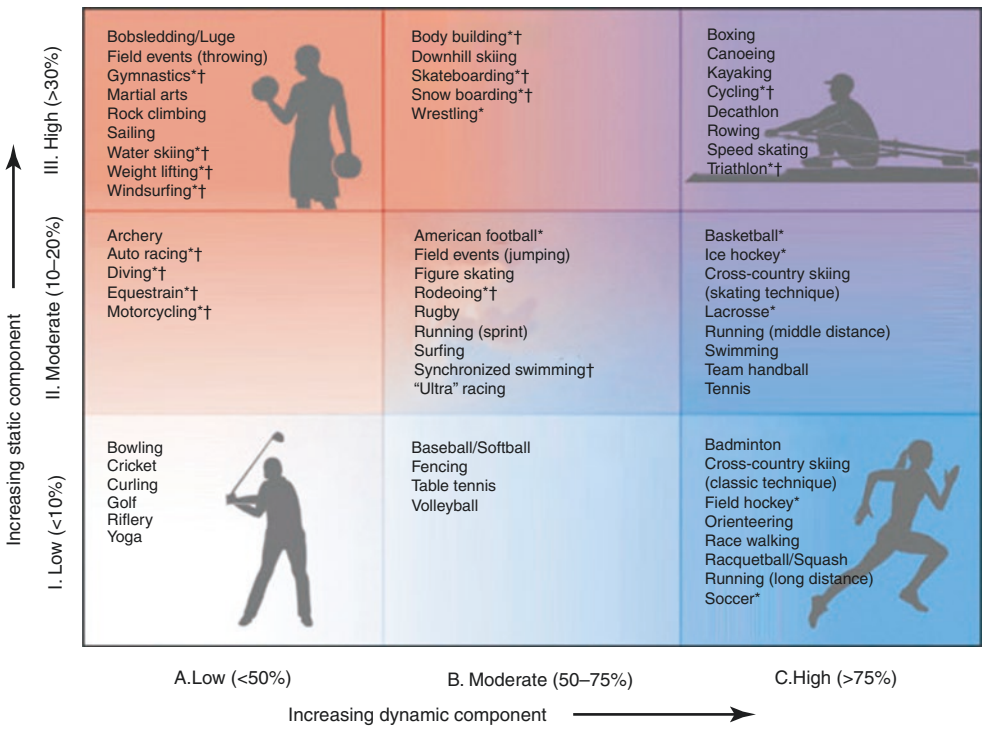

Fig. 9.7 The classification of sports activity by the AHA/ACC Task Force [106] is based on peak static and dynamic components achieved during competition. The increasing dynamic component is defined in terms of the estimated percentage of maximal oxygen uptake. The increasing static component is related to the estimated percentage of maximal voluntary contraction. The lowest total cardiovascular demands (cardiac output (dynamic) and blood pressure (static)) are shown in the palest color, with increasing demand indicated by increasing color intensity [106]

pressure response to exercise. The list of potential risk factors continues to evolve, such as the findings on a recent meta-analysis of data in adults with HCM indicating that positive delayed hyper-enhancement on CMR (DHE-MRI) correlates with all-cause mortality and demonstrates a trend toward significance for SCD [111]. There are also reports that some risk factors may need to be refined, such as a report of an "inverted U-shaped" risk associated with increased severity of maximum wall thickness wherein risk peaks at 3 cm with a fall in risk thereafter, such that the 5-year risk of SCD falls to near-baseline levels at wall thickness >43 mm [112]. The data on many of these risk factors are characterized by reports both in favor and against their significance, oversampling of populations with multiple reports evaluating overlapping cohorts, and identification of risk factors on univariate analysis with insufficient power to evaluate their significance on multivariate analysis. Some groups have reported that risk is higher in the presence of multiple risk factors, but this also remains controversial. The ACC/ESC and ACCF/AHA have published similar approaches to risk stratification in 2003 [113] and 2011 [2], and O'Mahony et al. [114] compared the performance of these sets of guidelines and found that the area under the curve (AUC) of the receiver operator curve between both systems was nearly identical (0.61 and 0.63). Unfortunately, this implies that both systems are only marginally more predictive than random chance (AUC = 0.5).

More recently, O'Mahony et al. [115] published a risk prediction model for sudden death based on a cohort of 3675 patients with HCM (an online calculator for their risk prediction model is available at http://www.doc2do.com/hcm/webHCM.html). Their model includes a family history of sudden death, maximum wall thickness, m-mode fractional shortening, left atrial diameter, maximum left ventricular outflow tract gradients at rest and with Valsalva, non-sustained ventricular tachycardia, and unexplained syncope. Potential advantages of their model compared to the prior risk models are the inclusion of maximum wall thickness as a continuous variable and addition of fractional shortening, left atrial diameter, and outflow tract gradients to the risk factors. When the utility of this risk scoring system was subsequently retested in an existing cohort of 1629 subjects by Maron et al. [116], they found that only 4 of 35 sudden death events met the criteria for ICD placement based on these criteria. This is not an unanticipated finding because although the majority of patients with HCM have a risk factor profile with ≤1 ACC/AHA risk factor, these patients so greatly outnumber the high-risk patients that most sudden deaths occur in the "low-risk" group despite the fact that individually they have a lower risk of SCD.

It is clear that even in adults, current methods for risk stratification for appropriate ICD use remain inadequate insofar as, based on current ICD utilization rates after implantation in high-risk subjects and an anticipated device life span of 5 years, 83% of devices will be not be used prior to replacement [117]. The published risk models for sudden death in HCM are based almost exclusively on adult cohorts, and models that incorporate body size, pubertal status, and age have not been developed. These limitations are further compounded in children since the risk-benefit ratio for the ICD is less favorable than in adults. For example, in a recent review, 28% of children with an ICD experienced appropriate, potentially lifesaving ICD discharges, 25% experienced inappropriate discharges, and there was a 21% incidence of lead failure [118]. Children are also at higher risk for device-related infections and adverse psychosocial impact than adults. Therefore, although potentially lifesaving, pediatric-specific implantation indications must be developed and tested before this technology will achieve its full potential in children.

Aborted SCD and sustained ventricular tachycardia are generally accepted as indications for ICD implantation in children, but the other proposed risk factors are at best controversial. Identification of a meaningful risk profile is particularly problematic in the young because of the rarity of the disease in children and the low rate of SCD. For example, in one of the few studies to include children, unexplained syncope (i.e., excluding neurally mediated syncope) was identified as a risk factor for SCD in children with a hazard ratio of 7.8 [119], but the small number of children and adolescents in this series who experienced syncope seriously limits the strength of this conclusion. Similarly, NSVT is uncommon in children with HCM and in one series [120] was not associated with SCD, although confidence in this result is seriously limited due to a small number of events in a single study. Similarly, one investigation of exercise blood pressure response in children found that it was predictive of non-SCD but not of SCD [121], but again the study sample is too small to exclude an association. Although severity of hypertrophy has been reported as risk factors for SCD in children in some reports [122], other reports have found it to be only a risk factor for non-SCD [121]. In a provocative report of a relationship between SCD and the presence of myocardial bridging in children with FHCM [123], Yetman et al. reported that surgical unroofing of the coronary can prevent SCD, whereas other investigations in children have reported that myocardial bridging is not a risk factor for SCD [124]. Most of the more recently reported potential risk factors such as DHE-MRI have not been investigated in children.

Overall, the data available concerning risk factors for SCD in children with HCM are not adequate to justify differentiation from adults. However, given the age-related risk of ICD implantation in children, an age-adjusted management approach is almost certainly required. Aborted SCD is considered an indication for ICD regardless of age. An ICD

is recommended for adolescents with sustained ventricular tachycardia. Reliance on the presence of two or more of the other reported risk factors (family history of SCD due to HCM in first-degree relative, abnormal blood pressure response to exercise, syncope, non-sustained ventricular tachycardia, extreme hypertrophy, or fibrosis on cardiac MRI) is at best controversial. For preadolescents, primary prevention is generally not considered, and only aborted sudden death or documented high-risk arrhythmias are used as indicators.

Conclusions This review emphasizes issues concerning diagnosis and management of the diverse set of disorders that fall within the clinical phenotype of HCM in children with a focus on the differences in the disease between children and adults, emphasizing how certain management recommendations must be modified when applied to pediatric patients. In addition to issues that are typically addressed in reviews such as this, there are additional practical considerations in the care of these patients that are commonly encountered in practice but are experientially based and are seldom discussed in academic presentations on the disease. Educating families concerning these practical issues is an important aspect of their care insofar as the medical and general community will often be unaware of the special considerations that can impact these patients. These observations can be summarized as clinical pearls as follows:

Clinical Pearls

- Anesthesia: Families and patients need to be aware that the hemodynamic response to anesthesia can present significant risks in patients with HCM and should be undertaken in facilities that have cardiac anesthesia support. Procedures such as oral surgery (e.g., third molar extraction) that are often performed in office settings with light anesthesia require a more controlled setting with a dedicated anesthesiologist.
- Stimulant drug therapy is often prescribed for attention-deficit disorders. For children with HCM, approval of this therapy is often sought from the managing cardiologist. The proarrhythmic effects of exogenous catecholamines and intense exercise have led to particular concerns related to the use of these drugs in HCM. Indeed, in 2006 the Food and Drug Administration received contradictory advice from two advisory panels concerning the advisability of a black box warning for use of these medications in children, even in the absence of heart disease. Ultimately the warning was not issued, and in fact no verified association with SCD has been documented. Although caution is undoubtedly warranted, these drugs have proven benefits in at least some of these patients. It is no doubt prudent to limit dosing to the minimally effective dose in conjunction with periodic Holter monitoring, and to continue use only in those who have clear improvement, but a categorical exclusion of these drugs is not advisable due to the positive risk/benefit ratio for their use.
- Stimulant drug abuse: Both prescribed and illicit stimulants are common recreational drugs and drugs of abuse. The cardiotoxic effects of acute and chronic cocaine use are well established, but it is fundamentally impossible to study this issue in humans, and therefore the information concerning the risks of other illegal stimulants in patients with HCM are limited to case reports. Open and non-accusatory discussions with teens, particularly those heading off to college and often separately from parental observation, can alert them to the fact that the issues for them go well beyond the usual legal and social taboos.
- Dehydration: Adequate vigilance for dehydration in infants is always a challenge, and gastroenteritis is common at this age. Similarly, active teenagers often do not realize when they are failing to keep up with fluid losses. Dehydration is poorly tolerated in HCM because of outflow tract obstruction and ventricular non-compliance. Although prevention is the best option, families need to seek help early in case of inadequate fluid intake or excess fluid loss.
- School activities: Institutions have variable policies concerning health-related risks, and although they occasionally push children beyond their safety zone, more commonly they will impose activity restrictions on children with HCM that are excessive, resulting in significant social isolation and stigmatization. The physician frequently needs to intercede and assume responsibility for the decision to permit participation in school outings and other activities.
- Syncope: Adolescents should be counseled as to how to respond to sensations of faintness and palpitations. Most are not aware of the dangers of being held upright during syncope, which interferes with alleviation of hypotension-induced cerebral hypoperfusion. It is similarly important to emphasize the significance of syncope in patients with HCM and to alert them to rapidly seek health-care attention.

- Situational depression: Newly diagnosed adolescents and those who have recently had ICD implantation are at increased risk for depression, suicidality, social withdrawal, decreased school performance, substance abuse, diminished exercise participation, and weight gain. More frequent follow-up and closer observation by parents and providers are required in the first year following either of these life-changing events, and anticipatory preemptive therapy is indicated in some patients.
- In-home automated external defibrillator (AED): Families frequently inquire as to whether they should purchase an external defibrillator for their home. Statistically, the odds of use of an in-home AED are limited by the average adverse event rate of ~1%/year and are further reduced by the amount of time spent in the house. The final decision is clearly up to the family, but in general patients who are felt to be at sufficient risk to justify continuous access to a defibrillator should have an ICD.
- In-school AED: Families frequently inquire as to whether they should insist that external defibrillators be available in schools. The benefits to availability of these devices in the school setting are well documented [125], and their availability and appropriate personnel training should certainly be encouraged as a general policy. However, for the same reasons as described for in-home AEDs, the probability of use for a specific child is quite low.
- Cardiopulmonary resuscitation (CPR) training: Patients and their families need to understand that in the case of an arrest, CPR should be undertaken regardless of whether an ICD has been placed, which is a common source of confusion on the part of nonmedical personnel. CPR training is a useful skill in general and family members should be encouraged to undertake it.

Questions

1. The definition of hypertrophic cardiomyopathy in childhood is the absence of a hemodynamic cause of left ventricular hypertrophy in conjunction with:
   A. Left ventricular wall thickness z-score >2
   B. Presence of known pathogenic sarcomeric gene
   C. Left ventricular wall thickness z-score >4
   D. A and B
   E. B and C

Correct answer = C. The disease is defined on the basis of severity of hypertrophy and does not depend on etiology. Based on incidence of disease, the AHA and ESC published criteria of z-score >2 are wrong, and to avoid overdiagnosis, a z-score >4–5 is used to make the diagnosis.

2. The incidence of sarcomeric hypertrophic cardiomyopathy in childhood is:
   A. >1/500
   B. <1/500
   C. <1/1000
   D. <1/10,000
   E. <1/100,000

Correct answer = E. Although the rate of pathogenic sarcomeric gene carriage in the population is estimated at 1/500, onset of the phenotype is uncommon prior to adolescence. The incidence of all forms of HCM in childhood is 1/100,000, but in fact in preadolescents, non-familial hypertrophic cardiomyopathy is more common than familial hypertrophic cardiomyopathy.

3. Etiologic diagnosis of hypertrophic cardiomyopathy is particularly important in infancy because:
   A. Etiology-specific therapies are available for some diseases.
   B. Decisions concerning surgical indications are etiology-specific.
   C. Spontaneous resolution is characteristic of some forms of infantile hypertrophic cardiomyopathy.
   D. All of the above.
   E. A and C.

Correct answer = E. A number of the inborn errors of metabolism have specific therapies that need to be initiated early in life in order to maximize long-term benefit, a situation that is likely to become more important over time as new therapies become available. Infants of diabetic mothers are expected to have full resolution of hypertrophic cardiomyopathy within months, and only supportive care is advised.

4. Therapeutic decisions in the management of hypertrophic cardiomyopathy associated with Noonan syndrome should take into consideration which of the following:
   A. Infants with congestive heart failure during infancy have <50% survival to 1 year.
   B. Biventricular outflow tract obstruction is more common than in other forms of hypertrophic cardiomyopathy.

C. Most childhood deaths in Noonan syndrome are related to arrhythmias.
D. A and B.
E. B and C.

Correct answer = D. Less than 1/3 of infants with Noonan-related hypertrophic cardiomyopathy who manifest congestive heart failure survive until 1 year of age and congestive heart failure is responsible for their demise in almost all cases. Because of the high incidence of pulmonary stenosis associated with Noonan syndrome, the finding of biventricular outflow tract obstruction should always raise the question as to whether Noonan syndrome is responsible.

5. The presence of a pathogenic sarcomeric gene in the absence of sufficient myocardial hypertrophy to meet criteria for hypertrophic cardiomyopathy is significantly associated with which of the following:
   A. An increased incidence of sudden cardiac death
   B. Increased incidence of exercise-related adverse events
   C. Diminished myocardial relaxation velocities
   D. A and B
   E. A and C

Correct answer = C. More than 50–80% of carriers of sarcomeric gene mutations associated with hypertrophic cardiomyopathy have evidence of diminished myocardial relaxation velocities. However, in the absence of hypertrophy, no increased propensity to arrhythmia or sudden death has been reported.

6. Potential individual benefits of gene testing in phenotype-negative first-degree relatives of subjects with hypertrophic cardiomyopathy for whom the pathogenic gene has been defined include which of the following:
   A. Prevention of transmission of the gene
   B. Eligibility for mutation-specific clinical trials and therapies
   C. Elimination of longitudinal monitoring for evolution of the disease
   D. Determination of whether his or her offspring requires screening for the phenotype
   E. All of the above

Correct answer = E. Embryo preselection can prevent disease transmission and is now a commonly available intervention. Clinical trials of drugs that may prevent disease expression are already under way. Neither the individual nor his or her first- and second-degree relatives who would otherwise require periodic screening for new disease expression can be excluded from this need unless they do not carry the gene.

7. Indications for myectomy in patients with hypertrophic cardiomyopathy include which of the following:
   A. NYHA heart failure class >II unresponsive to medical therapy
   B. Unexplained syncope or aborted sudden death
   C. Resting left ventricular outflow tract gradient >80 mm Hg unresponsive to medical therapy
   D. Exercise-induced ventricular outflow tract gradient >100 mm Hg
   E. All of the above

Correct answer = A. Myectomy has been shown to result in improved clinical status but has not been found to reduce the risk of sudden death. Some patients tolerate high outflow gradients without symptoms, and therefore even high resting or inducible gradients are not considered an indication for surgery. At present, symptoms unresponsive to medical therapy are considered the only indication for surgery.

8. Exercise testing for inducible left ventricular outflow tract obstruction is helpful for which of the following:
   A. Distinguishing physiologic from pathologic hypertrophy
   B. Assessing the risk of sudden death
   C. Evaluating the cause of exercise intolerance
   D. Determining the need for exclusion from sports participation
   E. Predicting the response to asynchronous pacing

Correct answer = C. The presence of exercise-induced outflow tract obstruction creates a greater propensity for exercise intolerance and therefore helps to predict the magnitude of potential benefit that may be obtained from myectomy. However, exercise-induced outflow tract obstruction can be seen in physiologic hypertrophy, is not a known risk factor for sudden death, is not an indication for sports exclusion, and is not related to the potential hemodynamic benefits of asynchronous pacing.

9. Factors which interfere with the application of adult recommendations for implantable cardioverter-defibrillator (ICD) implantation for primary prevention in children include:
   A. Lack of pediatric sudden death risk factor verification
   B. Lower efficacy rate for ICD in children
   C. Higher risk of adverse events related to the ICD
   D. All of the above
   E. A and C

Correct answer = E. The identified risk factors are derived exclusively in adults, and insufficient pediatric data exist to verify these risk factors in children. The rate of ICD

complications is considerably higher in children, but the efficacy of the ICD does not appear to be less than that in adult patients.

10. A difference between hypertrophic cardiomyopathy management in children vs adults is:
    A. Digoxin is more helpful in the pediatric population.
    B. Alcohol septal ablation is better tolerated in the pediatric population.
    C. Genetic testing is more cost-effective in the adult population.
    D. There is a much more diverse group of etiologies in the adult population.
    E. None of the above.

Correct answer: E. Genetic testing is more cost-effective in the pediatric population as there is a much more diverse group of etiologies in the pediatric population. Digoxin is relatively contraindicated in pediatric HCM patients. Alcohol septal ablation is not used in the pediatric population at this time.

11. A 15-year-old female with G+P- HCM status wishes to participate in competitive sailing. Which of the following statements is true?
    A. Sailing is not a 1A sport and should be discouraged.
    B. Her HCM status is not a contraindication to her participation in sailing.
    C. No competitive sports are allowed for patients with G+P- HCM status.
    D. Provided her Holter and exercise stress test are normal, she can participate and does not require follow-up until age 20 years.
    E. None of the above.

Correct answer: B. Pediatric patients with G+P- status do not have to avoid sports, but she should continue to have yearly echocardiograms.

12. An asymptomatic teenager with known HCM presents for routine follow-up at 12 weeks gestation with her first child. Which of the following statements is appropriate?
    A. She should strongly consider elective termination because her fetus has a 50% chance of HCM.
    B. She should strongly consider elective termination because pregnancy is not well tolerated in women with HCM.
    C. She should not deliver vaginally unless her left ventricular outflow tract gradient is <2 m/s during Valsalva.
    D. A fetal echo should be performed at 20 weeks of gestation; if there is no evidence of fetal hydrops, she may continue with the pregnancy.
    E. None of the above.

Correct answer: e. Pregnancy is usually well tolerated in asymptomatic women with HCM. There is no evidence to suggest that an LVOT>2 m/s during Valsalva is associated with the need for a cesarean delivery. Fetal hydrops is not typically associated with HCM and does not pose a risk to the mother. It is inappropriate to advise elective termination.

13. A 14-year-old male with a history of Friedreich ataxia presents to you for cardiac consultation. Which of the following statements are true?
    A. There is less than a 10% that he will manifest the phenotype of HCM, but an echocardiogram is indicated.
    B. There is a greater than 50% chance that he will manifest the phenotype of HCM.
    C. Patients with Friedreich ataxia have a higher incidence of SCD.
    D. Both A and C.
    E. Both B and C.

Correct answer: B. Patient's with Friedreich ataxia have a >50% incidence of HCM, and they rarely present prior to the onset of neurologic symptoms, tend to manifest symmetric hypertrophy without outflow obstruction, and do not appear to be at significant risk for SCD.

14. Which of the following statements is true?
    A. Parents are highly encouraged to purchase a portable AED for use at home and school.
    B. Parents are highly encouraged to learn CPR unless their child has an implantable defibrillator.
    C. Parents are highly encouraged to learn CPR, purchase a portable AED, and request that the school has one as well.
    D. CPR has not demonstrated any benefit to survivability of out-of-hospital arrests in pediatric patients with HCM.
    E. CPR should be undertaken in patients with out-of-hospital cardiac arrest regardless of the presence of an AICD.

Correct answer: e. Patients and their families should understand that in the case of an arrest, CPR should be undertaken regardless of whether an ICD has been placed. Statistically, the odds of use of an in-home/in-school AED are limited by the average adverse event rate of ~1%/year and are further reduced by the amount of time spent in the house or class.

The final decision is clearly up to the family, but in general patients who are felt to be at sufficient risk to justify continuous access to a defibrillator should have an ICD.

15. Which of the following would be most helpful to distinguish between HCM and athlete's heart in an ice hockey player?
    A. Significantly decrease intensity of on and off ice training for 6 months and reimage.
    B. Cessation of all activity for 1 year and reimage.
    C. Myocardial biopsy to look for myofibril disarray.
    D. Continuation of participation in practices but not games for 1 year.
    E. Perform a cardiopulmonary stress test and if normal, can participate.

Correct answer: A. The strongest evidence of physiologic hypertrophy (aka athlete's heart) is significant reduction in hypertrophy in response to detraining, a process that often requires 6–12 months of relative inactivity. Cessation of all activity in a young hockey player would be helpful but will most likely have a low level of compliance and places an unnecessary and excessive limitation on the patient's quality of life. Myocardial biopsy is both invasive and helpful only on infiltrative disorders. Practices in ice hockey are as intense if not more so than game situations where short shifts are emphasized. A normal cardiopulmonary exercise test does not rule out HCM.

16. Which of the following patients is most likely to have athlete's heart?
    A. An 18-year-old collegiate basketball player with a maximum septal thickness = 15 mm and a peak oxygen consumption >50 ml/kg/min
    B. A 16-year-old volleyball player with a maximum septal thickness = 15 mm and inverted T waves in the left lateral leads
    C. A 14-year-old track star with a maximum septal thickness = 20 mm and a VO2 >60 ml/kg/min
    D. A 12-year-old sedentary child with a maximum septal thickness = 13 mm
    E. A 14-year-old football player with a maximum septal thickness = 15 mm and a VO2 <45 ml/kg/min

Correct answer: A. While an IVS measurement is in the gray zone between athlete's heart and HCM, the fact that the VO2 obtained is >50 ml/kg/min is reassuring. Inverted T waves in the left precordial leads are typical for LVH with strain. An IVS measurement=20 mm is reasonably definitive for HCM. A sedentary child would not meet the definition for athlete's heart, and a VO2<45 ml/kg/min does not suggest a highly conditioned athlete.

17. Which of the following management strategies has thus far been the most efficacious in preventing sudden cardiac death in children with HCM?
    A. ICD implantation
    B. Exercise restriction
    C. Surgical myectomy
    D. Alcohol septal ablation
    E. Beta blockers

Correct answer: A. Implantable cardioverter-defibrillator (ICD) therapy remains the only therapeutic option that is unequivocally accepted as effective for improved survival in high-risk groups by reducing the incidence of SCD. Exercise restriction is only effective theoretically. Alcohol septal ablation is not employed in the pediatric population and has not been shown to improve survival. Surgical myectomy and beta blockers are effective in symptom management but have not been shown to reduce the risk of sudden death.

18. Hypertrophic cardiomyopathy has been associated with which of the following genetic syndromes?
    A. Trisomy 21
    B. Ehlers-Danlos
    C. Costello syndrome
    D. Turner syndrome
    E. Williams syndrome

Correct answer: C. HCM is seen in up to 20–30% of patients with Noonan's syndrome and other developmental syndromes of Ras/MAPK pathway dysregulation, the so-called RASopathies (Noonan syndrome, Costello syndrome, cardiofaciocutaneous syndrome, Noonan with multiple lentigines syndrome, and neurofibromatosis type 1). The other syndromes are not typically associated with HCM.

19. The typical EKG pattern in hypertrophic cardiomyopathy may include all of the following except:
    A. Third-degree AV block
    B. Left ventricular hypertrophy
    C. Inverted T waves in the left precordial leads
    D. Right bundle branch block
    E. None of the above

Correct answer: A. Complete heart block is associated with babies born to mothers with anti-Ro and anti-La antibodies, surgery, and Lyme disease. The EKG in HCM is abnormal >90% of the time with hallmark abnormalities including voltage criteria for LVH with or without strain, RBBB, left atrial enlargement, and deep Q waves.

20. What maneuver would you expect to increase the outflow murmur in this patient?
    A. Knee to chest in supine position
    B. Isometric handgrip

C. Phenylephrine
D. Amyl nitrate
E. None of the above

Correct answer: D. Amyl nitrate will decrease afterload, intensifying the dynamic left ventricular outflow tract murmur of HCM. Isometric handgrip and phenylephrine increase afterload, lessening the dynamic murmur of LVOT obstruction. Knee to chest will have a similar effect as squatting.

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Sudden Cardiac Death Risk Assessment

10

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Key Points

1. The overall annual incidence of SCD or equivalent is less than 1%.
2. Risk prediction strategies are based on the analysis of a number of risk factors that include age, unexplained syncope, family history of sudden cardiac death, maximum left ventricular wall thickness and non-sustained ventricular tachycardia.
3. Patients with multiple clinical risk factors and/or an estimated 5-year risk of sudden death ≥4% may be candidates for a primary prevention ICD.
4. There is no evidence that pharmacological therapy reduces the risk of SCD in HCM.

Hypertrophic cardiomyopathy (HCM) is a leading cause of sudden cardiac death (SCD) in young adults [1–4]. Small selected cohort studies from tertiary referral centres initially reported sudden death rates of >2%/year, but larger contemporary studies demonstrate a more favourable clinical course with SCD rates ranging between 0.6 to 0.9%/year [4–10]. Nevertheless, individuals at high risk of SCD need to be identified so they can be offered lifestyle advice and potentially life-saving treatment with implantable cardioverter defibrillators (ICD).

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Mechanism of Sudden Cardiac Death

Sudden cardiac death is a consequence of multiple interacting mechanisms including abnormal intracellular calcium flux, myocyte disarray, small vessel disease and fibrosis [7, 11–18]. Arrhythmic events may be triggered by myocardial ischemia, tachycardia and physical exertion. The interaction of triggers and the underlying substrate may be modified by abnormal peripheral vascular responses and left ventricular outflow tract obstruction [1, 3, 14–16, 19–26].

Assessment of Risk for SCD

As the risk of SCD is present over a whole lifetime, and can sometimes be dissociated from the structural abnormality or severity of symptoms, a proactive approach to the assessment of risk is paramount [7, 27]. Contemporary clinical practice guidelines recommend that SCD risk be estimated by evaluating clinical parameters that reflect the severity of the underlying myocardial disease. This assessment is then used to guide clinical decision-making with respect to prophylactic ICD implantation. Although many observational cohort studies suggest that this approach identifies patients at greatest risk, it has some limitations [27–30]. For this reason, new risk tools based on multi-parametric models derived from large patient cohorts are being developed [5].

Prior Cardiac Arrest or Sustained Ventricular Tachycardia

Patients with HCM who survive VF or sustained ventricular tachycardia are at very high risk of subsequent lethal cardiac arrhythmias [31–35]. In clinical practice, this population is very small, and decisions on ICD therapy rarely pose a clinical dilemma. There are few data on exercise-induced ventricular arrhythmias, but one study suggests that it is associated with a higher risk of sudden cardiac death [36].

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Primary Prophylaxis

There is an extensive literature on aspects of the HCM phenotype that associate with an increased risk of SCD, most of which can be determined from clinical history and a non-invasive evaluation that includes ambulatory ECG, transthoracic echocardiography (or cardiac magnetic resonance imaging (CMR) in the case of poor echo windows) and a symptom-limited exercise test. Some experts recommend CMR in all HCM patients, due to the incremental value it adds in both identifying areas not well visualised by transthoracic echocardiography and identifying scar burden through extent of delayed hyper-enhancement. The relative importance of individual clinical predictors ("risk factors") varies with age, but with the exception of prior cardiac arrest, there is little evidence that any one parameter is more predictive than another. Table 10.1 lists some of the most important clinical risk factors.

Risk Stratification Models

In 2003, the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) proposed an SCD risk stratification algorithm based on a number of major clinical risk factors: non-sustained ventricular tachycardia (NSVT), severe left ventricular hypertrophy, family history of sudden cardiac death, abnormal systolic blood pressure response during exercise (ABPRE) and unexplained syncope [1, 26, 34, 37–42]. This guidance was based on observational data showing that the numeric sum of risk factors reflects the risk of SCD [1, 25, 33–35, 43]. Patients without risk factors were considered to be at low risk of SCD, and no specific treatment was recommended, whereas individuals with multiple risk factors were deemed to be at sufficient risk to justify the implantation of an ICD. Treatment of patients with a single risk factor was left to the discretion of the treating physicians [35, 44].

Table 10.1 List of major risk factors for sudden cardiac death in hypertrophic cardiomyopathy

Risk factor	Comment
Age	There is an increased risk of SCD in younger patients Some risk factors are more predictive in younger patients, most notably, NSVT severe LVH and unexplained syncope
Non-sustained ventricular tachycardia	NSVT (defined as ≥3 consecutive ventricular beats at ≥120 beats/min lasting <30 s) occurs in 20–30% of patients during ambulatory ECG monitoring and is an independent predictor of SCD Increased rates and duration of NSVT may increase the risk
Maximum left ventricular wall thickness	The severity and extent of LVH measured by TTE are associated with the risk of SCD Several studies have shown the greatest risk of SCD in patients with a maximum wall thickness of ≥30 mm, but there are few data in patients with extreme hypertrophy (≥35 mm)
Family history of sudden cardiac death at a young age	A family history of SCD is usually considered clinically significant when one or more first-degree relatives have died suddenly at aged <40 years with or without a diagnosis of HCM or when SCD has occurred in a first-degree relative at any age with an established diagnosis of HCM
Syncope	Syncope is common in patients with HCM but is challenging to assess as it has multiple causes Non-neurocardiogenic syncope for which there is no explanation after investigation is associated with increased risk of SCD Episodes within 6 months of evaluation may be more predictive of SCD
Left atrial diameter	Two studies have reported a positive association between LA size and SCD, but there are no data on the association between SCD and LA area and volume
Left ventricular outflow tract obstruction	A number of studies have reported a significant association with LVOTO and SCD
Exercise blood pressure response	Approximately one third of adult patients with HCM have an abnormal systolic blood pressure response to exercise characterised by progressive hypotension or a failure to augment the systolic blood pressure that is caused by an inappropriate drop in systemic vascular resistance and a low cardiac output reserve Abnormal exercise blood pressure response is associated with a higher risk of SCD in patients aged ≤40 years

Adapted from Elliott et al. [48]

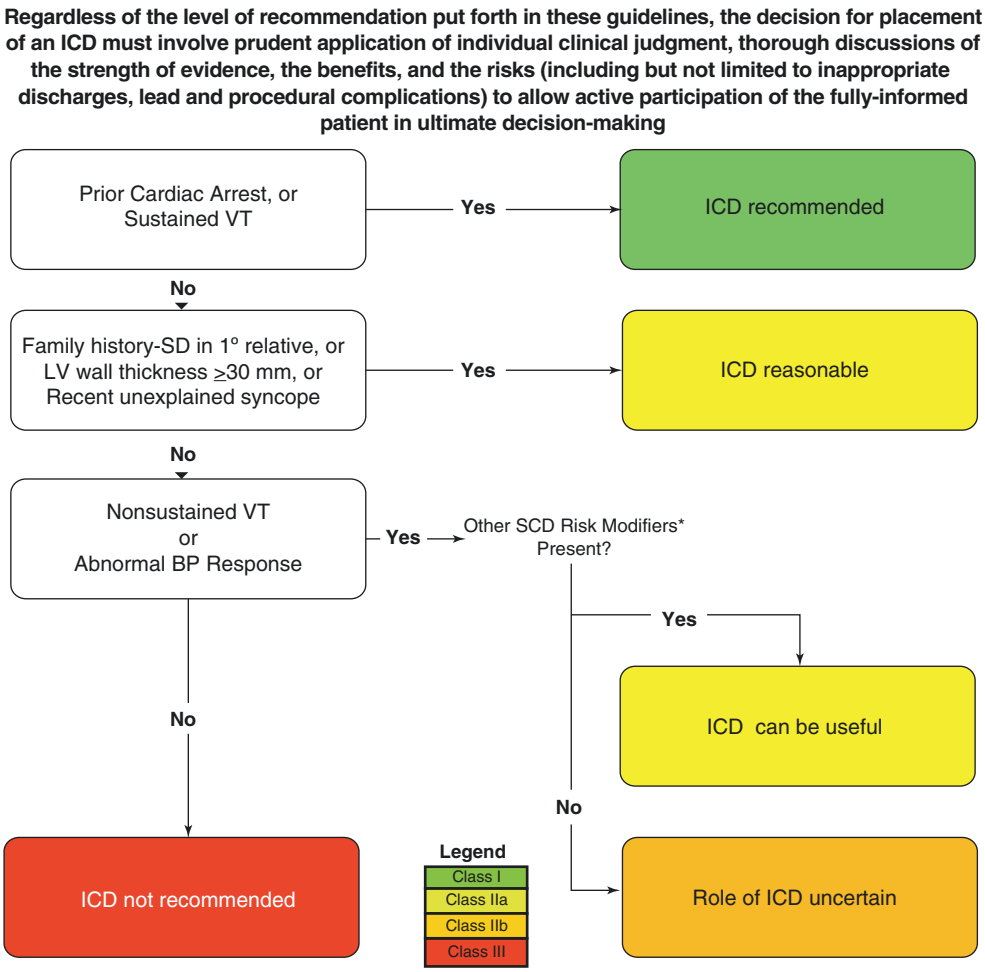


Fig. 10.1 Flow chart of the evaluation and treatment of patients with hypertrophic cardiomyopathy with regard to implantation of an implantable cardioverter defibrillator (ICD). (Reprinted from JACC. [2]) Other potential risk factors include LVOTO, late gadolinium enhancement on CMR, LV apical aneurysm and high-risk genetic mutations. BP blood pressure, ICD implantable cardioverter defibrillator, LV left ventricle, SCD sudden cardiac death, SD sudden death, and VT ventricular tachycardia

In 2011, the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published an updated guideline based on a similar algorithm [2]. Recommendations for patients with multiple risk factors were unchanged, but ICD implantation was also considered reasonable in patients with any one of severe LVH, unexplained syncope or FHSCD (Fig. 10.1). The ACCF/AHA guidelines considered NSVT and ABPRE as clinically relevant only when they occurred in the presence of other risk factors [2, 30]. This departure from the ACC/ ESC 2003 guidelines was partly based on data from studies of ICD recipients in whom the risk of appropriate ICD shocks did not associate with the risk factor profile [45–47].

In 2014, the European Society of Cardiology proposed a new risk prediction model (HCM risk-SCD) which uses seven established clinical parameters (Fig. 10.2) to estimate SCD risk within 5 years of clinical evaluation (http://doc2do.com/hcm/webhcm.html) [5]. HCM risk-SCD was derived from a retrospective, multicentre longitudinal cohort study of 3675 consecutive patients and, in contrast to other risk stratification methods, provided quantitative and individualised prognostic estimates. The ESC guideline recommends that patients with an estimated 5-year risk of SCD <4% should be considered at low risk and recommends regular assessment, whereas those with a risk of ≥6% should be considered for an ICD. In patients with an intermediate risk (4% to <6%), ICD implantation may be considered taking into account the age, co-morbid conditions and the psychological impact of therapy [48].

Irrespective of method used to determine risk, patients and physicians should be aware that clinical risk stratification is imperfect and that only a small subgroup of individuals currently treated with an ICD receives potentially life-saving shocks [49]. Conversely, many ICD recipients

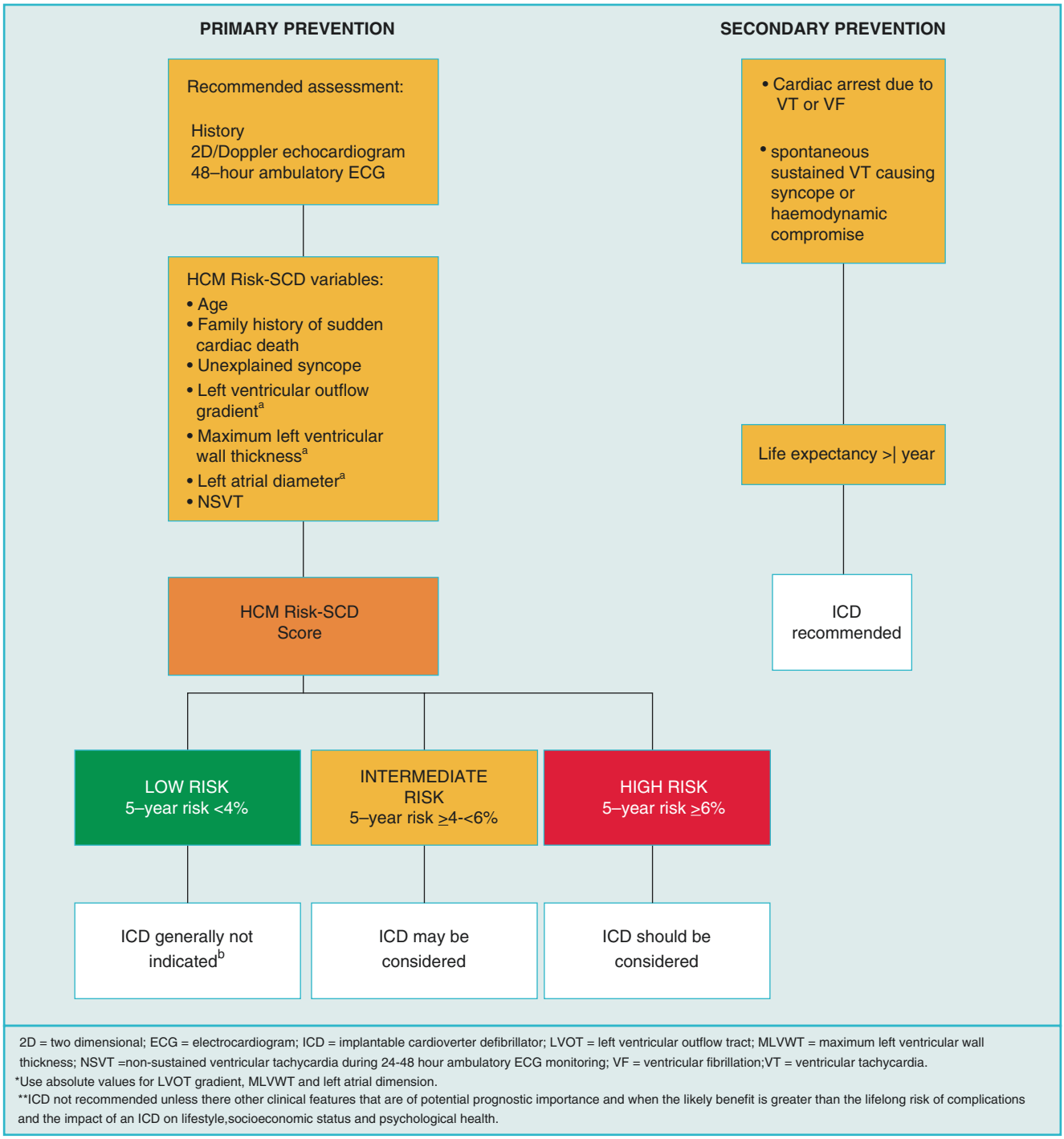


Fig. 10.2 Flowchart for ICD consideration in hypertrophic cardiomyopathy from the 2014 European of Society guidelines on diagnosis and management of hypertrophic cardiomyopathy [48]. The scheme is based on an individualised risk predictor that estimates 5-year risk of sudden cardiac death [5]

experience inappropriate shocks and implant complications over their lifetime [49, 50]. Many gaps in knowledge remain, not least in children and adolescents, elite athletes and in individuals with metabolic diseases, syndromes and other disease phenocopies. In addition, the effect of septal reduction therapy on SCD risk prediction is not known, and all methods for assessing risk should be used cautiously following intervention [51].

Other Potential Risk Factors for Sudden Cardiac Death

No risk stratification strategy will ever be able to predict SCD with absolute certainty, but work continues to reduce unexpected events to an absolute minimum. The conventional approach is to seek new predictors of SCD, but even with additional risk factors, there is still a need for models that provide accurate individualised risk estimates.

Genotype

The role of genotype in determining risk of SCD is still uncertain. Early genetic studies suggested that troponin T mutations (less than 5% of all cases) were associated with a particularly high risk of SCD [18, 52–55], but this has not been confirmed by longitudinal cohort studies [56, 57]. Similarly, some ß-myosin heavy chain mutations were thought to be benign [58, 59], but later reports suggest otherwise [17, 59]. A fundamental problem with the published literature is a lack of adequately powered studies that are able to determine the independent value of genotype in predicting outcomes. At present, data suggest that the presence of a sarcomere mutation is associated with a poorer outcome and that a complex genotype (compound heterozygotes or double heterozygotes) may have a worse prognosis [60–62].

Myocardial Scar Burden

Late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (representing extracellular myocardial collagen deposition) is present to some extent in most patients with HCM and is associated with other established risk factors for SCD including NSVT, severe hypertrophy and left ventricular outflow tract obstruction [63–67]. Recent meta-analyses suggest that the risk of SCD increases with the extent of LGE [68], but individual studies have used different quantification methods in relatively small cohorts with few events and limited follow-up. It is also clear that the absence of LGE does not equate with immunity from SCD [11, 69]. The general consensus is that LGE should not be considered as the sole arbiter of SCD risk, but it is reasonable to consider it in borderline clinical scenarios.

Left Ventricular Apical Aneurysms

Some patients with HCM develop LV apical aneurysms that are typically ringed with scar and associated with transmural myocardial scarring and fibrosis, which likely serves as an arrhythmogenic substrate [70]. A number of studies have suggested that the presence of an aneurysm is associated with a substantially increased risk of adverse events including sudden death, heart failure and thromboembolism, but the independent value compared to other risk factors remains to be determined [70–72].

End-Stage Phase

The end-stage phase of HCM, with LV systolic function less than 50%, is characterised by poor outcomes and increased risk for sudden death. In a large multicenter cohort of HCM patients, end-stage disease had a SCD prevalence of 3.5%, with an overall annual mortality rate of 11%/year and appropriate ICD interventions in 10% of patients annually [73]. These observational data suggest that end-stage disease may be regarded as another risk marker for SCD [73]. Importantly, patients with HCM with end-stage disease may not fulfil traditional criteria for ICD implantation in the non-ischemic population, where ejection fractions below 35% are typically required. An ejection fraction below 50% in a patient with HCM, where the function is usually hyperdynamic, indicates significant systolic dysfunction and elevated risk. Therefore, this ejection fraction cut-point is recommended to trigger ICD implantation.

Prevention of Sudden Cardiac Death

Implantable Cardioverter Defibrillators

ICDs are the modern standard of care for the prevention of SCD, but there are no randomised controlled trials of these devices in patients with HCM. The justification for ICD therapy is that recipients of an ICD receive appropriate shocks that terminate potentially life-threatening ventricular arrhythmias. This observation is interpreted as evidence of survival benefit, and all contemporary guidelines recommend ICD therapy for the primary and secondary prevention of SCD.

Prior to ICD implantation, patients should be made aware of the risk of inappropriate shocks, implant complications and social/occupational/driving restrictions. Despite the increased cardiac mass and thickened substrate in HCM, ICDs still have excellent efficacy in terminating lethal arrhythmias [74]. High-risk patients with ICDs placed for primary or secondary prevention experience annual appropriate discharge rates for ventricular arrhythmias of 4–7%/year (Fig. 10.2), with appropriate treatment occurring more

frequently when placed for secondary prevention (7–11%/year) compared to primary prevention (3–5%/year) [33, 34, 74, 75]. There is often a delay of many years to first therapy [75, 76]. Unfortunately, inappropriate discharges are also common in HCM patients, with up to 25% receiving inappropriate shocks [50, 75]. Younger age and a history of atrial fibrillation have been associated with inappropriate ICD shocks [50]. Inappropriate discharge due to sinus tachycardia, atrial fibrillation or lead malfunction is the most common ICD complications in HCM, followed by infection, haemorrhage/thrombosis, lead fracture, dislodgement and oversensing, which are found at rates similar to the general population of patients with pacemakers and ICDs [77, 78]. Complications of ICD therapy appear more common in patients with HCM due to the young age at which they are typically implanted, necessitating numerous modifications during the course of a lifetime, active lifestyle of younger individuals which may produce more physical wear and the higher mechanical wear and tear produced by the hypertrophied myocardium, which may result in a higher incidence of lead fracture in these patients [78].

The majority of HCM patients should receive a single-lead ICD since atrial leads do not reduce the incidence of inappropriate shocks and may predispose to implant complications [79]. An atrial lead should be reserved for patients with LVOTO where right ventricular pacing with a short AV delay may reduce the severity of obstruction or conventional conduction system disease [34]. Patients with supraventricular arrhythmias may also benefit from an atrial lead to help with long-term monitoring on a case-by-case basis. In HCM patients without an indication for anti-bradycardia pacing, a subcutaneous ICD may be an attractive option since the complications of intravascular leads can be avoided, as long as there is optimal R-wave sensing [80, 81]. The VF zone of the device should be programmed at ≥220/min to minimise shocks from rapidly conducted atrial fibrillation and even though anti-tachycardia pacing is effective in terminating ventricular arrhythmias, but may not reduce the incidence of appropriate shocks [79]. ICD recipients should be followed up regularly to monitor symptoms, as well as device and disease-related complications.

Exercise Restriction

Although most ICD therapies for ventricular arrhythmias occur at rest and documented exercise-induced sustained ventricular arrhythmias are rare, there is consensus that patients with HCM should be advised to refrain from participation in competitive sports and discouraged from intense physical activity, particularly when they have risk factors for SCD or left ventricular outflow tract obstruction. However, patients should be encouraged to maintain a healthy lifestyle as there is no evidence that mild forms of physical exercise predispose to a higher risk of SCD.

Antiarrhythmic Drugs

Before the introduction of ICDs, amiodarone, β-blockers, calcium antagonists and type I-A antiarrhythmic agents were used prophylactically [46, 82, 83]. While early reports suggested that amiodarone was potentially protective, it is clear that it does not provide absolute protection from sudden death in patients with HCM [46, 84]. Moreover, amiodarone is associated with significant cumulative toxicity, making it a poor treatment option in young patients needing long-term treatment [82, 84]. No other drug has been shown to reduce the incidence of SCD.

Although insufficient as sole therapy for primary or secondary prevention against SCD, medical therapy may have a role in patients with an ICD who continue to present with symptomatic ventricular arrhythmias. The greatest experience is with amiodarone but sotalol may occasionally be beneficial [33].

Primary Prevention of SCD in Children with HCM

Children with HCM have a higher prevalence of inborn errors of metabolism, malformation syndromes and neuromuscular disorders [85, 86] and when diagnosed <1 year of age have a worse mortality than adults, but heart failure is more common than SCD [85, 86]. Data on SCD in children derive from limited data from small observational studies and extrapolation of data from adult cohorts [75, 85, 87–89]. A recent systematic review and meta-analysis identified four conventional major risk factors that were statistically associated with an increased risk of death in at least two studies: previous adverse cardiac event, non-sustained ventricular tachycardia, unexplained syncope and extreme left ventricular hypertrophy [90].

Conclusions

In patients with HCM, SCD is the predominant risk in young patients, while progressive heart failure and associated symptoms dominate in the later years [8]. Risk assessment schemes, performed at initial presentation and repeated

annually or when new risk factors arise, are vital in the primary and secondary prevention of SCD as appropriately targeted therapy with ICDs is life-saving.

Questions

1. A 37-year-old female with HCM presents with several episodes of syncope of the last year. They only occur in the shower and only with premenstrual. She has premonitory symptoms of warmth. She has never had exertional syncope but does have palpitations. A Holter did not show NSVT. Her echo has a 16 mm septum, left atrial size of 4.6 cm, and an intracavitary gradient of 144 mmHg. No FMH of SCD or hypotensive response to exercise. Should she get an ICD?
   A. Yes
   B. No
   C. Maybe

   Answer: **B**. By US criteria she has no high-risk features. Her syncope is most consistent with neurally mediated syncope, and thus she should generally not be treated with an ICD. By European (http://www.doc2do.com/hcm/webHCM.html) criteria, she has a 3.81% chance of SCD in 5 years, an intermediate risk. Thus, by ESC criteria, she is also not a candidate for ICD.

2. A 32-year-old male, diagnosed with HCM 4 years ago. Holter with NSVT of 6 beats at 150 bpm. No FMH of SCD or personal syncope or hypotensive response to exercise. Echo with LA dimension of 4.4 cm, maximal septal thickness of 23 mm, and outflow tract gradient of 77. Should he get an ICD?
   A. Yes
   B. No
   C. Maybe

   Answer: **A**. US-risk factor of NSVT which is a minor risk factor and thus other risk modifiers such as MRI scar burden, apical aneurysm, double-hit genetic abnormalities, or LVOT gradient need to be weighed. He does have a significant LVOT gradient which increases his risk of SCD. If MRI scar burden is >15%, then both of these would argue for an ICD. European risk calculator places him at 8.92% 5-year SCD risk, and thus he should get ICD.

3. A 17-year-old standout basketball player with syncope during basketball. Echo with maximal thickness of 21 mm, LA size of 4.2 cm, and LVOT gradient of 5 mmHg. No FMH of SCD or hypotensive response to exercise. Should she get an ICD?
   A. Yes
   B. No
   C. Maybe

   Answer: **A**. By US guidelines he has a single but strong risk factor and thus should get ICD. By ESC calculator a 5-year SCD risk of 15%, and therefore very high risk and should have ICD.

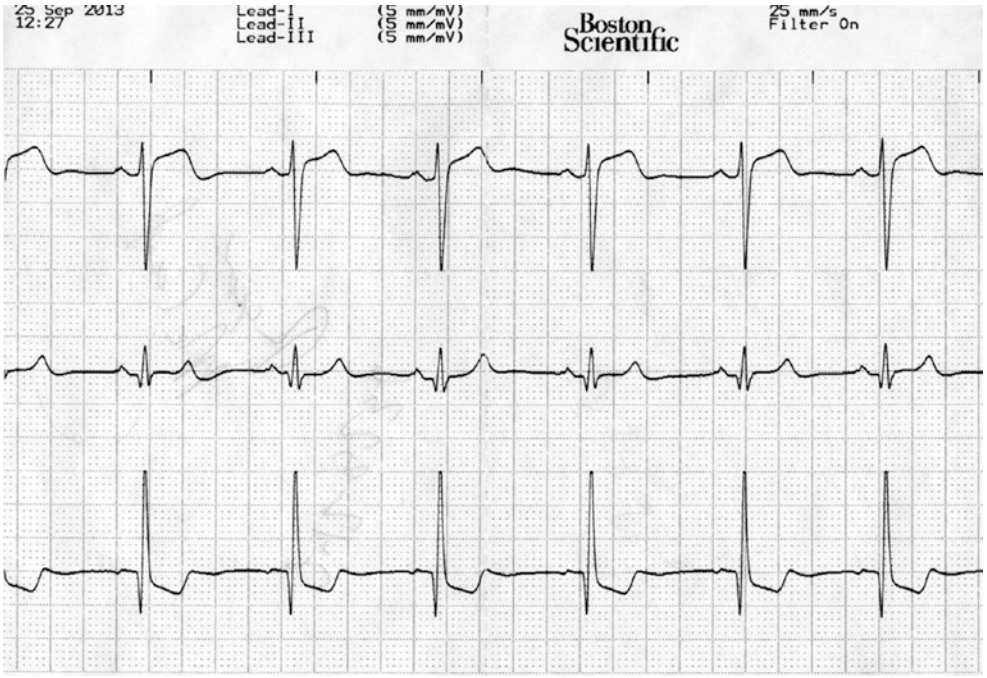
4. A 15-year-old female whose father died suddenly of HCM when he was 32. Echo showed maximal thickness of 17, LA dimension of 35 mm, and no LVOT gradient. No NSVT or syncope or hypotensive response to exercise. Should she get an ICD?
   A. Yes
   B. No
   C. Maybe

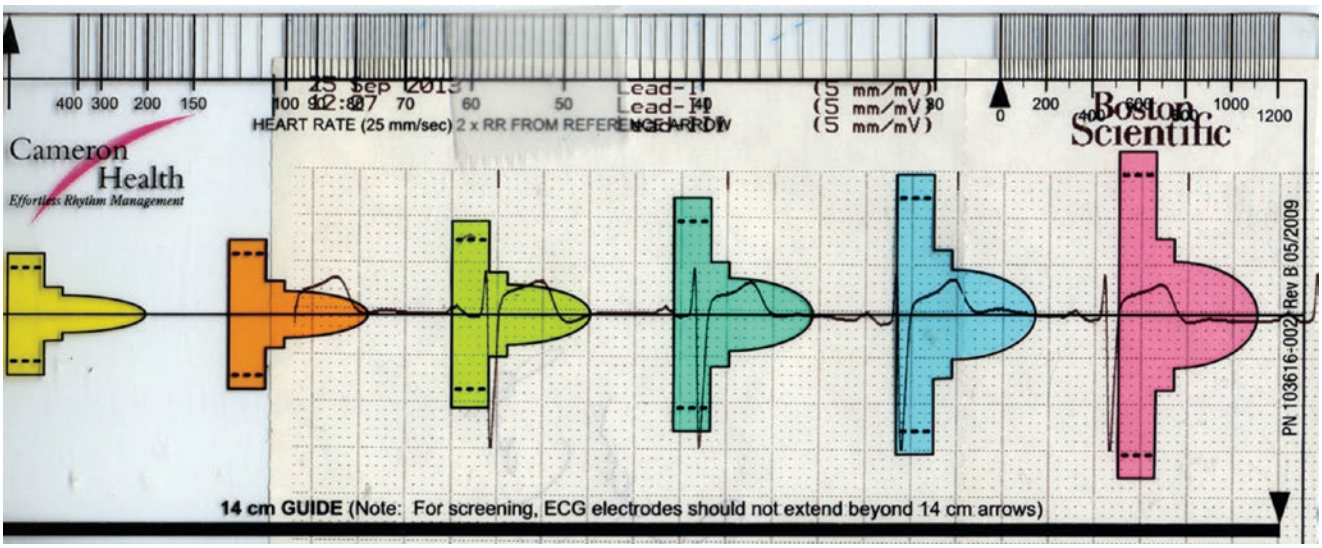
   Answer: **C**. By US criteria she does have a major risk factor and so ICD should be considered. By ESC calculator her 5-year risk is 3.79% and therefore ICD generally not indicated. In these situations, individualized decision-making taking into consideration potential complications and patient wishes is appropriate after a thorough discussion.

5. A 28-year-old male with HCM diagnosed because of LVH on ECG. His echo shows a maximal thickness of 3.2 cm, LA size of 3.8 cm, and no LVOT gradient. Holter with 7 beats NSVT of 140 bpm. No FMH of SCD. No personal history of syncope or hypotensive response to exercise. Should he get an ICD?
   A. Yes
   B. No
   C. Maybe

   Answer: **A**. By US criteria he has a major and a minor risk factor so ICD is indicated. By ESC, 5.92% 5-year risk of SCD, thus, ICD is also indicated.

6. The patient in question 5 is a laborer digging graves for a funeral home. A 3-lead screening ECG is shown below. Should he get a SC ICD?
   A. Yes
   B. No
   C. Maybe





Answer: **C**. He does meet criteria for S-ICD based on the figures, which show that T wave oversensing should not occur. While there is not as much data about S-ICDs compared to transvenous ICDs, the S-ICD is an attractive alternative for him because of his job. Nevertheless, several drawbacks to S-ICD in the HCM population exist including inability to ATP, no backup pacing, and inability to identify atrial arrhythmias, and thus a careful discussion about the risks and benefits and the lack of long-term data should be performed prior to implantation.

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Youth and Athletic Screening: Rationale, Methods, and Outcome

11

David S. Owens and Sanjay Sharma

Key Points

1. Sudden cardiac death (SCD) in youth and athletes is an uncommon but tragic event that profoundly affects both families and communities.
2. In athletes with susceptible heart conditions, exercise (particularly burst activities) can increase the risk of SCD acutely.
3. SCD in youth and athletes (≤35 years of age) is most commonly due to inherited heart conditions or congenital abnormalities such as hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, or coronary artery anomalies.
4. The conditions that cause SCD in youth and athletes often have long latent periods and would often be identifiable premortem using routine testing methods.
5. Athletes undergo cardiac adaptation to exercise that can result in morphologic and electrical changes mimicking disease, and these "gray zones" pose challenges for diagnosis.
6. Although there is consensus among developed societies that it is appropriate to screen athletes for inherited heart conditions, there is considerable controversy as to the best screening methods.
7. ECG screening for youth and athletes is endorsed by the European Society of Cardiology and many international sports organizations but not by US professional societies, largely due to concerns about false-positive rates, cost-effectiveness, and logistics of healthcare delivery.
8. Despite the US professional society recommendations against ECG screening, many universities and local foundations offer voluntary screening programs for youth and athletes due to the high impact of SCD in athletes and public interest in screening.
9. New athlete-specific ECG criteria reduce the false-positive rate and costs of screening, allowing ECG screening to be considered in small cohorts of young people under conditions of sufficient provider expertise and quality control.

Introduction

Sudden death, occurring without preceding symptoms and seemingly striking at random, is a shocking occurrence under any circumstance. When it occurs in youth, adolescents, or athletes who are otherwise the epitome of health, these events are especially tragic. Frequently, the cause of death is an undiagnosed genetic or congenital disorder that may have been identifiable premortem. There is consensus across developed societies that youth and athletes should undergo screening for potentially life-threatening heart disorders, but the rigorousness and resources devoted to screening efforts vary widely based on health system resources and society valuations. At present, there remains considerable controversy over what screening methods should be employed, the acceptable financial and practical costs of screening, and whether more intensive screening leads to reduced morbidity or mortality.

The present chapter will review current knowledge about the etiologies and incidence of sudden cardiac death in youth and athletes, discuss the rationale for screening programs and their potential benefits and limitations, and review data from real-world screening experiences and outcomes.

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In particular, this chapter will focus on hypertrophic cardiomyopathy (HCM) as a cause of sudden death, given its prominence numerically, and the benefits and limitations of screening for HCM on a population basis.

SCD in Youth and Athletes

Sudden death is defined as an abrupt loss of life in the absence of prior symptoms (or with symptoms of short duration) and is most often due to cardiovascular causes such as myocardial infarction, ventricular arrhythmias, cerebrovascular accidents, or ruptured aortic aneurysms. The incidence of sudden cardiac death (SCD) in the general population increases with age and the presence of underlying heart disorders, but overall SCD is a significant contributor to all-cause mortality. Estimates of the annual incidence of SCD vary widely, with estimated 180,000–450,000 deaths in the USA [1, 2]. Because of this, there have been considerable public health efforts to raise awareness of SCD and to increase the availability and utilization of cardiopulmonary resuscitation and automated electrical defibrillators.

The epidemiology of SCD is largely age-dependent. SCD in individuals over 35 years of age is most often caused by acquired forms of heart disease and coronary heart disease in particular, whereas SCD among youth and athletes under 35 years is more often due to inherited or congenital heart disorders and primary arrhythmia syndromes. A partial list of disorders capable of causing SCD in youth and athletes is shown in Table 11.1.

Table 11.1 Causes of sudden cardiac death in athletes

Cardiomyopathies
Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy
Dilated cardiomyopathy
Left ventricular non-compaction
Aortopathies
Marfan syndrome
Loeys-Dietz syndrome
Ehlers-Danlos disorder
Thoracic aortic aneurysm and dissection
Channelopathies
Long QT syndrome
Short QT syndrome
Catecholaminergic polymorphic ventricular tachycardia
Brugada syndrome
Wolff-Parkinson- White syndrome
Congenital abnormalities
Coronary artery anomalies
Bicuspid aortic valve with aortopathy
Acquired disorders
Myocarditis
Coronary artery disease
Commotio cordis

The incidence rate of SCD among younger individuals – frequently defined as ≤35 year of age – is estimated to be approximately 0.7–3.0 cases per 100,000 person-years. The exact incidence has been challenging to determine, largely due to differences in populations being studied and incomplete case identification when relying on media reports or insurance claims. Among active military personnel <35 years of age, the rate of SCD was observed to be 13.0 per 100,000 person-years (1:9000) among military recruits during initial training [3] but only 1.2 per 100,000 person-years over a 10-year period of observation [4].

Observational studies have consistently demonstrated that rate of SCD is higher among males compared to females, both in the general population and among youth [5] and athletes [6–9]. Whereas men have an estimated 1.3-fold relative risk in the general population [1, 2], this may be as high as 5.6-fold relative risk for athletes. The reason for the higher relative risk among athletes is unclear but may be related to biologic or societal factors, including the historic underrepresentation of women in more vigorous athletic endeavors. Individuals of African descent appear to have an increased risk of SCD compared to Caucasians, both in the general population [10] and among athletes [8, 9], but may be less likely to experience SCD due to coronary heart disease [11].

Additionally, there are regional variations in the reported distributions of underlying causes of SCD in youth and athletes. Whereas definite or possible hypertrophic cardiomyopathy (HCM) appears to be the most common cause of SCD in the USA and the UK [12, 13], arrhythmogenic right ventricular cardiomyopathy (ARVC) is the most common cause of SCD in Italy (Fig. 11.1) [6]. This may be due to population differences in the frequency of gene mutations for these disorders, societal differences in healthcare and screening, or differences in the medical examiners' approach to postmortem diagnosis. Importantly, sudden unexplained death (SUD), in which the autopsy reveals a structurally normal heart and in which primary arrhythmia syndromes are suspected, may be present in 15–40% of cases [4, 13, 14].

Although exercise has myriad benefits on health and overall well-being, exercise has clearly been shown to increase the risk of SCD. Data from the Physicians' Health Study estimated a 16.9-fold (95% CI: 10.5–27.0) increased risk of SCD during or within 30 min of exercise [15]. This risk was highest among sedentary individuals who exercised intermittently [15]. A prospective study of Italian youth (aged 12–35 years) comprising 29 million person-years of observation suggested that the relative risk of SCD was 2.8 (95% CI: 1.9–3.7) times higher among athletes compared to nonathletes, with 89% of athlete deaths and 9% of nonathlete deaths occurring in the setting of acute exercise [6].

In both young and old alike, SCD is thought to arise from an acute trigger superimposed on an underlying susceptible substrate, and there are a number of mechanisms by which

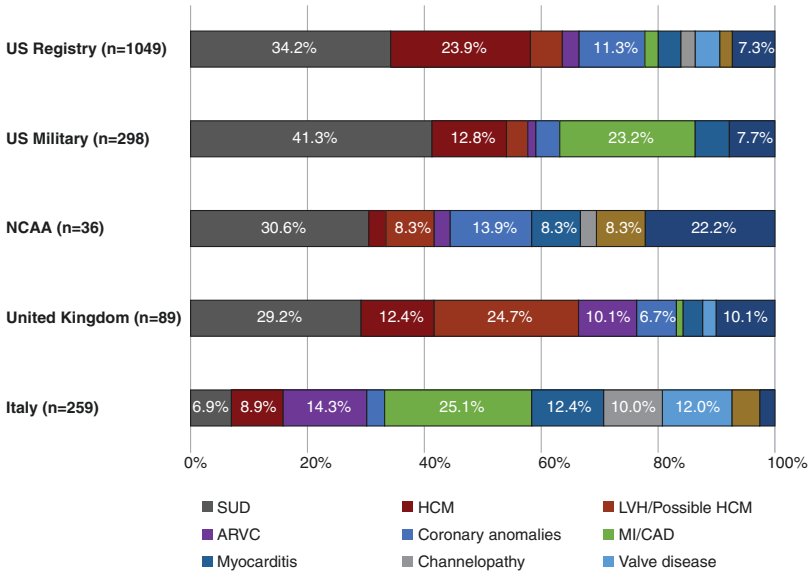

Fig. 11.1 Comparison of etiologies of sudden cardiac death among youth and athletes from (**a**) US Registry [12] (age ≤ 39 years), (**b**) the UK [13] (age ≤ 35 years), (**c**) US military [4] (age < 35 years), (**d**) NCAA athletes [8] (ages 17–26 years), and (**e**) Italy [6] (age 12–35 years)

exercise may serve as an arrhythmogenic trigger. Exercise increases catecholamine levels, may cause dehydration and electrolyte imbalance, increases blood pressure and shear stress on the aorta, and may induce myocardial ischemia in susceptible individuals [16]. It has been observed that sports involving burst activities (e.g., basketball, soccer, football) have a higher rate of SCD than other sporting disciplines [8, 16, 17]. The exact reasons for this are unclear but may be related to abrupt changes in heart rate and/or greater periods of "supramaximal" exercise. Alternatively, patients with underlying heart disorders may be underrepresented in sporting disciplines that require high aerobic conditioning due to inability to compete at high aerobic levels [18].

Several studies have suggested intensity of the sporting discipline is proportionally related to the risk of sudden death among NCAA athletes (2004–2008, aged 17–23 years) and showed differences based on gender, ethnicity, and sporting discipline [8]. The overall risk of SCD was 1:43,770 person-years but was observed to be higher in males (1:33,134 person-years) and in African-Americans (1:17,696 person-years). Male basketball players had the highest rate of SCD (1:3100 person-years). In this series, SUD and coronary anomalies were the most common causes of death in these athletes, and HCM was less common than in other US registries [14]. This is consistent with data from Basavarajaiah et al. suggesting that the prevalence of HCM in elite athletes may be rare [18].

SCD can also be caused by direct blow to the anterior chest by a blunt object, even in structurally normal hearts. Such a blow at just the right moment of the cardiac cycle can induce ventricular fibrillation, and this phenomenon, termed commotio cordis, is a not insignificant cause of SCD in athletes [19]. Thus no amount of screening will prevent all SCD, and there is a need for readily available automatic external defibrillators and first responder action plans in practice and competition arenas alike.

Rationale for Screening

Pre-participation cardiovascular screening is the systematic evaluation of athletes and adolescents prior to the participation in sport activities for the purpose of both identifying underlying cardiovascular abnormalities that can lead to SCD and enhancing the safety of sports participation. There is consensus across developed societies that athletes and youth should undergo pre-participation cardiovascular screening, albeit considerable disagreement surrounding the proper methods to employ. The American Heart Association views pre-participation screening as an important public health issue that is *justifiable*, *necessary*, and *compelling* on the basis of ethical, legal, and medical grounds [20].

In 1968, the World Health Organization established criteria for evaluating the appropriateness of health screening programs (Table 11.2) [21], and these criteria remain applicable today. Pre-participation cardiovascular screening fulfills many if not all of these criteria. Important features of pre-participation screening for underlying heart disorders in adolescents and athletes include the following:

- SCD in athletes has been deemed by many professional organizations to be an important health problem, and many community-based non-profit organizations have arisen to meet the societal demands for more intensive youth and adolescent screening.
- Whereas adolescents and athletes are often asymptomatic prior to SCD, most of the inherited heart conditions and congenital abnormalities that confer increased risk have a

Table 11.2 World Health Organization criteria for effective screening programs [21]

The condition should be an important health problem
There should be a treatment for the condition
Facilities for diagnosis and treatment should be available
There should be a latent stage of the disease
There should be a test or examination for the condition
The test should be acceptable to the population
The natural history of the disease should be adequately understood
There should be an agreed policy on whom to treat
The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole
Case finding should be a continuous process, not just a "once and for all" project

years-long latent period during which disease may be detectable.

- The natural histories of these disorders are well understood, and guidelines for treatment and SCD risk reduction are generally available. Recommendations may include implantable cardioverter-defibrillator (ICD) placement and lifestyle changes including avoidance of vigorous or competitive exercise.
- The underlying conditions that place youth and athletes at increased risk are identifiable using widely accepted cardiac testing, including medical examination (history and cardiac auscultation), electrocardiography, and echocardiography.

Thus, many of the WHO criteria for effective screening are fulfilled, and in several important respects, inherited and congenital heart conditions are ideally suited for screening programs. However, there are practical challenges to implementing these screening programs that have rendered preparticipation screening controversial.

Screening tests are generally imperfect and false-positive results that require evaluation with more expensive testing are expected. The sensitivity (ability to detect true disease) and specificity (ability to not falsely detect normal individuals) of the screening test and the underlying disease prevalence are all factors that must be considered when evaluating the effectiveness of a screening program.

The costs of screening include both the financial costs of performing the screening tests as well as the costs of any downstream testing of suspected cases. For many suspected cardiovascular disorders, this additional diagnostic testing can be extensive. And finally, both personal and psychological costs of screening must be considered. Athletes identified as potentially having cardiovascular disease may experience anxiety, and temporary or permanent sports disqualification may have important personal ramifications and health consequences.

Finally, there are ethical concerns related to who should undergo cardiovascular screening – specifically if it is justifiable to limit screening efforts to athletes, especially because a large percentage of SCD occur in nonathletes as well [22, 23]. Additionally, critics of home-grown regional screening programs argue that funding targets wealthy communities, leaving poorer communities unprotected. Such disparities in care would not be likely to improve the incidence of SCD among athletes in the broader sense and pose significant ethical questions.

Cardiac Adaptation to Exercise

A major challenge to pre-participation cardiovascular screening in athletes is the fact that cardiac structure and function adapt to and remodel in response to repetitive exercise. This physiologic adaptation may lead to abnormalities (classically defined) on electrocardiography or echocardiography, including left ventricular hypertrophy. In some instances, it becomes challenging to differentiate the "athletic heart" from an underlying cardiomyopathy capable of causing sudden death, such as HCM or ARVC [24, 25]. Indeed, these "gray zones" can be the source of considerable consternation for medical professionals, which can lead to unnecessary and expensive diagnostic testing or to excluding an athlete from sporting competition unnecessarily. It is therefore essential for clinicians who care for or evaluate athletes to have a fundamental understanding of the ways in which athletic training can affect the cardiovascular system.

The "Morganroth hypothesis" postulates that the manner of cardiac remodeling is in large part determined by the type of exercise performed [26, 27]. Athletes who participate in high-dynamic sports (e.g., running, cycling, rowing) experience a repetitive increase in cardiac output with high-flow states and lesser increases in afterload. In response, cardiac chambers are believed to undergo balanced eccentric dilation and hypertrophy resulting in enlargement of all four cardiac chambers. In contrast, athletes who participate in high resistance sports (e.g., weight lifting) experience a repetitive increase in afterload with less increase in cardiac output and are thought to develop concentric left ventricular hypertrophy.

Recent studies have cast doubt on this hypothesis, particularly in regard to resistance training. Studies of sedentary individuals who begin endurance training clearly show an increase in chamber size and volumes in response to training, findings which comport with the large LV cavity volumes seen in elite athletes [28]. While the idea that resistance training results in LV hypertrophy makes theoretic sense, LV hypertrophy is not consistently seen in strength-trained individuals, and coexistent hypertension may be confounding some of this association [27, 29]. Additionally, the increases in afterload may be short in duration or offset by increases in intrathoracic pressure during Valsalva maneuver.

In addition to cardiac structural remodeling, exercise also induces changes in cardiac autonomic tone. Endurance training generally results in an increase in vagal parasympathetic innervation. As a result, bradycardia, junctional escape rhythms, and Mobitz I second-degree AV block (i.e., Wenckebach) are not uncommonly seen on ECG or rhythm monitoring and should not be confused with disease.

Black athletes in particular may have greater degrees of cardiac remodeling in response to exercise. Black hypertensive patients have greater degrees of LV hypertrophy compared to white patients with similar age, gender, and blood pressures [30]. Similarly, black athletes have greater LV wall thickness and LV mass index compared to white athletes (Fig. 11.2) [31–33] and are more likely to demonstrate ECG abnormalities [34]. In a study of 300 normotensive male black athletes in the UK, 18% demonstrated LV wall thickness ≥13 mm and 3% were ≥15 mm [35]. Because of this, black athletes in particular may fall into the "gray zone" between athletic remodeling and HCM more often, and careful diagnostic evaluation is needed so as to ensure proper diagnosis and to not inappropriately disqualify athletes with physiologic LV hypertrophy.

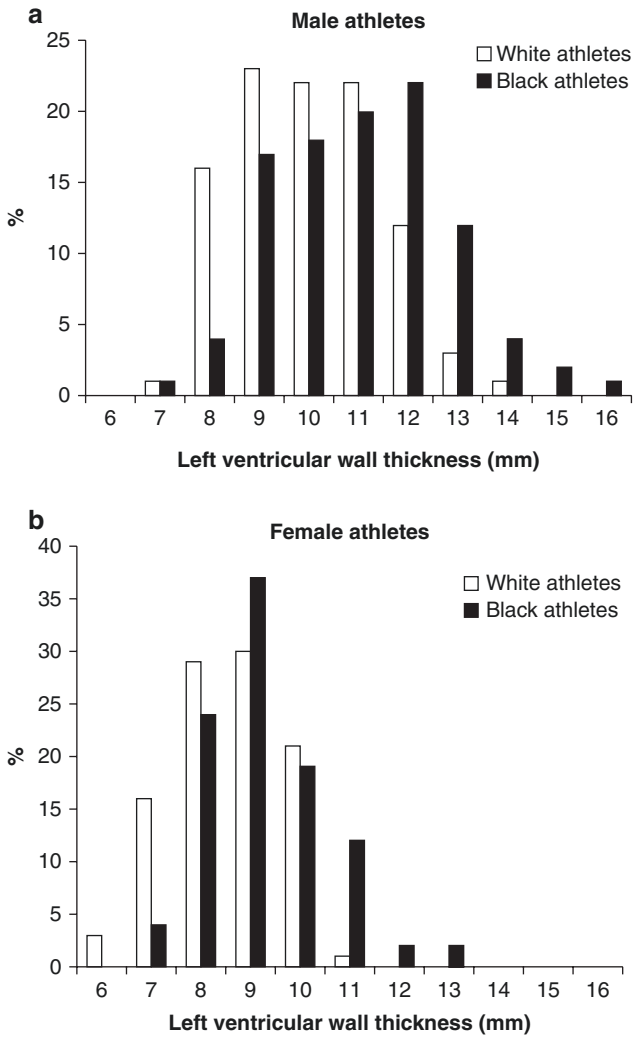

Fig. 11.2 Distribution of LV wall thickness among (**a**) white and black male athletes [35] and (**b**) white and black female athletes [33]. (Reproduced from Chandra et al. [32], copyright 2012 with permission from BMJ Publishing Group Ltd.)

Basic Pre-participation Cardiovascular Screening

Pre-participation cardiovascular screening can take many forms. Basic screening programs, such as those advocated by the American Heart Association [20] and the joint professional guidelines Preparticipation Physical Evaluation (PPE) Monograph (fourth edition) [36], consist of a history and physical examination with additional evaluations as indicated based on physician judgment. The AHA recommends a 14-point pre-participation cardiovascular screening for competitive athletes (Table 11.3), recommendations that are chiefly based on standard of care and expert opinion [37].

Table 11.3 The 14-element AHA recommendations for pre-participation cardiovascular screening of competitive athletes [37]

Medical history[a]
Personal history
Chest pain/discomfort/tightness/pressure related to exertion
Unexplained syncope/near syncope[b]
Excessive and unexplained dyspnea/fatigue, associated with exercise
Prior recognition of a heart murmur
Elevated systemic blood pressure
Prior restriction from participation in sports
Prior testing for the heart, ordered by a physician
Family history
Premature death (sudden, unexpected, or otherwise) before 50 years of age attributable to heart disease in ≥1 relative
Disability from heart disease in a close relative <50 years of age
Specific knowledge of certain cardiac conditions in family members: Hypertrophic or dilated cardiomyopathy, long QT syndrome or other ion channelopathies, Marfan syndrome, or clinically important arrhythmia
Physical examination
Heart murmur[c]
Femoral pulses to exclude aortic coarctation
Physical stigmata of Marfan syndrome
Brachial artery blood pressure (sitting position)[d]

[a]Parental verification is recommended for high school and middle school athletes

[b]Judged not to be neurocardiogenic (vasovagal); of particular concern when related to exertion

[c]Refers to heart murmurs judged likely to be organic and unlikely to be innocent; auscultation should be performed with the patient in both supine and standing positions (or with Valsalva maneuver), specifically to identify murmurs of dynamic left ventricular outflow tract obstruction

[d]Preferably taken in both arms

In the USA, most PPE examinations are performed by pediatricians and/or family medicine physicians in the context of a healthy child visit, and these providers often lack specialized training in cardiology and in evaluating athletes. Real-world data suggests that the AHA recommended pre-participation screening is rarely performed in full [38], and because screening is performed by local physicians, there may be barriers to pursuing additional cardiovascular evaluation because ECG and echocardiography testing may not be available on site. In contrast, pre-participation screening in Europe is often performed in more centralized practice, and the providers who perform the screening often have expertise in evaluating athletes. This serves to limit the number of unnecessary follow-up or diagnostic tests performed.

Whether cardiovascular screening should be performed in all youth and adolescents or only in those participating in sports is an important ethical issue. At present, US screening programs have focused on athletes because of the observed increased risk compared to nonathletes, but this raises issues of equality and fairness. Several European countries perform cardiovascular screening routinely for all youth and adolescents.

Electrocardiography

The use of the electrocardiogram (ECG) for cardiovascular screening is controversial [39–41]. Some practitioners advocate for including ECG in a standard pre-participation screening program, and this is the standard of care in the UK and many countries in Europe and for international sporting competitions including the Olympic Games and FIFA World Cup. Up to 90–95% of athletes are asymptomatic or minimally symptomatic prior to experiencing SCD [12], and ECG provides a potential means to diagnose asymptomatic cardiomyopathies and electrical heart disorders (e.g., ion channelopathies, WPW). It has been estimated that 85–90% of asymptomatic HCM patients are potentially identifiable by the presence of an abnormal ECG [42]; conversely, HCM patients with a normal ECG have a favorable prognosis and are at low risk of SCD [43].

Opponents of ECG screening as a component of pre-participation evaluations point to a number of challenges [44]. False-positive ECGs (up to 10–20% or more using standard criteria) can lead to expensive, unnecessary evaluations and/or inappropriate exclusion of individuals from sport competition, and given that SCD in athletes is a rare event, these expenses – financial, personal, and psychological – may not be justifiable. Moreover, widespread ECG screening may not easily translate from Europe to the USA given its expansive geography and decentralized evaluations that would take place.

Recognizing that exercise-induced cardiac remodeling is an important factor in the high false-positive rate, there have been serial attempts to redefine the criteria used for interpreting ECGs in athletic populations. In the first such effort, the European Society of Cardiology in 2010 enumerated the ECG changes considered to be due to training and differentiated these from ECG changes potentially related to disease [45]. Over time, these criteria have been iteratively modified and improved, with examples of these efforts being the Stanford Criteria (2011) [46], the Seattle Criteria (2013) [47–50], and the Refined Criteria (2015) [51]. In 2017, an international group of sports cardiologists and sports medicine physicians revised these criteria further in what has become known as the "International Consensus Criteria" (Table 11.4) [52]. While these criteria are largely based on expert opinion, there is growing research data to provide evidence base for the recommendations. Serial modifications of these athlete-specific ECG criteria have been shown to incrementally decrease the false-positive rate (to as low as <5%) without significantly compromising specificity (94%) [34]. Although these criteria require expertise and training in athlete-specific ECG interpretation, the development of software interpretation algorithms tailored to these criteria is available and may facilitate broader adoption (Fig. 11.3).

Several important features of these athlete-specific ECG criteria merit discussion. First, voltage criteria for LV hypertrophy are commonly seen in athletes due to cardiac remodeling and thin body habitus and are generally not applied to adolescent and young adult populations. Additionally, it is now recognized that individuals of Afro-Caribbean descent may demonstrate a pattern of early repolarization involving ST segment elevation and T wave inversion in the anterior leads (Fig. 11.4) [53]. The recognition of this pattern as a normal variant will decrease the need for unnecessary testing.

Echocardiography

Currently there are no professional or medical organizations that advocate for the inclusion of echocardiography as a component of cardiovascular screening. However, echocardiography may be able to detect asymptomatic and electrically silent cardiovascular abnormalities such as aortic aneurysms, coronary artery anomalies, and the subset of cardiomyopathies with normal ECGs. After several high-profile sudden cardiac deaths in athletes, many amateur and professional organizations are including echocardiography as part of their standard screening. For example, both the National Basketball Association and National Football League currently include routine echocardiographic screening, and many NCAA institutions have chosen to do the same.

Table 11.4 Recommended criteria for ECG interpretation in athletes (2017 International Consensus Criteria) [52]

Normal ECG findings	
These training-related ECG alterations are physiologic adaptations to regular exercise, considered normal variants in athletes, and do not require further evaluation in asymptomatic athletes with no significant family history	
Increased QRS voltage	Isolated QRS voltage criteria for LVH or RVH
Incomplete RBBB	rSR' pattern in V1 and a qRS pattern in V6 with QRS duration <120 ms
Early repolarization	J-point elevation, ST segment elevation, J waves or terminal QRS slurring in the inferior and/or lateral leads
Black athlete repolarization variant	J-point elevation and convex ("domed") ST segment elevation followed by T wave inversion in leads V1-V4 in black athletes
Juvenile T wave pattern	T wave inversion in V1-V3 in athletes <age 16 years
Sinus bradycardia	Heart rate 30–60 bpm
Sinus arrhythmia	Heart rate variation with respiration: rate increases during inspiration, decreases during expiration
Ectopic atrial rhythm	P waves are a different morphology compared with the sinus P waves, such as negative P waves in the inferior leads
Junctional rhythm	QRS rate is faster that the resting P wave or sinus rate and typically <100 bpm with narrow QRS complex unless the baseline QRS in aberrant
1° AV block	PR interval 200–400 ms
Mobitz type I 2° AV block (Wenckebach)	PR interval progressively lengthens until there is a non-conducted P wave with no QRS complex, the first PR interval after the dropped beat is shorter that the last conducted PR interval
Borderline ECG findings*	**Definition**
These ECG findings in isolation likely do not represent pathologic cardiovascular disease in athletes, but the presence of two or more borderline findings may warrant additional investigation until further data become available	
Left axis deviation	QRS axis between −30° and −90°
Left atrial enlargement	P wave duration of >120 ms in leads I or II with negative portion of P wave ≥1 mm in depth and ≥ 40 ms in duration in lead V1
Right axis deviation	QRS axis > 120°
Right atrial enlargement	P wave ≥2.5 mm in II, III or aVF
Complete RBBB	rSR' pattern in lead V1 and an S > R in lead V6, with QRS duration >120 ms
Abnormal ECG findings	**Definition**
Note: These ECG findings are unrelated to regular training or expected physiological adaptation to exercise, may suggest the presence of pathological cardiovascular disease, and require further diagnostic evaluation	
T wave inversion	≥1 mm in 2 or more leads, excluding aVR, III and V1
Anterior	TWI in V2-V4. Excludes: black repolarization variant, athletes <16 years with TWI in V2-V3 and biphasic TW in V3
Lateral	I and aVL, V5 and/or V6 (only 1 lead of TWI in V5 or V6)
Inferolateral	II and aVF, V5-V6, and aVL
Inferior	II and aVF
ST segment depression	≥0.5 mm in depth in 2 or more contiguous leads
Pathologic Q waves	Q/R ratio ≥ 0.25 or ≥ 40 ms in duration in 2 or more leads (excluding III and aVR)
Complete LBBB	QRS duration ≥120 ms, predominantly negative QRS complex in lead V1 (QS or rS) and upright notched or slurred R wave in leads I and V6
Profound IVCD	Any QRS duration ≥140 ms
Epsilon wave	Distinct low amplitude signal (small positive deflection or notch) between the end of the QRS and onset of the T wave in leads V1-V3
Ventricular pre-excitation	PR interval < 120 ms with a delta wave (slurred upstroke in the QRS) and wide QRS (≥120 ms)
Prolonged QT interval[a]	QTc ≥470 ms (males) QTc ≥480 ms (females) QTc >500 ms (definitive long QT syndrome)
Brugada type 1 pattern	Coved pattern: initial ST-segment elevation ≥2 mm (high takeoff) with downsloping ST elevation followed by a negative symmetric T wave in ≥1 leads V1-V3
Profound sinus bradycardia	Heart rate < 30 bpm or sinus pause ≥3 s
Profound 1° AV block	PR interval ≥ 400 ms
Mobitz type II 2° AV block	Intermittently non-conducted P waves with a fixed PR interval
3° AV block	Complete heart block (atrial rate > ventricular rate)
Atrial tachyarrhythmias	SVT, atrial tachycardia, atrial flutter, atrial fibrillation
≥ 2 PVCs	Per 10 s ECG tracing
Ventricular arrhythmias	Ventricular couplets, non-sustained VT, sustained VT

[a]The QT interval corrected for heart rate is ideally measured with heart rates of 60–90 bpm. Consider repeating the ECG after mild aerobic activity for borderline or abnormal QTc values with a heart rate < 50 bpm

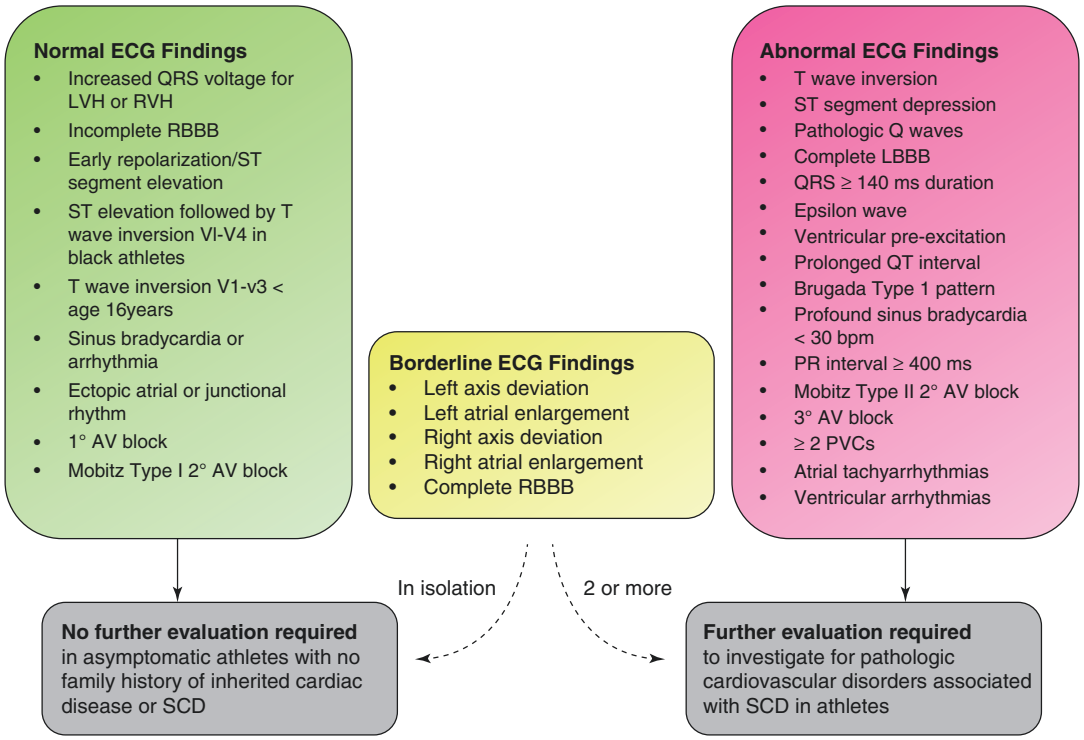

Fig. 11.3 Algorithm depicting the International Consensus Criteria for ECG interpretation in athletes [52]. AV, atrioventriular block; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; PVC, premature ventricular contraction; SCD, sudden cardiac death. (Reproduced from Sharma et al. [52])

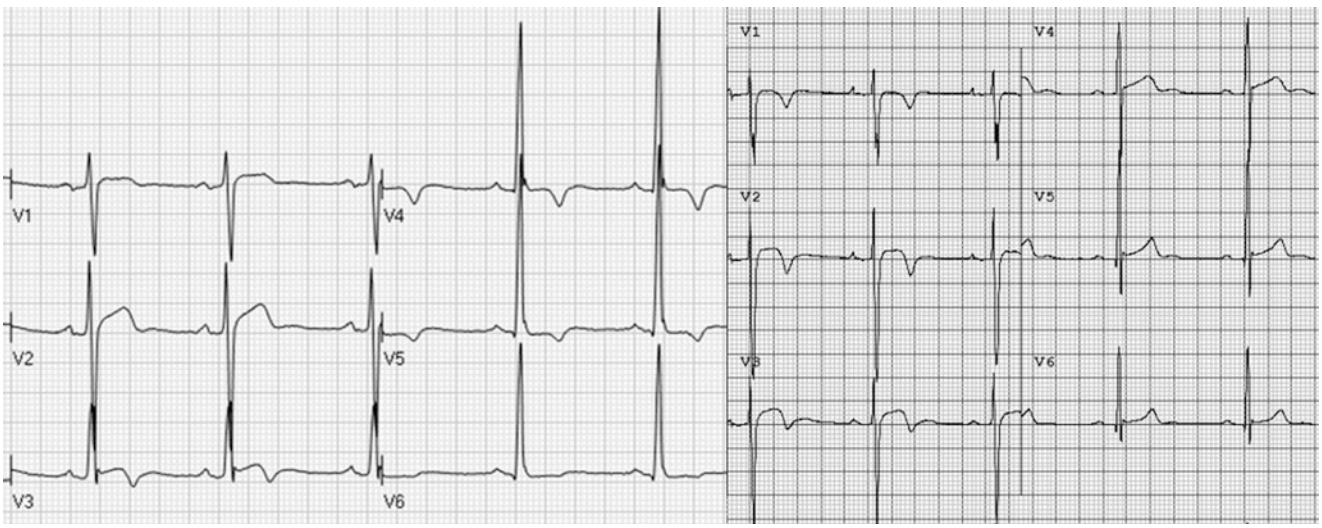

Fig. 11.4 Precordial ECGs from a patient with hypertrophic cardiomyopathy (left) and a normal variant repolarization pattern in an athlete of Afro-Caribbean decent (right), with domed (convex) ST segment elevation and T wave inversion in leads V1–V3

Point-of-care echocardiography is being increasingly utilized and may decrease the costs associated with echocardiographic screening. However, routine use of echocardiography may identify more individuals who fall into the "gray zones" between health and disease, increasing costs through downstream diagnostic testing and increasing the potential for false-positives and unnecessary sports disqualifications. One particularly troublesome area is the differentiation of benign LV hypertrabeculation from LV non-compaction, which can be seen in the setting of normal ejection fraction and normal ECG. LV hypertrabeculation is more common in blacks and athletes, and current diagnostic criteria for LV non-compaction may be overly sensitive [54, 55]. At present, the overall costs and additive value of screening echo-

cardiography on top of more basic screening are unclear, and echocardiography screening should be approached with caution and only by echocardiographers experienced in athlete evaluations.

ECG Screening: Cost-Effectiveness and Outcomes

Whether ECG screening reduces the rate of SCD within the population remains uncertain. In the absence of randomized controlled trials, temporal and observational studies provide the best guidance. Beginning in 1982, Italian law began requiring pre-participation screening of young athletes (aged 12–35) including ECG analysis. The rate of SCD was observed to be 3.6 per 100,000 person-years in the years prior to the law's enactment and 0.4 per 100,000 person-years during the late follow-up period [56]. This represented an 89% reduction in the rate of SCD among athletes over 20 years, while unscreened nonathletes showed no significant change in the rate of SCD over this same time period. This study suggests that pre-participation screening may save lives, but because this was an observation study, the cause of this improvement cannot be conclusively assigned and other temporal factors could be playing a role.

A comparable analysis in Israel challenged these results. Investigators used media reports to capture SCD events for the 10-year period before and after implementation of a mandatory screening law in 1998 [57]. The rate of SCD was estimated to be 2.54 per 100,000 person-years in the period before the law and 2.66 per 100,000 person-years afterward ($p = 0.88$). This study could not control for other temporal factors, such as changes in media coverage of SCD events, and the different results have to be placed in context of each society. For example, it is unclear if Israel's mandatory conscription (and subsequent health evaluations) influences the efficacy of pre-participation screening. At the least, these results add uncertainty to the debate.

More recently, a large population-based evaluation of exercise-associated SCD in Ontario, Canada, found that rates of SCD occurring in the setting of competition were rare (0.8/100,000 athlete-years) and that only 19% (3 of 16) of the deaths that occurred during competitive exercise would have been detected on screening [58]. This study thus suggests that screening has a limited role for preventing SCD in athletes. However, other US registry and observational studies have shown a much higher rate of ECG-detectable disorders [4, 12, 13, 59, 60], and the findings may not be generalizable to larger regions.

Several studies have evaluated the cost-effectiveness of ECG screening for athletes but lead to disparate conclusions based on differences in assumptions. Wheeler and colleagues examined the costs of screening high school and college-aged athletes and estimated that the addition of ECG would save 2.06 life-years for every 1000 athletes screened at an incremental cost of $89 per athlete or $42,900 per life-year saved [61]. On the other hand, Halkin et al. estimated that a mandatory ECG screening program in the USA would cost between $2.55 and $3.45 billion annually and would be expected to save approximately 240 lives, yielding a cost per life saved between $10.6 and $14.4 million [62]. The marked discrepancy in the estimates is reflective of many of the uncertainties related to false-positive rates, costs of diagnostic testing, and usefulness of ECG screening for preventing SCD events.

Summary

Exercise and athletic competition is associated with an increased risk of SCD for individuals with susceptible heart conditions, and when it strikes, SCD is devastating to families and communities alike. Because of this, there is significant public health interest in pre-participation screening of youth and athletes. A major challenge to pre-participation screening is that athletes undergo cardiac adaptation to exercise, with structural and functional changes that can resemble cardiac pathology capable of causing SCD. Substantial expertise is needed to reliably differentiate health from disease and avoid unnecessary sports disqualification. Although there is widespread agreement that pre-participation screening is useful, there is disagreement as to the best methods to employ, particularly in regard to whether ECG should be a standard component of screening. Athlete-specific ECG criteria have been developed to reduce the false-positive ECG rate in athletes, and ongoing research will help provide an evidence-base for many of the current recommendations.

Clinical Pearls

1. When performing pre-participation screening for athletes, perform cardiac auscultation both at rest (supine) and with a provocative maneuver to decrease preload such as Valsalva or stand from a squat position. These maneuvers will help to unmask a murmur in the 1/3 of HCM patients with provocable LVOT obstruction.
2. Athletes may demonstrate a number of "abnormal" ECG and rhythm findings due to high vagal tone, including extreme bradycardia, ectopic atrial or junctional escape rhythms, or first- or second-degree (Mobitz 1, Wenckebach) heart block. These are seldom the sources of symptoms and are considered benign findings.

3. A subset of black athletes demonstrate a variant of early repolarization characterized by domed ST segment elevations followed by negative T waves in leads V1–V4. This pattern is training-related, will often resolve with deconditioning, and does not require additional evaluation.
4. Endurance athletes generally manifest balanced chamber enlargement. Right ventricular enlargement without left ventricular chamber enlargement is concerning for ARVC or left to right shunts (e.g., atrial septal defect or anomalous pulmonary venous return) and should be evaluated further.
5. Athletes (particularly black athletes) may exhibit left ventricular hypertrophy, but most commonly this hypertrophy is 15 mm or less, with the upper limits of physiologic remodeling generally considered to be 17 mm. Evaluation of athletes in the "gray zone" between athlete's heart and HCM can be extensive and relies on assessment of family history, diastolic function, cardiopulmonary functional capacity, Holter monitoring, and cardiac MRI among other tests.

Questions

1. The following are true about pre-participation athletic screening except:
   A. The USA recommends the 14-question AHA questionnaire.
   B. Italy recommends an ECG routinely.
   C. The USA recommends a history and physical.
   D. The UK recommends an echocardiography.
   E. It has not definitively reduced incidence of SCD.

Answer: **D**. All of these are true except D. Currently, no society recommends echocardiography as a routine part of pre-participation screening, due to cost and false-positive rates.

2. The upper limit of hypertrophy for physiologic remodeling is:
   A. 13 mm
   B. 15 mm
   C. 17 mm
   D. 19 mm

Answer: **C**. While experts generally consider 15 mm as a diagnosis of HCM, especially when asymmetric and in the absence of loading conditions that could otherwise produce this level of hypertrophy, general agreement is that up to 17 mm can be seen in the trained athlete. This represents a significant overlap area, especially for Black athletes, who typically may have higher degrees of hypertrophy.

3. Etiologies of SCD in athletes include the following:
   A. Hypertrophic cardiomyopathy
   B. Commotio cordis
   C. ARVC
   D. Coronary anomalies
   E. Myocarditis
   F. Channelopathies
   G. All of the above

Answer: **G**. All of the above can be associated with sudden cardiac death in athletes, although the frequency differs in different societies. These differences may be explained by genetic distribution of cardiac conditions in segregated populations. In the USA, the largest contributor is HCM, whereas in Italy it is ARVC.

4. SCD in athletes has the following themes, except:
   A. It is more common in males than females.
   B. It is more common in Blacks than Caucasians.
   C. It is more common in burst athletics than lower intensity athletics.
   D. It is more common in weight lifting than in endurance athletics.

Answer: **D**. All of these are true with the exception of weight lifting, although weight lifting is not advisable in HCM due to the increased afterload that might stimulate further LVH.

5. Challenges to screening include the following except:
   A. Cost-effectiveness indicates routine population-wide screening even with ECG would be cost-prohibitive.
   B. False-positive rates are high, leading to unnecessary testing and psychological and financial impact to the athlete or youth.
   C. Homegrown screening initiatives focus on wealthier demographics, leaving many communities with disparities in care delivery.
   D. There is a higher false-positive rate in Blacks than Caucasians.
   E. All of the above.

Answer: **E**. All of the above are challenges to screening programs. Therefore, current guidelines recommend a focused history and physical examination and the AHA 14-point questionnaire in an attempt to screen all individuals prior to sports participation. Patients with concerning features move on to ECG and echocardiography, based on findings.

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Lifestyle Modification: Diet, Exercise, Sports, and Other Issues

12

David S. Owens

Key Points

1. Diet and hydration factors can have a large impact on HCM patient symptoms due to the dynamic nature of LVOT obstruction.
2. Patients without a history of congestion should drink plenty of fluids and avoid eating large meals.
3. Caffeine and alcohol can potentially worsen LVOT obstruction and should be avoided in symptomatic patients. At a minimum, patients should drink in moderation and avoid "binge drinking."
4. Exercise increases the risks of sudden cardiac death acutely, but this risk needs to be balanced against the known chronic health benefits.
5. In accordance with the HCM guidelines, HCM patients should be restricted from competitive sports, with the possible exception of low dynamic, low static sports (e.g., bowling, archery).
6. Recommendations for recreational activities should be individualized. High-intensity and burst activities should be avoided, but brisk walking, swimming, and/or jogging may be permitted as components of a healthy lifestyle.
7. Patients with ICDs can usually live everyday life without major adjustments, though adjustments may be needed if large sources of electromagnetic interference are encountered occupationally. The presence of an ICD, however, does not modify the recommendations on allowable levels of exertion or sports participation.
8. HCM patients may be unable to work in specific professions (e.g., airline pilots or active duty military) due to public safety concerns if transient loss of consciousness were to occur.
9. Several recent patient rights legislations offer protection against discrimination on the basis of genetic information or preexisting conditions, but these protections do not generally apply to life or long-term care insurance.

Introduction

As a lifelong condition and one that carries risk of sudden death, an HCM diagnosis can have profound impact on patients' health behaviors, lifestyle, and psychological outlook. Patients may have a number of questions about how HCM affects their everyday life, and this is especially true for patients with ICDs. Patients with LVOT obstruction or congestion often find that their symptoms are dependent on their dietary choices and hydration status. Moreover, patients are confronted with restrictions on exercise, employment, and insurability. This chapter will focus on lifestyle issues for patients with varied clinical manifestations of HCM, including issues related to diet and hydration, obesity and weight loss, and recommendations for physical activity. It will also address some of the lifestyle considerations for patients with ICDs.

Dietary and Fluid Intake

A common question patients have when they are first diagnosed with HCM is whether dietary or lifestyle factors caused or contributed to the condition. HCM is defined as a genetic condition caused by variation in cardiac sarcomere and related proteins, and currently there are no known lifestyle factors that cause or contribute to disease

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manifestation [1]. Systemic hypertension may contribute to LV hypertrophy, but hypertensive heart disease is considered a separate entity with unique natural history.

However, lifestyle factors can profoundly affect symptomatology by modulating the contractility and loading conditions under which the heart operates. Approximately 2/3 of HCM patients have resting or provocable outflow tract obstruction [2]. This obstruction is most often "dynamic," and factors such as preload, afterload, and contractility can greatly influence its severity. Factors that decrease preload (e.g., dehydration, some medications, or Valsalva maneuver) can decrease LV cavity volumes, bring the mitral leaflets closer to the LV outflow septum, and thereby worsen the LV outflow tract obstruction. LVOT gradients may vary widely from day to day or even throughout the course of a single day depending on when patients last ate, drank, or took their medications.

A postprandial increase in symptoms of dyspnea and angina or exercise limitation is a common complaint for patients with obstructive HCM [3, 4]. As splanchnic vessels vasodilate to allow an increase in blood flow, there is a resultant decrease in systemic vascular resistance and effective circulating plasma volume (decreasing LV preload), both of which can increase LVOT gradients (Fig. 12.1). Taking advantage of this physiology, it has been proposed that stress testing in the postprandial state provides increased sensitivity for detecting obstruction [5]. For patients with a postprandial increase in symptoms, it may be prudent to avoid large meals and eat smaller, more frequent meals or snacks.

It is important that all patients with HCM avoid dehydration, which can increase LVOT obstruction by reducing preload and increasing contractility; patients with nonobstructive HCM are also susceptible to the consequences of low preload. Although there have been no scientific studies in HCM patients, the general rule of drinking eight 8-ounce glasses of water (or other low calorie beverage) per day seems reasonable for patients who do not have signs or symptoms of congestion.

A subset of patients with HCM develop overt congestive heart failure, either due to progression to "end-stage" phenotype with low ejection fraction or, in the setting of preserved systolic function, due to the presence of LVOT obstruction or due to diastolic dysfunction and reduced LV compliance [6]. Indeed, any impairment of cardiac systolic or diastolic function, including both obstructive and nonobstructive HCM, may result in volume overload over time. For these patients,

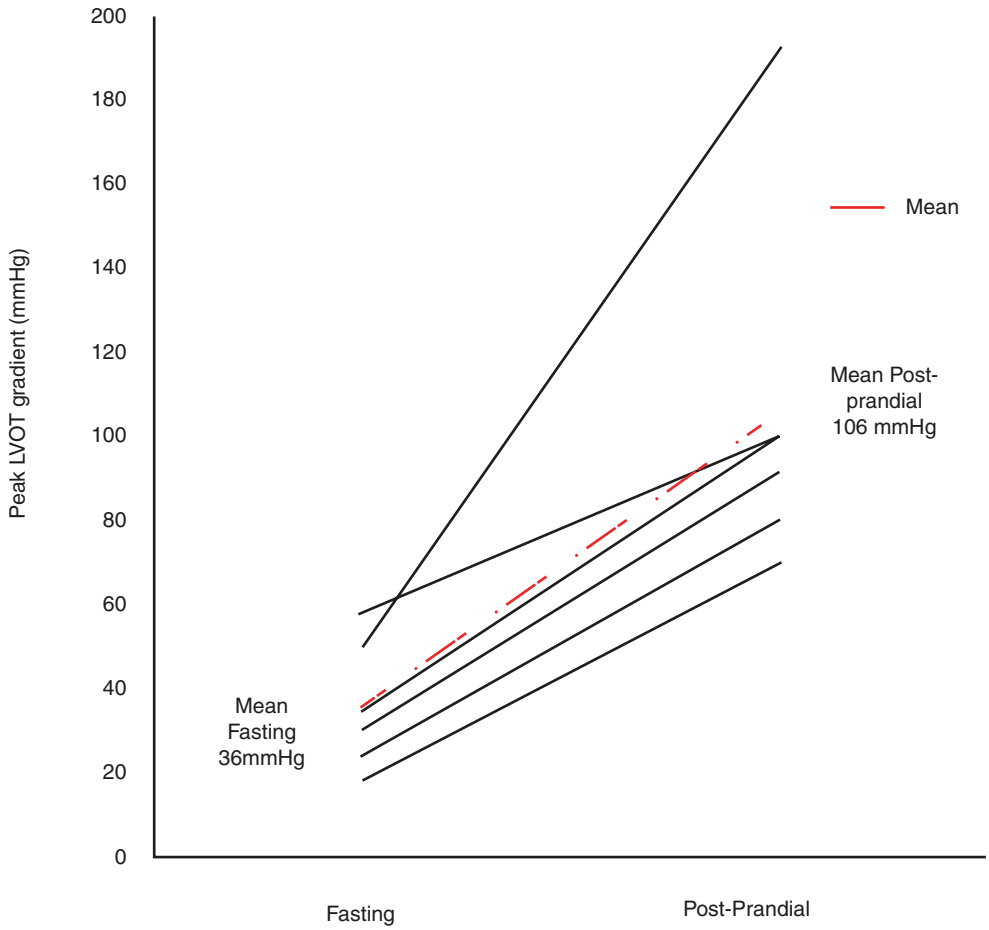

Fig. 12.1 Fasting and postprandial peak LVOT gradients among six patients with symptomatic, obstructive HCM and postprandial increase in symptoms [4]. (Reprinted from Kansal et al. [4], Copyright (2010), with permission from Elsevier)

salt and fluid restriction along with judicious use of diuretics may be needed. Standard heart failure management strategies, including daily weights with a triggered diuretic titration protocol, may be beneficial. In those with obstructive physiology, however, care must be taken to avoid overdiuresis and inadvertently increasing obstructive symptoms. Gradually increasing diuretics, starting with less potent agents such as hydrochlorothiazide, and moving to triamterene, loop diuretics, or adjunctive metolazone or zaroxolyn as needed may be a prudent strategy, with careful attention to electrolyte balance.

Caffeine

Another common question from patients is whether it is safe to drink coffee. Coffee, caffeinated teas, and energy drinks with caffeine supplements are widely available and widely consumed, and daily intake is common. Caffeine is a xanthine alkaloid that stimulates the central nervous system via adenosine receptor antagonism and is often used to reduce fatigue and increase mental alertness. While a standard 8-ounce cup of coffee may contain 50–200 mg of caffeine, energy drinks are growing in popularity and may contain up to 500 mg. The rate of caffeine metabolism varies widely between individuals due to variability in the hepatic CYP1A2 enzyme, which accounts for much of the marked variability in the response to caffeine seen clinically.

Caffeine has acute effects on the cardiovascular system, including mild positive inotropic effects from phosphodiesterase inhibition, increased norepinephrine release, and increased intracellular calcium availability and sensitivity. Caffeine can also induce vasoconstriction, which can result in up to a 10 mmHg increase in systolic BP in caffeine-naïve individuals, particularly in patients with resting hypertension. Caffeine in higher doses (250–300 mg) can also have diuretic effects, although little net diuretic effect is seen with a standard cup of coffee. All of these effects appear to be attenuated in individuals with habitual caffeine intake.

There is no data on the effects of caffeine on HCM patients specifically, but the known physiologic effects of caffeine may be theoretically adverse. The increased contractility and mild diuretic effects of caffeine could combine to worsen LVOT obstruction, although this may be offset by an increase in afterload. Although there is concern about caffeine being pro-arrhythmic, caffeine does not appear to increase the risk of atrial fibrillation in the general population [7], nor does it appear to increase inducibility of ventricular tachycardia in patients with symptomatic VT [8]. Moreover, small randomized trials of caffeine intake in patients with symptomatic PVCs or dilated cardiomyopathy did not show an increase in ectopy or arrhythmias [9, 10]. On the other hand, population studies have suggested that moderate caffeine consumption may have protective effects on cardiovascular health [11].

Energy drinks and energy shots are widely consumed among adolescents and young adults and may pose additional health concerns for HCM patients. These supplements are designed and marketed to provide energy, increase mental alertness, and enhance physical performance. The main ingredient in energy drinks is caffeine, with the most popular drinks containing 70–140 mg per 8 ounce serving, or equivalent to 1–2 cups of coffee [12]. Common additional ingredients include simple sugars as well as taurine, guarana, ginseng, and B vitamins. Guarana and other supplements are sources of additional, unreported caffeine content. Studies looking at the effect of energy drinks on cardiac function show positive chronotropic and inotropic effects, including increases in heart rate, blood pressure, and stroke volume, due to an increase in plasma catecholamine levels [13, 14]. While the arrhythmogenic potential of energy drinks has not been definitively studied, there have been a number of case reports linking energy drink consumption to arrhythmias, even in structurally normal hearts [12, 14]. Because of these proven stimulatory effects and arrhythmogenicity concerns, energy drink consumption should be discouraged in patients with HCM.

The 2011 HCM ACCF/AHA Guidelines do not make specific recommendations concerning caffeine intake [1]. Given the above data, strict caffeine prohibition does not appear to be warranted for all HCM patients. However, caffeine intake should be limited – and preferably avoided – in patients with resting or labile LVOT obstruction, patients who have intermittent dysrhythmias, or patients whose symptoms are temporally linked to caffeine consumption. For patients who choose to drink coffee, it should be consumed in moderation (1–2 cups of coffee per day), with avoidance of caffeine binge drinking.

Alcohol

Alcoholic beverages (including beer, wine, and liquors) are also commonly consumed, and in one study up to 90% of HCM patients reported drinking ≥12 alcoholic beverages within the past year [15]. Ethanol is the principle component in alcohol and the source of its psychoactive effects, due to its interactions with GABA receptors in the brain. Alcoholic beverages differ in their ethanol content, and for purposes of standardization, one alcoholic drink contains 10–14 g of ethanol, which is approximately the equivalent of 12 ounces of beer (~5% alcohol), 5 ounces of wine (~12% alcohol), or 1.5 ounces of hard liquor (~40% alcohol).

In addition to its acute psychoactive effects, alcohol has both acute and chronic effects on cardiac function. Acute ethanol ingestion is associated with reduced myocardial con-

tractility, a decrease in vascular tone, and a reflexive tachycardia. Alcohol also has diuretic effect that can promote dehydration. Thus alcohol can induce both reductions in preload and afterload that may worsen LVOT gradients, although this may be offset somewhat by reduction in contractility.

One study examined the effects of ethanol on patients with HCM and systolic anterior motion (SAM) of the mitral valve (but not necessarily resting obstruction) [16]. After ingesting the equivalent of about one alcoholic drink, there was on average an 8 mmHg drop in systolic blood pressure, an increase in SAM severity, and an increase in peak LVOT gradients from 38.1 to 62.2 mmHg, while there were no such changes in a placebo group (Fig. 12.2). These subjects were asymptomatic with this change, but this represented only a small amount of alcohol compared to levels that may be consumed socially.

In the general population, there is evidence for a "J curve" for the effect of alcohol on overall health, with benefit at low levels and harm at high levels of exposure [17, 18]. A number of large, prospective studies have demonstrated improvement in coronary heart disease outcomes and overall mortality with moderate alcohol consumption (1 drink per day for women, 1–2 drinks per day for men), with an estimated risk reduction of 30–50% [19]. The mechanisms of this benefit are uncertain, but improvements in insulin sensitivity, HDL cholesterol, and endothelial function and reductions in inflammatory markers have been described. High levels of alcohol consumption are cardiotoxic and clearly adverse, with increased risk of hypertension, nonischemic dilated cardiomyopathy, atrial fibrillation, and stroke in addition to liver cirrhosis and other organ damage.

In contrast to the "J curve" effect on coronary heart disease outcomes, there appears to be a linear increase in risk of atrial fibrillation across the range of alcohol consumption. Heavy alcohol consumption has long been known to be a precipitant of atrial or ventricular arrhythmias (aka, "holiday heart"), but even at lower levels of consumption, each additional one drink per day appears to increase the risk of atrial fibrillation by about 10% [20]. It is unknown if this linear association holds true for HCM patients, and it is possible that the risk is greater in this population because of their increased susceptibility to arrhythmias and their higher incidence of LA enlargement overall.

There is evidence that an HCM diagnosis may modify patients' health behaviors in a positive manner. After adjusting for age, gender, and body mass index (BMI), HCM patients were found to consume 0.9 fewer alcoholic drinks per day on average over the 1-year prior to the survey and were 41% less likely to have engaged in binge drinking (≥5 drinks in 1 day) over the course of their lifetime.

The 2011 HCM Guidelines did not make recommendations concerning alcohol consumption in patients with HCM. There are clear adverse consequences of heavy alcohol consumption both acutely and chronically, and "binge drinking" should certainly be discouraged. Patients with resting or labile LVOT obstruction should limit or abstain from alcohol consumption, as should patients who experience symptoms temporally linked to alcohol consumption. Abstinence may reduce the occurrence of atrial fibrillation in

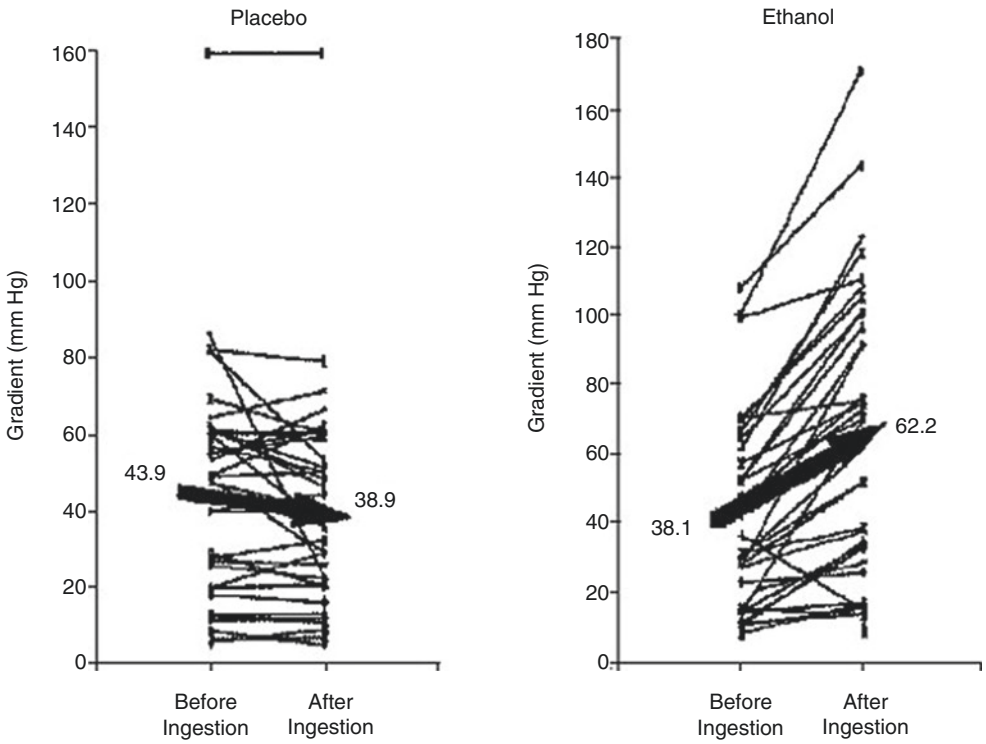

Fig. 12.2 Peak LVOT gradients before and after ingestion of placebo (left) or 50 mL of 40% ethanol (right) in patients with HCM and systolic anterior motion of the mitral valve [16]. (From Paz et al. [16]. Copyright ©1996 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society)

patients experiencing or at risk for atrial dysrhythmias. However, it is unclear if strict prohibition from alcohol is appropriate for all HCM patients given evidence that it may have a cardioprotective effect at low to moderate levels of consumption. Recommendations regarding alcohol consumption must therefore involve a discussion about the risks and benefits for individual patients.

Other Drugs

Tobacco use, in addition to increasing risks of lung, throat, and other cancers, is associated with increased cardiovascular morbidity and mortality. There have been extensive public health efforts aimed at educating the general population about the risks of tobacco use and about smoking cessation resources. Nicotine is the main active ingredient in tobacco. Nicotine binds to nicotinic acetylcholine receptors, impairs acetylcholine neurotransmitter reuptake, and thus serves as a stimulant to both the central and autonomic nervous systems. Additionally, it stimulates adrenaline release from the adrenal glands. Smoking has been shown to increase heart rate, blood pressure, and cardiac contractility acutely meanwhile reducing coronary blood flow, all of which have potential detriment in patients with HCM, especially those with obstruction or microvascular ischemia.

Since there are no known acute or chronic health benefits of tobacco use, a clear and strong recommendation for tobacco cessation should be given to all HCM patients who smoke. Although 20% of HCM patients are current smokers, they compare favorably to the general population: HCM patients are 25% less likely to be past or current smokers and 74% less likely to be current smokers comparatively [15].

There are recent trends in the USA toward legalization of marijuana and cannabinoids for either medical or recreational purposes. Although there are over 125–200 million marijuana users worldwide, the effects of marijuana on the cardiovascular system are not well studied [21, 22]. Moreover, it is often difficult to separate the effects of marijuana from other drugs, as tobacco or other recreational drugs are often used concurrently. Acutely, marijuana appears to increase heart rate and catecholamine levels, with a reduction in peripheral vascular resistance [23] and an increase in the risk of coronary vasospasm [24]. Marijuana consumption may be associated with worsened cardiovascular outcomes in patients with known CAD, including increasing risks of myocardial infarction and overall mortality [25–27], but was not associated with cardiovascular outcomes in an otherwise healthy population [28].

There are several reports of patients experiencing myocardial infarctions, arrhythmias, and/or sudden death after marijuana use [29], including an autopsy series of six young individuals (all aged <45 years) with likely cardiac deaths in which marijuana was the only drug found on toxicology [30]. However, none of these individuals appeared to have HCM, and it is unclear if marijuana was a causal factor. Several case reports and series have suggested a link between acute marijuana use and onset of atrial fibrillation in otherwise low-risk individuals [31, 32]. This raises some concern that marijuana may have heightened effects in individuals at risk for atrial fibrillation, although this has not been studied.

As there is no data on the safety of cannabis use in HCM patients, it seems prudent to recommend against its use on a recreational basis (where legal). If cannabis is being prescribed for medical reasons (e.g., chronic oncologic pain), the benefits should be weighed against its unknown risks.

Medications and Supplements

The mostly commonly prescribed medications for the treatment of HCM are beta-adrenergic blocking agents (e.g., metoprolol, atenolol) and calcium channel blockers (e.g., verapamil). Beta-blockers are the first-line agent for the treatment of obstruction and are also commonly prescribed for patients with nonobstructive HCM. Beta-blockers have both negative chronotropic and negative inotropic effects, decreasing resting and exertional heart rates, improving LV filling, decreasing peak exertional gradients, and possibly reducing arrhythmias. However, these medications can have numerous side effects, especially in young people. Fatigue, general malaise, depression, and erectile dysfunction are common, often dose-limiting complaints. Some providers have suggested that Toprol XL, the name brand formulation of metoprolol succinate, is better tolerated and that using divided doses for more consistent blood levels may reduce severity of side effects.

For patients that do not tolerate beta-blockers or remain symptomatic, calcium channel blockers such as verapamil are often used. Verapamil comes in both short and extended-release (both once and twice daily) formulations. Verapamil improves diastolic filling and can reduce resting LVOT gradients to a greater degree than beta-blockers [33]. Additionally, some providers prefer verapamil over beta-blockers for the treatment of microvascular angina. Common side effects include constipation, fatigue, and lower extremity edema. Calcium channel blockers should be used with caution when added on to a beta-blocker therapy, as the combination may induce AV block. In addition, high doses of verapamil may reduce afterload and provoke obstruction and are therefore best avoided. Diltiazem is less well studied and generally not considered a first-line agent.

Disopyramide is a class IA antiarrhythmic that was originally designed to treat ventricular tachycardia. It is also a potent negative inotropic agent, and the combined effects can be especially beneficial for patients with LVOT obstruction and refractory symptoms. This agent can prolong the QT interval and speed up AV nodal conduction. The ACCF/AHA

guidelines recommend inpatient monitoring during drug initiation and simultaneous use of an AV nodal blocking agent [1], but a recent study suggests outpatient loading is safe and effective [34]. It is important to remember that disopyramide can only be prescribed in addition to AV nodal blocking agents and should never be given in isolation. Disopyramide comes in both short-acting (TID or QID) and long-acting (BID) formulations, though there have been frequent manufacturing shortages of the long-acting agent. Because of the potent effects but short half-life of the drug, patients are often reminded to take their next dose because of worsening of their symptoms. In general, however, disopyramide ER is preferred but may require non-formulary insurance approval.

The side effects of disopyramide are chiefly anticholinergic in nature and mostly dose-dependent. At starting doses, dry mouth, constipation, and urinary retention may begin; at higher doses, blurred vision becomes a common complaint. Pyridostigmine is a cholinesterase inhibitor that can counteract the anticholinergic side effects of disopyramide. Pyridostigmine is best prescribed as a long-acting agent, with doses of 180–360 mg daily to match the severity of the side effect symptoms. It is generally not necessary to monitor blood levels of disopyramide, though periodic symptom and QTc assessment are warranted.

Over-the-counter medications may contain hidden stimulants, and it is important for HCM patients to be aware of ingredients of all OTC remedies. For instance, pseudoephedrine is commonly found in "nondrowsy" cold therapies and decongestion/antihistamine combinations. It functions primarily as a vasoconstrictor due to its α-adrenergic effects but can have both direct and indirect cardiac effects including a rise in heart rate and blood pressure. As with all stimulants, there is concern about arrhythmias, and therefore these should be avoided if possible.

In addition, many patients take vitamin, herbal, or health supplements, either to promote general health or for perceived benefits on HCM. To date there is little data on the safety or efficacy of most of these supplements. One supplement commonly taken by HCM patients is Coenzyme Q-10, which is commonly found in dietary sources (e.g., meats, poultry, and oils) and is purported to have antioxidant properties and improve mitochondrial energetics. While Coenzyme Q-10 supplementation has been tested in several medical disorders and in low doses it appears safe [35], there is no data proving its efficacy or safety in HCM patients.

Obesity, Sleep Apnea, and Coronary Artery Disease Risk Factors

Recent survey data has shed light on how HCM patients compare to the general population in some of their health behaviors and physical activity levels [15]. Using the National Health and Nutrition Examination Survey (NHANES) data and propensity matching for age and gender, HCM patients were found to have higher body mass index (BMI) and are more likely to be obese (BMI >30 kg/cm^2). However, there were no clear differences in eating habits between HCM patients and controls. HCM patients reported eating fewer fast food meals but were more likely to eat ready-to-eat meals in the 30 days prior to the survey.

The relationship between obesity and HCM is complex. It is unclear to what extent obesity is a result of physical inactivity caused by disease-related exercise limitations or by physician-advised exercise restrictions and to what extent HCM phenotype and/or symptoms are impacted by obesity. Obese HCM patients have higher blood pressure, greater LV mass, and worse NYHA functional status and exercise tolerance compared to nonobese HCM patients [36, 37]. They may also have greater likelihood of provocable LVOT obstruction [37]. There are some potential and interesting biological pathways that may mediate this association (e.g., leptin-induced hypertrophy), but the direction of causality here remains uncertain [38].

Obesity is often (but not always) accompanied by coronary artery disease risk factors of hypertension, dysglycemia (insulin resistance, metabolic syndrome, or diabetes), and hypercholesterolemia. It is unknown if these risk factors are more common in HCM patients compared to the general population, but the coexistence of coronary artery disease and HCM has been linked to increased mortality [39], and coronary disease prevention is an essential component of the care of HCM patients. Coronary artery disease risk factors should be treated according to standard primary and secondary prevention guidelines [1], although the treatment of hypertension in the setting of LVOT obstruction can be particularly challenging (see chapter on hypertension elsewhere in this textbook) [40].

Obstructive sleep apnea is also common in HCM patients, with up to 40% of HCM patients having an apnea-hypopnea index >15 events/h [41] and up to 71% having repetitive nocturnal desaturations [42]. Moreover, OSA has been independently linked to atrial fibrillation in HCM patients [41], and a low index of suspicion should be used for diagnosis and treatment. More information on OSA is found in a dedicated chapter elsewhere in this textbook.

Weight loss is primarily determined by the balance of caloric intake and expenditures, and patients with HCM may find it challenging to achieve and maintain weight loss due to exercise limitations or restrictions. Symptomatic HCM patients tend to gain weight because of inactivity, and obesity taxes cardiac reserves and increases symptoms. Obesity can also increase the peri-procedural risks of either surgical myectomy or alcohol septal ablation. Patients may benefit from a referral to a dietician, and in some instances a referral for bariatric surgery can be considered.

Competitive Sports and Recreational Exercise

Both US and European professional guidelines provide detailed recommendations for the types and intensity of exercise activities appropriate for patients with HCM. These guidelines make the important distinction between competitive sports and recreational exercise [43, 44]. In competitive sports, there are usually external motivators in the form of a coach, monetary reward, or the thrill of victory. Athletes train intensively with the goal of pushing their limits and achieving personal bests and may disregard their short-term physical health to reach these goals. In contrast, recreational activities are less vigorous and usually self-regulated, with a primary goal of maintaining fitness.

The 2015 AHA/ACC Guideline update to the 36th Bethesda Conference recommendations addresses HCM patient participation in competitive sports [45, 46]. These guidelines continue to recommend that patients with a "probable or unequivocal" diagnosis of HCM should be excluded from all competitive sports with the possible exception of low-intensity sports. These recommendations are universal and apply to all HCM patients regardless of age, sex, or race, the presence of outflow obstruction or prior septal reduction procedures, the number of sudden death risk factors present, and the use of medications or ICDs. Additionally, medications such as beta-blockers or antiarrhythmics should not be given to permit sports participation. A list of sporting disciplines categorized by intensity of static and dynamic components is shown in Figure 12.3 [47, 48]. The AHA/ACC update to the 36th Bethesda Guidelines continue to recommend that HCM patients only participate in Class IA competitive sports that have both low static and low dynamic components, such as billiards, bowling, cricket, curling, or golf (bottom left panel in Fig. 12.3). However, in recognition of the SPORT-ICD data (discussed below), the guidelines now state that if the athlete has an ICD, then participation in high-intensity sports can be considered – after proper counseling of the risks and benefits involved – if the athlete is free of episodes of ventricular arrhythmias requiring device therapy for 3 months [49].

The European Society of Cardiology consensus statement on competitive sports participation is largely in agreement with these recommendations (Table 12.1) [44]. However, they differ from the AHA/ACC recommendations in regard to patients with preclinical HCM (i.e., individuals who carry an HCM-causing gene mutation but who do not express LV hypertrophy) [50]. The ESC recommends disqualification from competitive sports due to the uncertainty in the natural history of the disease, though recreational exercise is permitted. In contrast, the Bethesda Conference recommendations do not place any restrictions on competitive or recreational activities for this group.

The decision to exclude an athlete from competition can have profound consequences on the athlete both financially (realized or potential) and psychologically and should only be undertaken when there is high probability or conclusive evidence of HCM. It has been proposed that these challenging situations be approached using a shared decision-making model rather than diagnose and exclude template [51]. These

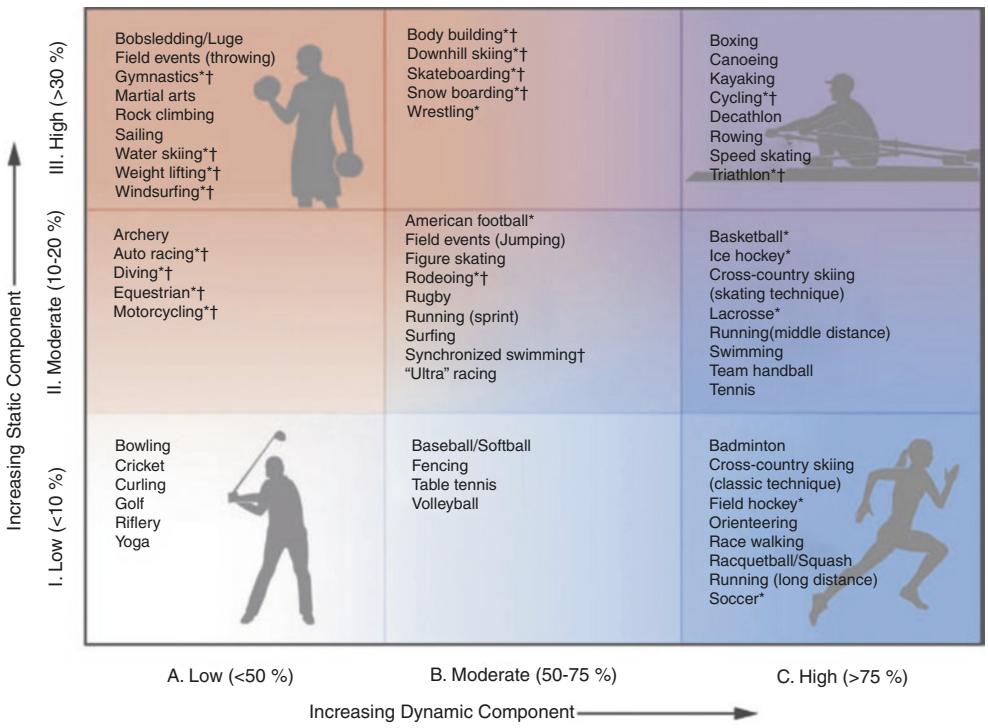

Fig. 12.3 Classification of sports based on peak static and dynamic components achieved during competition

Table 12.1 Comparison of US and European guideline recommendations for participation in competitive sports and recreational exercise

	USA	Europe
Overt HCM		
Competitive sports	Class 1A sports only	Class IA sports if low-risk profile, otherwise no competitive sports
Recreational activities	Some restrictions	Some restrictions
Preclinical HCM[a]		
Competitive sports	No restrictions	No competitive sports
Recreational activities	No restrictions	No restrictions

[a]Gene carrier without HCM phenotype

are difficult discussions, and it is not easy separating out the athlete's psychologic acceptance of a new diagnosis and the immediacy of external rewards to come to a truly unconflicted and informed decision in light of the often unknown and unquantifiable risks involved. Additionally, the athlete must be aware that there is usually a third-party stakeholder (the professional team, organization, or university) in the decision to allow an athlete to return to play, and this party may or may not be willing to allow the athlete to compete. These decisions have medicolegal implications for all stakeholders [52], and it is strongly advised that athletes confronted with these situations seek out second opinions from HCM specialists who have experience navigating these discussions.

There has been a misconception by some medical providers that patients with HCM should not engage in any forms of exercise other than those outlined for competitive sports. There are myriad benefits of exercise on cardiovascular health and overall well-being, and complete exclusion from recreational exercise could have negative consequences on overall health [53]. Regular, moderate levels of exercise promote weight loss; combat hypertension, hypercholesterolemia, and dysglycemia; maintain bone density; and improve sleep, self-esteem, and mental outlook.

Not only are stringent restrictions potentially detrimental to overall health, they can also have a profound psychological impact on patients. In a survey of HCM patients, 60% felt that exercise restrictions had a negative impact on their emotional health and 71% expressed anxiety toward exercise although this was generally mild and did not correlate with physical activity [15]. To help patients navigate these issues and to encourage safe physical fitness, clinicians at the Peter Munk Cardiac Center have developed tailored and graduated fitness programs specific for HCM patients [54]. These programs (available at www.hcmfitness.ca) can be tailored to patient age and ability and conform to the HCM guideline recommendations on exercise.

Acknowledging the health benefits of regular, low to moderate-intensity exercise, both US and European expert panels have provided recommendations for the intensity and types of recreational activities that might be appropriate for patients with HCM [1, 44, 55]. These recreational activity guidelines are less restrictive than those for competitive sports.

European consensus recommendations divide activities into categories of "not recommended," "allowed on an individual basis," or "permitted" (Table 12.2) [44]. In general, vigorous activities, burst activities (e.g., basketball), and activities where a transient loss of consciousness would have profound impact (e.g., scuba diving) are to be avoided. The US guidelines are very similar in their scope and purpose but grade activities on a 0–5 point scale of "permissibility": activities with scores of 0–1 are "not advisable," 2–3 are "intermediate," and 4–5 are "probably permitted" [55]. The US guidelines are more lenient toward biking/cycling and baseball (intermediate sports) and swimming (probably permitted) but are more strict toward running (not advisable), although both categorize jogging as a medium-risk activity. Additionally, the US guidelines do not comment on rowing sports and track events and divide weight lifting into machine weights (probably permitted) and free weights (not advisable).

Until recently there has been little objective data on which to base exercise recommendations. However, a recent multi-

Table 12.2 European Society of Cardiology recommendation for amateur and leisure-time sport activities in patient with HCM (based on recommendations provided in Pelliccia et al.) [44]

Sports not recommended	Sports allowed on individual basis	Sports permitted
Baseball	Moderate-intensity weights	Stationary bicycle
Basketball	Cross-country skiing (flat)	Bowling
Road cycling	Horseback riding[a]	Brisk walking
Ice hockey[a]	Jogging	Golfing
Rowing/canoeing	Running	Moderate hiking
Rock climbing	Motorcycling[a]	Skating
Scuba diving	Sailing[b]	Tennis (doubles)
Sprinting	Stationary rowing	Treadmill
Soccer	Swimming[b]	Low-intensity weights
Squash[a]		
Tennis (singles)		
Track events		
High-intensity weights		
Windsurfing[b]		

[a]These sports involve the potential for traumatic injury, which should be taken into consideration for individuals with a risk for impaired consciousness

[b]The possibility of impaired consciousness occurring during water-related activities should be taken into account with respect to the clinical profile of the individual patient

center trial of moderate exercise in patients with HCM begins to support the notion that moderate exercise may be safe and potentially should be encouraged [56]. In this study, Saberi and colleagues randomized 136 subjects with HCM to 16 weeks of moderate intensity exercise training versus usual care. The exercise program involved unsupervised cycling, elliptical, or walk-jog exercise to a peak heart rate of 60–70% of heart rate reserve, with exercise duration gradually increasing to 60 min per session, 4–7 times/week. After 16 weeks, the group assigned to exercise showed a modest improvement in peak VO2 (+1.35 ml/kg/min, 95%CI, 0.50–2.21) versus no improvement in the usual care group. Importantly, there were no sustained ventricular arrhythmias, sudden cardiac arrests, appropriate ICD shocks, or deaths in either group, providing preliminary data regarding the safety of moderate exercise within the HCM population.

In an effort to provide an evidence base for exercise recommendations in patients with HCM, the Lifestyle and Exercise in Patients with Hypertrophic Cardiomyopathy ("LIVE-HCM," www.livehcm.org) study is an ongoing, NIH-funded prospective registry of HCM patients. This study seeks to obtain information on the risks and benefits of exercise in HCM by tracking – using self-reported data and wearable technology – subjects' voluntary recreational activities and habits, along with prospective clinical events. The results of this study will greatly inform future guideline recommendations.

Ultimately, the proper balance between the risks and benefits of exercise is not a one-size-fits-all recommendation but involves a conversation with individual patients. Several general observations and commonsense strategies can inform this conversation:

- The goal of exercise should be for health maintenance, not a competition against the clock, yourself, or others.
- The activities that appear to carry the most risk are high-intensity sports and those that involve intermittent bursts (e.g., basketball, soccer).
- The risks associated with exercise appear to be highest for patients who exercise intermittently (0–1 times per week). Exercise should be incorporated into a daily routine.
- For patients that desire a heart rate target for exercise, 60–70% of heart rate reserve appears to be a safe, reasonable threshold.
- If patients are too dyspneic to hold a conversation, they are exercising too vigorously.
- Patients should exercise with a partner or a group whenever possible and ideally with someone who knows about their heart condition. If there is an event, someone should be around to initiate emergency response; many gyms now have AEDs on site.
- Patients need to listen to their body and stop exercising if things do not feel right.

Because of the guideline recommendations against competitive or vigorous exercise, as well as the underlying cardiac limitations to exercise that come with HCM, it is surprising that a higher percentage of HCM patients engaged in moderate or vigorous recreational activities compared to the NHANES control population, although the time spent doing those activities was lower [15]. Moreover, approximately 10% of HCM patients were engaging in >1 competitive sport. This may in part be due to inadequate patient education, as only 29% of HCM patients were aware of the professional guideline recommendations on exercise and only 46% of HCM patients reported having conversations about exercise with their doctor. This may also represent a selection bias, with more active individuals participating in the registry. Among patients who were aware of the exercise recommendations, only 59% reported being adherent, which seems to reflect a disconnect between patient and physician attitudes toward exercise, at least in this cohort. HCM patients with ICDs were less likely to engage in vigorous exercise but equally likely to engage in moderate exercise activities compared to HCM patients without ICDs.

Sexual Activity

Sexual activity is less frequently discussed but is another important topic to patients. This topic was not addressed in either the 2004 guidelines on recreational activity or in the 2011 HCM guidelines [1, 55]. The 2012 AHA Scientific Statement on Sexual Activity and Cardiovascular Disease states that sexual activity is reasonable (class IIa recommendation) for most patients with HCM but should be deferred in severely symptomatic patients [57].

Erectile dysfunction (ED) is a common side effect of beta-blockers and channel blockers, which serve as the cornerstone of HCM therapy. Phosphodiesterase type 5 (PDE5, e.g., sildenafil) inhibitors may be requested by patients to help overcome drug-induced ED, but the safety of these agents in HCM – and obstructive HCM in particular – is not well established. PDE-5 inhibitors exert their effect through venodilation, which can reduce cardiac preload. In patients with resting or provocable LVOT obstruction, there are concerns that this decreased preload – in conjunction with increased heart rate – will worsen obstruction and cause hemodynamic compromise or arrhythmias. Worsening LVOT obstruction [58] and atrial fibrillation [59] have been reported after use of sildenafil, although the guideline committee was unaware of any deaths in patients with HCM or outflow stenosis [57]. The safety of PDE5 inhibitors in patients with clearly documented *nonobstructive* HCM has not been proven and should be considered only after careful discussion about the risks and benefits. In some cases, echo

assessment of LVOT gradients following drug administration may be useful.

For patients of childbearing age, a proactive conversation regarding contraception is warranted. Although pregnancy is usually well tolerated hemodynamically in women with HCM and maternal mortality remains low, pregnancy may be discouraged in some patients with severe symptoms, congestion, or active arrhythmias [60, 61]. Most forms of contraception carry acceptable risks for HCM patients, including barrier methods, combined hormonal agents (e.g., estrogen/progestin formulations), progestin-only regimens, intrauterine devices, or sterilization [62, 63]. Patients with atrial fibrillation or prior strokes or those on anticoagulation should avoid estrogen combinations that could increase the risk of thrombus formation. In all cases, preconception counseling should include a discussion about contraception options, an evaluation of the risk of pregnancy, a review of medications and their safety during pregnancy, and prenatal genetic counseling to inform the prospective parents about the risks of transmitting the gene mutation and other options available.

Patients with ICDs

There are special considerations for patients with ICDs. These patients have been identified as being higher risk, either because of a prior event or because of the presence of SCD risk factors. There are additional concerns about electromagnetic interference, inappropriate shocks, or damage to the device. And finally, there is concern about the effectiveness of appropriate ICD shocks in an exercise milieu that may involve increased adrenergic tone, electrolyte imbalances, and/or myocardial ischemia.

Following ICD placement, some lifestyle modifications may be prudent. In the modern world, there are a number of potential sources of electromagnetic interference (EMI) including microwaves, cellular telephones, portable media players, slot machines, and metal detectors [64]. While there are occasional reports of ICDs being impacted by these devices, they are generally considered safe in the context of typical daily exposures. It is recommended that patients do not carry cellular phones and other electronic equipment within 6 inches of the ICD generator and avoid their use during device interrogation [65, 66]. It is considered safe for patients with an ICD to walk through metal detectors, such as those at an airport, at a normal pace although the device may trigger the alarm [64]. However, patients should avoid lingering near the detectors for prolonged periods. Wand screening or manual "pat-down" searches are safe alternatives [67]. Occupational or recreational exposures to EMI in the form of welding, chainsaws, electric motors, and magnetic coils may present greater sources of EMI and need to be considered on a case-by-case basis [64, 68]. Occasionally the implantation of an ICD will have ramifications on type or place of employment.

Following ICD placement, several precautions are generally recommended, including restrictions on ipsilateral arm motion and heavy lifting/pulling. Although regulations differ from state to state, patients should generally avoid driving for 1 week after ICD placement and for 6 months after an appropriate ICD shock or VT/VF event [69, 70]. Long-term recommendations regarding competitive sports and recreational activities are similar to those for all patients with HCM, but some additional precautions might be recommended due to concerns for lead fracture or generator injury. Inappropriate shocks are common in patients with HCM [71], who are often younger and more active than other patients with ICDs.

The SPORT-ICD study evaluated the safety of sports participation in individuals with an ICD who voluntarily chose to exercise at greater than recommended levels [72]. There were 372 registry participants, of whom 13% and 11% had at least one appropriate and inappropriate ICD shock, respectively. More shocks occurred during exercise than at rest (16% vs. 6%, $p < 0.0001$), but these shocks were just as likely to occur during recreational activities as compared to competition or training. There were two deaths over a median 31-month follow-up period, and neither death occurred during or after exercise. Lead malfunctions were present in 13–14 participants, which was higher than would be predicted by temporal trends. Among the 65 registry participants who carried an HCM diagnosis, 13 participated in competitive sports. The numbers of shocks that occurred in this HCM subgroup was not reported, but one had an ICD shock that required multiple shocks before return to spontaneous circulation. Overall, in this registry setting, sports participation for this higher risk subgroup of HCM with an ICD appeared safe, and this bore out in midterm (median 44 months) follow-up as well. However, additional data and longer follow-up are needed before these findings can be confidently extrapolated to HCM patients more broadly.

Employment and Insurability

Because HCM is a lifelong disorder potentially associated with periods of incapacitation (e.g., syncope, collapse, dizziness) or SCD, and because of the recommendations for restricting exercise, an HCM diagnosis can have important implications on employment and insurability.

Some occupations that involve public health risk require medical clearance as a component of employability, and in many instances, HCM patients will be excluded from these positions regardless of prior events, number of SCD risk factors, or presence of ICD. The Federal Aviation Administration is cautious about issuing medical certificates for commercial

pilot's license to patients with HCM, and most individuals will be excluded [73, 74]. However, the criteria for a recreational pilot's license are less strict and may be individualized by an FAA-designated aviation medical examiner. The Federal Motor Carrier Safety Administration has similar regulations for commercial motor vehicle licenses [75]. In general, because HCM carries an unpredictable risk of periodic incapacitation, these vocations should be avoided both for personal and public health reasons.

The US military has medical standards for enlistment and appointment (Department of Defense Directive 6130.3), and a current or prior diagnosis of HCM is considered disqualifying, as is LV hypertrophy with a wall thickness ≥15 mm [76]. However, some military members become newly diagnosed with HCM after enlistment. These individuals will go before a Medical Evaluation Board (MEB) and their cases will be assessed on a case-by-case basis taking into consideration their ability to perform their assigned duties. Some individuals may undergo an administrative discharge from the military based on medical grounds.

Other physically demanding occupations, such as law enforcement, firefighting, construction, and other activities may not have specific medical criteria for employment. In these cases, either the physician or the employer may have concerns about their ability to perform work without endangering public safety or the safety of coworkers.

The Genetic Information Nondiscrimination Act (GINA), enacted in 2008, is another patient's rights legislation that has positively impacted the care of HCM patients [77]. GINA prohibits the use of genetic information in health insurance and employment, thereby barring insurance companies from using the results of genetic testing to deny health insurance or increase premiums or to make employment decisions (e.g., hiring, firing, promoting workers). Once again, however, this legislation does not apply to life insurance or long-term care insurance, and these insurance companies are free to use genetic information in making coverage decisions. It is recommended that all patients undergoing genetic testing speak with a genetic counselor in advance to ensure that they understand these ramifications. Some patients may choose to delay testing until after they obtain life insurance. This is an important consideration when testing children of affected individuals.

Conclusions

HCM is a lifelong, chronic condition and patients have many questions about how this diagnosis impacts everyday life, including health behaviors, lifestyle factors, and the safety of exercise. For some patients, an HCM diagnosis may not have a major impact on everyday life, while others may be required to stop playing competitive sports, change careers, or otherwise make profound lifestyle changes. Given the multiple lifestyle aspects that must be discussed, a dedicated and frank discussion with the patient and family, often repeated over multiple visits, will be necessary in order to develop trust and partnership in their effective management.

Clinical Pearls

- Patients with resting or provocable LVOT obstruction may have postprandial exacerbation of symptoms. When present, patients should be encouraged to drink plenty of fluids and eat smaller meals spread throughout the day.
- Recommendations on fluid intake may vary based on stage of HCM. Patients with robust contractility and LVOT gradients should be encouraged to hydrate; patients with end-stage phenotype and congestion may require strict fluid management akin to standard heart failure protocols. Typically, younger patients fit the former category, while older patients who have had their HCM disease progress over decades fit the latter category.
- Although competitive sports and vigorous exercise should be avoided (particularly burst activities), the SCD event rate for the average HCM patients is low, and moderate levels of exercise should be encouraged as a part of a healthy lifestyle. Exercising in groups or at a gym improves the chances that there is someone available to seek assistance if an event occurs.
- Most patients with ICDs (transvenous or subcutaneous) will not encounter significant electromagnetic interference in the course of daily living, but the presence of an ICD may have important implications on location or type of employment.
- Recent legislation has improved patient protections for health insurance based on preexisting conditions or the results of genetic testing, but patients with HCM may legally be denied life or long-term care insurance. Family members should be informed of these issues prior to ECG/echo screening and genetic testing.

Questions

1. Common day to day activities or states that exacerbate obstructive physiology include all of the following except:
   A. Large meals
   B. Dehydration
   C. Rapidly standing
   D. Laying down
   E. Energy drinks and excessive caffeine

Answer: **D**. Laying down will increase preload, which should minimize or lessen obstruction. In contrast, postprandially, especially after large meals, drops in preload and afterload may stimulate obstruction significantly. Dehydration and rapid standing also decrease preload, whereas energy drinks and excessive caffeine may increase contractility.

2. The following sports are typically allowable for competitive participation:
   A. Football
   B. Bowling
   C. Basketball
   D. Billiards
   E. None of the above
   F. B and D only

Answer: **F**. Bowling and billiards are typically allowable per the 2011 ACCF/AHA guidelines, but all "burst" activity sports are considered contraindicated due to high risk of SCD.

3. GINA (Genetic Information Nondiscrimination Act) bars discrimination on the basis of known genetic mutations with regard to the following:
   A. Health insurance
   B. Employment
   C. Life insurance
   D. A and B only
   E. A and C only

Answer: **D**. GINA makes it illegal to discriminate on the bases of genetic testing results, for the issuance of health insurance or for employment. However, currently, GINA does not protect from discrimination for the purchase of life insurance.

4. The SPORT-ICD study evaluated the safety of sports participation in individuals with an ICD and resulted in the following findings except:
   A. Exercise was associated with increased shocks.
   B. Competitive athletics resulted in more shocks than recreational athletics.
   C. No difference was found between types of exercise and frequency of shocks.
   D. There were two deaths over roughly 2.5 years of follow-up.
   E. None of the above.

Answer: **B**. Surprisingly, while exercise was associated with more shocks, a difference between competitive and recreational exercise could not be found. The other findings are true.

5. General recommendations for exercise include which of the following:

A. Routine exercise, multiple times a week, is recommended over intermittent exercise.
B. A safe heart rate goal is 60–70% of heart rate reserve.
C. Patients need to listen to their body and know when to stop.
D. Patients should not exercise alone, so that bystanders are available in case of need.
E. All of the above.

Answer: **E**. All of the above are good general recommendations regarding exercise in HCM.

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Diet, Nutrition, and Managing Obesity

13

Lisa Salberg and Aslan Turer

Key Points

1. Obesity is common in patients with HCM, due to their fear or inability to exercise.
2. Diet and nutrition need to be tailored to the individual patient with HCM, based on whether the patient needs to avoid dehydration or needs to avoid hypervolemia. Whereas patients with obstructive physiology as the primary feature require adequate salt and hydration, those with later-stage disease and congestion need a diet low in salt and fluid intake. Patients with both problems require more careful diet modification.
3. Obesity can exacerbate heart failure symptoms for any degree of cardiac dysfunction and can also potentiate other comorbidities including sleep apnea and atherosclerosis.
4. Exercise, safely prescribed, should be encouraged in most patients with HCM.

Introduction

Patients with HCM not uncommonly develop weight gain and obesity, which can over years contribute to or exacerbate cardiovascular symptoms related to their disease. Obesity results in reduced cardiac index for any degree of cardiac output. Obesity-related changes in respiratory effort drive dynamic swings in preload which may aggrevate obstructive physiology. Modifications of diet and nutrition can aid in effort tolerance and reduction in dynamic symptoms and help in avoiding septal reduction therapies, as NYHA class can oftentimes be improved with modest weight loss. In addition, obesity is a common cause of obstructive sleep apnea in patients with HCM, which can further drive symptoms. This chapter will discuss diet and nutrition in more detail, and efforts aimed at losing weight in this population.

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Nutrition and Diet

The optimal diet for patients with HCM is unknown. This is in distinction to chronic coronary artery disease where the low-fat low-cholesterol diet or perhaps more preferably a Mediterranean-type diet is recommended. As discussed in more detail below, HCM patients are at risk to become overweight, and while caloric restriction is important, the particular micronutrition content of the "ideal" diet to maintain a healthy weight is not clear. With coincidental metabolic comorbidities, such as hypertension and diabetes, patients may be best off following a data-driven, Guideline-recommended diet to treat their comorbid conditions, such as the DASH diet in the case of hypertension. The current iteration of the HCM Guidelines does, in fact, recommend defaulting at least the asymptomatic patients to be treated for their comorbid illnesses by the relevant other Guideline [1].

It should be remembered, however, that certain diets may be low in sodium, as frequently prescribed for patients at risk for volume retention or with hypertension, or may induce diuresis, e.g., a low carbohydrate, ketogenic diet, which may, in theory, lead to subsequent hemodynamic changes in patients with HCM. It would be advisable for patients and physicians to interface regularly when committing to diets which go beyond simple portion control. Low-salt diets may be necessary for patients with later disease and hypervolemia as a feature but would be inappropriate for patients with obstructive physiology.

Indeed, patients with HCM can present unique and sometimes vexing issues regarding fluid intake and management. Current HCM Guidelines do not specifically address fluid status in detail beyond to avoid dehydration and excessive

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alcohol to avoid worsening of LVOT gradients under these circumstances [2]. These considerations are especially germane to patients with obstruction but are less of an issue among patients who are nonobstructive. Some patients with hypotension are sometimes placed on high salt diets for the patient that cannot ingest enough salt. When plasma volume fails to increase despite salt supplementation, fludrocortisone (Florinef) should be considered. The clinically challenging position is managing fluid balance among patients with coincidental obstruction and elevated filling pressures.

Management of HCM patients who go on to develop left ventricular dysfunction parallels more traditional forms of dilated cardiomyopathy. In addition to medical management for reduced EF (i.e., beta-blockers, ACEi, ARNI, etc.), patients may also be advised to watch the food and salt intake. It should be recognized, however, that even in the context of overt heart failure with reduced ejection fraction, it is somewhat contentious whether the prescribing of salt restriction is advisable. Current AHA/ACC Heart Failure Guidelines give salt restriction a IIa recommendation with a level of evidence of C indicating it is probably reasonable to do, but there is no good evidence for this recommendation [3]. While observational studies demonstrate a relationship between salt and fluid intake and the risk of CHF hospitalizations, studies also have shown an adverse set of neurohormonal activations which may paradoxically lead to more avid fluid retention. Future large-scale randomized studies will be needed to inform on this very important, and frequently espoused, recommendation.

It has been well documented that patients with HCM may experience worsening of symptoms after a meal, a finding that has been estimated to occur in 30–40% of patients [4, 5]. The presence of these symptoms is associated with the presence of more severe baseline symptoms such as dyspnea, obstruction, and pre-syncope [4]. It is associated with lower perceptions of quality of life as measured by the Minnesota Living with Heart Failure Questionnaire.

Normally, eating results in shunting of blood to the digestive tract. This occurs due to splanchnic vasodilation, which itself results in drops in systemic afterload. This, in turn, results in a compensatory increase in heart rate. These changes occur within 30–60 min of a meal. Although this physiology may be well-tolerated and unnoticeable to most, for patients with HCM, these changes may lead to increase in LVOT gradients and myocardial oxygen demand. Kansal et al., in a series of six patients, documented significant increases in LVOT obstruction from 36 mmHg fasting to 106 mmHg after a meal [6]. Post-meal increases in heart rate are also greater among HCM patients with postprandial symptoms [7]. Although post-meal cardiac output increases among patients with HCM, this increase is explainable only via increases in heart rate, not stroke volume, which remains relatively fixed or reduced. In contrast to patients with congestive heart failure in whom splanchnic vasodilation drops afterload and improves ventricular filling pressures, patients with HCM demonstrate increases in right atrial and pulmonary capillary wedge pressures in response to food [8].

There are no firm recommendations to avoid postprandial symptoms as no intervention has been rigorously studied. Some patients will learn to adapt by avoiding certain foods which they recognize with precipitate symptoms, e.g., carbohydrate-rich meals. Maintaining adequate hydration and avoiding large meals in favor of several smaller ones have been espoused to lead to improvement of these troublesome symptoms [7]. These recommendations are embedded within the ESC Guidelines for management of the HCM patient.

Exercise to Manage or Prevent Obesity

There is, perhaps, no other topic in the management of these patients which is as contentious and confusing as the role and prescription of exercise in the management of HCM. Proper nutrition and exercise are key to a healthy lifestyle and managing weight, yet many patients with HCM have been told by their physicians to avoid exercise and sports for their whole lives. To some degree, the medical profession may be partially culpable for propagating an attitude of fear to exercise in patients with HCM; but to be fair, the anecdotes of young, otherwise healthy athletes dying on the fields and pitches juxtaposed with our inherent difficulty in identifying individuals at highest risk have led us, at least as a starting step, to err on the side of being fairly restrictive in terms of allowable activities and dosages of exercise. Currently a study "LIVE-HCM" is examining over 2000 HCM patients aged 8–60 to better understand the pros and cons of various levels of activity in HCM patients; data should be available in the next 4–5 years. It will take additional research and observation to gradually move the Guidelines forward to balance the health benefits of exercise with the potential for risks.

Current US Guidelines do not explicitly recommend exercise for patients with HCM, while the European Guidelines recommend patients maintain "a healthy lifestyle." Based on the recommendations from the Bethesda Conferences, both sets of Guidelines recommend against patients performing high-intensity, competitive sports; the US Guidelines go a step further and list out a set of allowable activities. However, this has still left much to interpretation, particularly for the nonathlete seeking guidance on exercise. To emphasize the scope of the question at hand, an observational study comparing exercise habits of respondents from the Hypertrophic Cardiomyopathy Association with NHANES suggested that more than 60% of respondents were engaged in moderate recreational activity and

nearly one quarter in vigorous activities, a finding similar, if not more, than the general population [9].

The Randomized Exploratory Study of Exercise Training in Hypertrophic Cardiomyopathy (RESET-HCM) randomized 136 participants with HCM to individualized moderate-intensity aerobic exercise training versus usual care and followed them through 16 weeks [10]. Exercise training was associated with a modest increase in peak VO2, and, importantly, no short-term signal of arrhythmia promotion or adverse cardiac event was noted. The magnitude of VO2 increase with exercise training was greater than that seen in HF-ACTION in patients with systolic dysfunction [11] and nearly identical to the increases seen with exercise training in HFpEF [12].

Although RESET-HCM provided some reassurance into the short-term safety of moderate exercise, the long-term safety is still an outstanding question. The ongoing LIVE-HCM study, sponsored by the NIH, will help to address the longitudinal safety and outcomes of patients with HCM recruited across ages and activity levels.

Patients may benefit both physically and psychologically from cardiac rehab programs or similar medically monitored lifestyle programs. These programs can help patients identify what is normal and safe versus what is dangerous and creates an exacerbation of symptoms. While no clinical studies have been reported, there have been a large number of patients from the Hypertrophic Cardiomyopathy Association that have employed this strategy with positive results.

Managing Obesity

Proper nutrition and adequate exercise are important for maintaining a healthy body weight. Obesity is an upstream risk factor for hypertension and diabetes, and all of these factors are directly linked to subsequent development of left ventricular hypertrophy in the general population. This fact is especially important as it pertains to the patient with hypertrophic cardiomyopathy, who is already at risk for significant hypertrophy. In addition, as obesity potentiates metabolic syndrome and the development of cardiovascular atherosclerosis, managing obesity can help prevent the development of this serious comorbidity as the HCM patient ages into later adulthood.

Olivotto et al. reported on the association between obesity and increasing left ventricular mass [13]. Among 275 patients with hypertrophic cardiomyopathy, being overweight was associated with a 65% greater likelihood of having a LV mass index in the highest quartile (>120 g/m^2). Being obese (BMI > 30) was associated with greater than threefold increase odds of having a LV mass index in the highest quartile. The proportion of obese (55%) and overweight (48%) patients with late gadolinium enhancement on MRI was higher than those of normal weight (28%). Furthermore, the prevalence of severe heart failure symptoms (NYHA class III/IV) was twofold higher among obese patients compared with nonobese patients.

These data parallel what is known more generally from the systolic and diastolic heart failure field. In these populations obesity is a well-recognized contributor to the development of heart failure, independent of traditional risk factors, such as coronary atherosclerosis and hypertension [14]. Despite its effect on incident heart failure, obesity itself is paradoxically associated with better survival rates among patients with existing heart failure [15]. Whether this "obesity paradox" holds true in HCM is currently unknown.

The prevalence of overweight and obesity in the community has increased dramatically over the past several decades. Studies looking at the prevalence of obesity specifically in HCM populations have not been performed, but obesity is likely to be at least as high as in the general community. Not only does obesity seem to play a direct role in promoting hypertrophy, it also leads itself to decreased exercise capacity and dyspnea. This may in turn increase the need for invasive septal reduction therapies, as they are typically driven by refractory symptoms. It can be, therefore, challenging for physicians to unravel what symptoms are HCM related, and hence potentially addressable by medical or procedural intervention, and what will require slow and dedicated nutritional and exercise programs to improve. It is important to note that gastric sleeve surgery has been performed safely in a number of HCM patients with only moderate complications related to hydration in the postoperative 1–2-week period. Therefore, patients undergoing this procedure should do so in collaboration with their HCM care team to avoid serious complications. Objective measures with cardiopulmonary exercise testing may be required in these cases to lend some additional insights into etiology of a particular patient's limitations. Nevertheless, obese patients derive significant benefits in symptoms from modest weight loss, and the motivated and compliant patient may avail him or herself of a 3–6-month trial of weight loss prior to consideration of septal reduction therapy or other interventions.

Other Lifestyle Interventions

Yoga has been testing in a variety of cardiovascular outcomes. It has been shown to generally increase vagal stimulation and decrease sympathetic activation [16]. The impact of yoga training has been examined in a few small randomized studies of patients with congestive heart failure. Among patients with CHF, a yoga intervention was shown to improve treadmill time, peak VO2, and inflammatory biomarkers [17]. This translated into improved perception of quality of life [17, 18]. Yoga has been shown to decrease shock-related anxiety and ICD firings among patients with ICDs [19]. Although not

studied to date in HCM specifically, given its safety and potential benefits, yoga would seem a reasonable recommended lifestyle intervention for motivated HCM patients.

Tai chi has been studied over a number of small series among patients with systolic heart failure. In meta-analysis, participation in Tai chi significantly improved quality-of-life measures, but did not improve objective measures of disease or functional capacity [20]. It seems reasonable to offer Tai chi as an alternative to aerobic training exercises for motivated patients with HCM.

The HCM Center in Toronto has worked with a personal trainer to create an online training program under the direction of skilled HCM specialist, Dr. Harry Rakowski, also an author in this textbook. This program has mild, moderate, and expert levels for patients to evaluate and choose the one most suitable for their status. A link to this program can be found on the Hypertrophic Cardiomyopathy Association website, 4hcm.org.

Psychosocial interventions, such as mindfulness education, have been shown to improve perceived measures of quality of life and disease severity among patients with congestive heart failure [21–23].

Conclusions

Patients living with HCM have questions about diet, nutrition, and weight loss and other lifestyle changes which will help them live longer and live better and potentially avoid invasive testing or treatments. Future research should focus on the needs of these patients and practical and tailored approaches to optimal weight management. Leveraging networks of HCM patients, such as through the HCMA and other social media avenues, may identify important questions and solutions that can be broadened to the wider HCM population.

Clinical Pearls

1. Patients with central obesity oftentimes have more obstructive symptoms, as the changes in intrathoracic pressure required with daily activities can result in marked changes in preload. Modest weight loss is especially recommended in such patients.
2. Maintenance of ideal body weight can help avoid hypertension, diabetes, and other comorbidities and should be sought in all patients.
3. Since no specific diet is tested in HCM, low calories to effect modest weight loss is the best first step in the obese HCM patient, rather than micromanaging content.
4. Patients with postprandial exacerbation of symptoms should be advised to keep portions smaller and to avoid significant exertion after meals.

Questions

1. A patient with HCM comes to your office for consultation. She has NYHA class II symptoms of dyspnea and CCS class II symptoms of angina. She also mentions to you that for the past several years, she has noticed chest pain after eating meals, particularly larger ones. Her exam is notable for an S4 and a 3/6 LVOT murmur which accentuates with Valsalva. The most likely cause of her postprandial symptoms is:
   A. Coronary insufficiency from high-grade proximal vessel CAD
   B. Hiatal hernia
   C. Microvascular dysfunction
   D. **Worsening LVOT obstruction and tachycardia with eating**
   E. Esophageal spasm

While any of these can cause chest pain, the description is classic for postprandial angina in a patient with HCM. Splanchnic vasodilation results in a drop in systemic vascular resistance which, in turn, leads to worsening dynamic LVOT gradient and a compensatory tachycardia (**D**). This is thought to lead to increased oxygen demand and resultant ischemia.

2. A patient with HCM comes to your office for consultation. He is asymptomatic and, while he has no resting gradient, he has a 70mmHg gradient with exercise. He is not currently interested in medical therapies but is wondering about dietary advice. In addition to recommending avoidance of dehydration, you should tell him:
   A. To follow a low-fat/low-cholesterol diet
   B. To follow a salt-restricted diet
   C. To follow a low-carbohydrate ketogenic diet
   D. **That there is currently no macronutrient dietary recommendation for patients with HCM**

There are currently no dietary recommendations for patients with HCM to follow (**D**). The most important thing appears to be to maintain a healthy weight. Specific macronutrient recommendations may be made if the patient develops additional comorbidities, such as diabetes or hyperlipidemia. Salt-restricted and low-carbohydrate diets may result in lower circulating blood volume and should be used under the observation of the physician.

3. A 45-year-old patient with HCM presents to your clinic for follow-up. He is currently moderately symptomatic on beta blocker therapy. His BMI is 36kg/m2. Which of the following is *not* true relating to the association between this patient's BMI and HCM?

A. Elevated BMI is associated with greater LV mass index among patients with HCM.
B. HCM patients with elevated BMI are more likely to have severely symptomatic disease compared with those with normal BMI.
C. **Obese patients with HCM have a higher mortality rate than normal weight patients.**
D. Obesity is associated with higher prevalence of late gadolinium enhancement by MRI.

Obesity is associated with greater LV mass, higher severity of HF symptoms, and the presence of scar by MRI. Despite this, it has not been associated with higher risk of death (**C**). It is not at this time known whether obesity is "protective" against death – as the obesity paradox has been shown for coronary artery disease and HFrEF.

4. A 37-year-old patient with nonobstructive HCM comes to your office inquiring about starting an exercise regimen. Which of the following should you tell her?
A. She should avoid any time of exercise until data come out for safety.
B. **Moderate levels of activity appear to be safe, at least over the short term.**
C. Singles tennis would be preferable to bicycling according to the US guidelines.
D. The presence of an ICD would allow her to participate freely in any intensity of exercise.

At least low-intensity exercise can be recommended based on current guidelines. RESET-HCM demonstrated that moderate-intensity activity was safe over the short term and was associated with modest increases in VO2 (**B**). The US guidelines assign a point score to various aerobic activities. Singles tennis (score 0) is regarded in that schema as higher risk than bicycling (score 4). The presence of an ICD does not obviate limitations on activity based on current guideline recommendations.

5. Although not specifically studied in HCM, in small studies alternative lifestyle interventions such as yoga, tai chi, and meditation have been shown in heart failure patients to:
A. Reduce the frequency of ICD firings.
B. Improve perceived quality of life.
C. Improve maximal oxygen uptake.
D. **All of the above.**

Although the data are limited to small, short-term trials, these therapeutic lifestyle interventions appear to be associated with both objective and subjective improvements in disease status among patients with HFrEF (**D**). It seems reasonable, therefore, to offer them to patients with HCM.

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Family Screening: Who, When, and How

14

Michelle Michels

Key Points

- Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease.
- HCM has an age-related variable penetrance; cardiac analysis has to be repeated over time.
- Only truly pathogenic mutations can be used for predictive testing in family members.
- The clinical screenings algorithm consists of an ECG and TTE at regular intervals.
- Cardiac events are virtually absent in G+/LVH− subjects with normal ECG.

Introduction

For over 50 years, hypertrophic cardiomyopathy (HCM) has been recognized as an autosomal dominant familial cardiac disease, with a risk for sudden cardiac death (SCD) and progression to advanced heart failure or end-stage disease [1, 2]. With HCM being a familial disease, family screening is important to identify relatives at risk. Guidelines have encouraged family screening by electrocardiogram (ECG) and transthoracic echocardiogram (TTE) since 2003. According to the most recent European clinical guideline on HCM, genetic testing of relatives should precede clinical evaluation in families with a definitive mutation (class I, level of evidence B). In families without a definitive mutation, cardiac evaluation of first-degree relatives should be performed [3].

In this chapter we will focus on the importance of family screening and the genetic – and clinical – aspects of family screening and provide practical tips for the organization of family screening in HCM.

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The Importance of Family Screening

The most devastating presentation of HCM is SCD in a previously asymptomatic and presumed healthy person. HCM is accountable for a significant portion of SCD cases, especially in young persons [4]. Since HCM is an autosomal dominant disease, there is a 50% risk of transmission to first-degree family members. Once the diagnosis of HCM is made, SCD risk can be modified by lifestyle adjustments (especially cessation of intensive physical activity) and by prescription of high doses of beta-blockers in children [5–7]. At adult age, medication does not protect against SCD, but the implantation of an implantable cardioverter-defibrillator can protect against SCD in high-risk patients [8].

The goals of family screening are therefore to identify relatives with unrecognized HCM and to follow at-risk individuals for risk factors of SCD and disease development. Family screening also helps build awareness of the various phenotypes within a given family and the likelihood that multiple family members may be affected despite the lack of overt symptoms.

General Aspects of Family Screening

Proband

Family screening in HCM always starts with the confirmation of the clinical diagnosis of HCM (phenotype) in the proband (the first person of a family presenting with HCM); other causes of left ventricular hypertrophy (LVH), like aortic valve stenosis, hypertension, or storage diseases, should be excluded. After confirmation of the diagnosis, the HCM patient should be informed about the familial character of the disease, the high potential for familial transmission, and the possibility to perform genetic testing. During genetic counseling attention should be given to the risks and possible benefits of genetic testing [2, 3, 9].

In specialized cardio-genetic outpatient clinics, this familial and genetic counseling is performed in close collaboration

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between the cardiologist and the clinical geneticist. The flowchart used at the cardio-genetic outpatient clinic of the Erasmus MC, Rotterdam, the Netherlands, is provided in Fig. 14.1.

The Role of the Clinical Genetics/Genetic Counselor

The cardiac genetic counselor gives information about inheritance risk; provides pre- and posttest counseling; investigates and confirms family history by retrieving medical information of family members with possible HCM (i.e., family members with SCD or heart failure) from general practitioners, cardiologists, and/or pathologists; and discusses worries and fears about the HCM diagnosis for individual patients and their family. During genetic counseling, family members at risk are identified, and first-degree relatives, those sharing 50% of genetic material with the proband, are selected for further analysis. The legal framework for informing relatives varies around the world; in

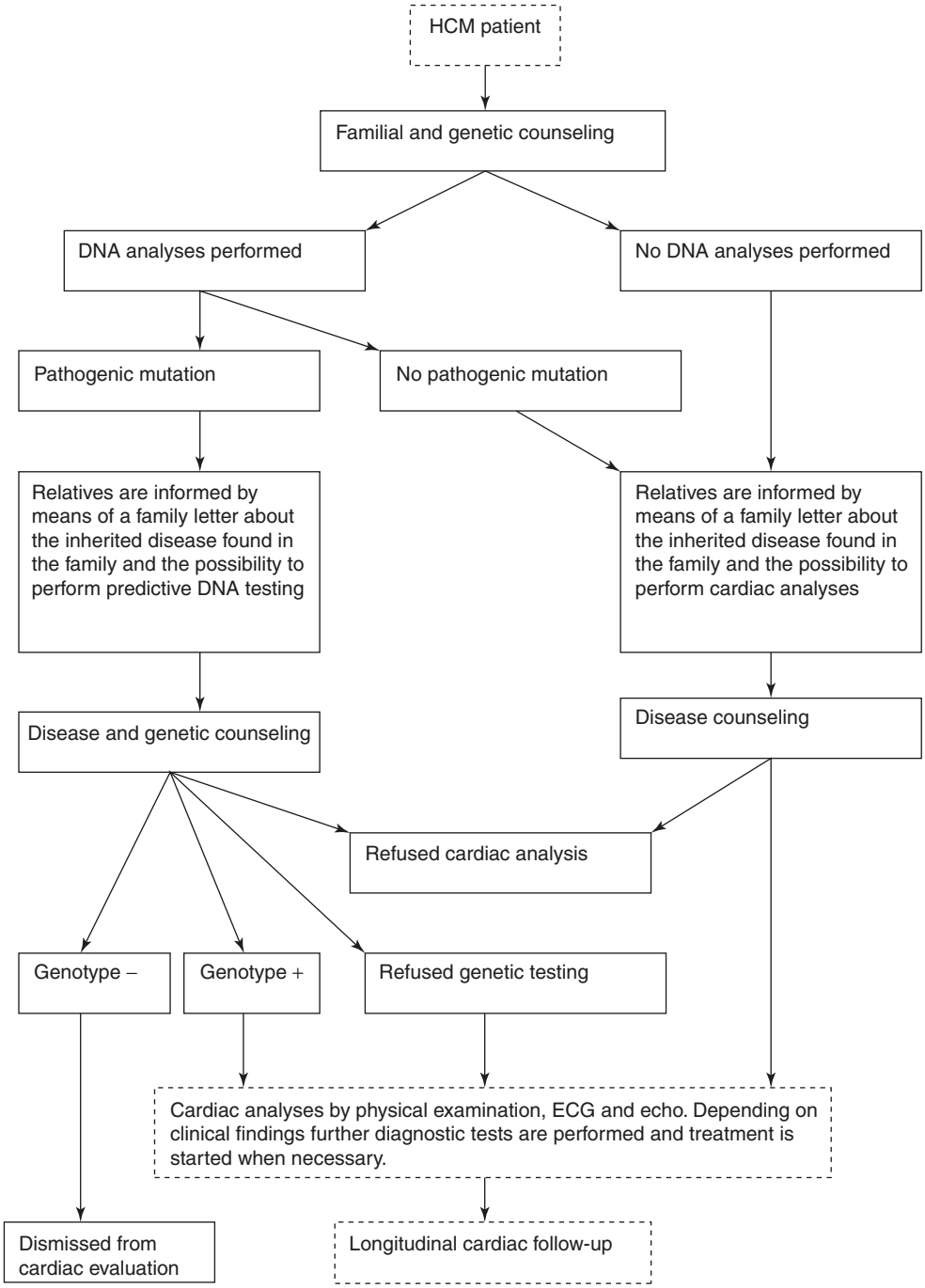

Fig. 14.1 Flowchart used at cardio-genetic outpatient clinic at the Erasmus MC, Rotterdam, the Netherlands. Dashed boxes are taking care of by the cardiologist; solid line boxes are taking care of by the clinical geneticist or genetic counselor. (HCM hypertrophic cardiomyopathy, ECG electrocardiogram, and echo echocardiogram)

most cases first-degree family members are provided with information on HCM through a family letter provided to them via the proband or via direct communication. In the United Kingdom and the Netherlands, direct medical contact, with consent of the proband, has been used for screening of familial hypercholesterolemia. Although family members accept this approach, another study shows that family members prefer indirect cascade screening [10, 11]. Genetic counselors assist in determining the best method of contacting family members, who also may be at some distance or reluctant to learn more.

Genetic Testing of the Proband

After counseling and consent, blood is drawn for DNA analysis. For the proband the potential medical, physiological, financial, and familial implications of genetic testing are minimal, as all these consequences are determined by the phenotype, which is already documented. Since the costs of genetic testing are not covered by general health insurance in all countries, reimbursement of costs may be a problem and may lead to a limited access to genetic testing.

Currently, not all genes causing HCM have been identified, and the likelihood of obtaining a positive genetic test in a proband is about 50–60%. The chance of finding a pathogenic mutation increases in HCM patients with a reverse septal curve morphology, a family history of HCM or SCD, age of HCM diagnosis <45 years, and maximal wall thickness ≥ 20 mm [12]. The relatively low percentage of HCM families in which a mutation is found and the fact that only truly pathogenic mutations can be used for predictive testing in family members exclude a reasonable portion of the HCM families to be screened with genetic testing [9, 13]. Data from population-based exome data are questioning the pathogenicity of previously HCM-associated genetic variants. This reclassification of mutations in HCM patients might lead to misdiagnosis of family members, and this could have potentially devastating clinical consequences. It is therefore crucial that variants being reported as causative of HCM are truly disease causing. The complexity of interpreting genetic test results further warrants close collaboration with clinical geneticists [14].

Predictive Genetic Testing in Family Members at Risk for HCM

Currently, the power of HCM mutational analysis lies most prominently in identifying G+ family members who are at risk for developing disease and excluding unaffected, genotype-negative (G-) relatives of further cardiac evaluation; this is information not achievable otherwise. In Fig. 14.2 a 20-year follow-up of an HCM family is described, in which the advantages of genetic testing are made clear. Predictive genetic testing provides a cost-effective and definitive means of family screening as longitudinal evaluation can be focused on G+ family members because only they are at risk for disease development [15]. The ACCF/AHA guidelines state that genetic testing, preceded by genetic counseling, is reasonable (class IIa) to facilitate the identification of at-risk family members [2]. The latest ESC guidelines on HCM advise to start with genetic testing after pretest counseling in first-degree relatives before cardiac evaluation (class Ib) [3]. Predictive genetic testing can only be offered in HCM families in which a truly pathogenic mutation is identified. In other families, family screening should be offered by cardiac testing of first-degree relatives. It is essential that family members be counseled about the potential medical, physiological (including psychological), financial, and familial implications of genetic and cardiac test results to enable informed decision-making about potential risks and benefits before blood is drawn. If a pathogenic mutation is identified in a family member, this may lead to consequences for employment and insurances, especially life and disability insurances. As much of this testing is performed on a young, asymptomatic population, these concerns are indeed real and must be discussed at length prior to proceeding [2, 3, 14].

The legal implications of genetic testing are dependent on the country of residence; in the United States, the Genetic Information Nondiscrimination Act (GINA), a federal law, prohibits denying or terminating of health insurance, employment, or promotion solely on the presence of a mutation or a family history of genetic disease. However, GINA does not protect against discrimination for disability, life, or long-term care insurance or when there is a documented medical condition [16]. In the Netherlands, the Dutch Medical Examination Act protects unaffected HCM mutation carriers for life insurance below 260,000 euro; above this amount, carriers will have to disclose their HCM risk status, potentially resulting in an increased life insurance premium [17].

G+ family members should subsequently undergo cardiac testing to determine if the HCM phenotype (presence of LVH) is present. Identifying a G+ family member will also lead to extension of the family screening, as the first-degree relatives of the newly diagnosed genotype-positive (G+) subject will be offered genetic testing (so-called cascade screening). This has far-reaching implications to the family as a whole and may allow screening to cross borders including distant countries.

Predictive Genetic Testing in Children

Whether or not to offer predictive genetic testing to children is subject to debate; there may be a good reason to defer testing, including to enhance the opportunity of the child to participate

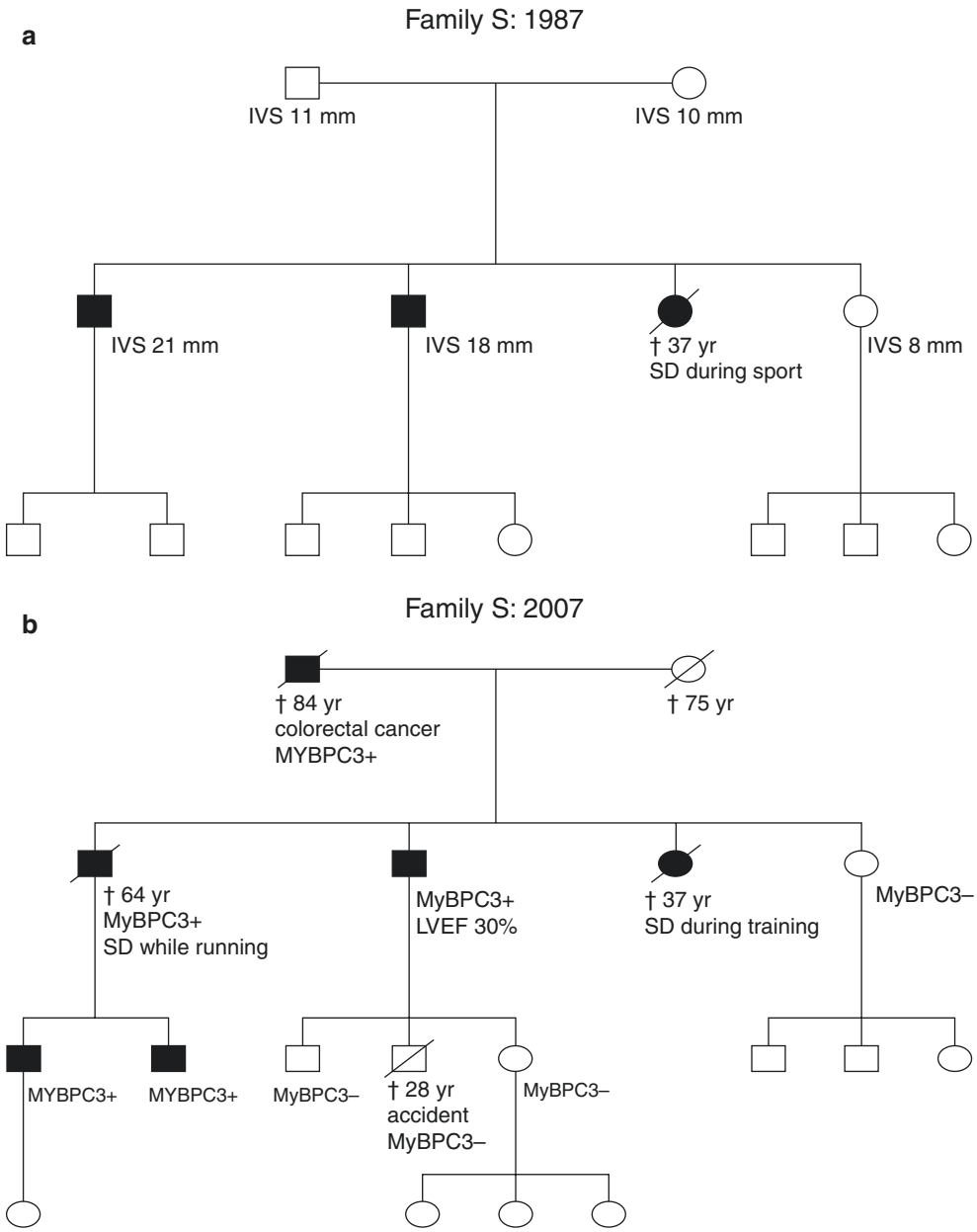

Fig. 14.2 Pedigree of a hypertrophic cardiomyopathy (HCM) family followed at the cardio-genetic outpatient clinic of the Erasmus MC, Rotterdam, the Netherlands. (**a**)**:** Pedigree at presentation in 1987. The proband presented after resuscitation for ventricular fibrillation; she died of severe neurological damage. Her first-degree relatives underwent cardiac evaluation by electrocardiogram and echocardiogram. Her two elderly brothers had HCM; her parents and younger sister had no signs of HCM. (**b**)**:** Pedigree drawn in 2007. Genetic testing revealed a pathogenic mutation in myosin-binding protein C, after which predictive genetic testing was offered to family members. The father was G+/LVH− and died of colorectal cancer. The eldest brother experienced SCD during running; both his sons are G+/LVH−. The other brother developed end-stage HCM; his three children are genotype negative and dismissed from follow-up. The youngest sister is also reassured, since she is genotype negative

in the discussion. However, it is likely that young children are not fully able to comprehend the implications of genetic testing. With the current lack of prognostic value of a pathogenic mutation on disease development and risk, and the possible negative consequences of predictive testing, we are reticent to perform predictive genetic testing routinely in children. An argument in favor of genetic testing of children lies in the fact that knowing that the young child is at risk can be beneficial for advocating and encouraging alternative pastimes [18]. This however can also lead to unnecessary stigmatization and unfounded withdrawal from competitive sports, since cardiovascular events in G+/LVH− subjects are virtually absent. A recent study focusing on follow-up of G+/LVH− children found a very low conversion rate to G+/ LVH+ of 6% in a follow-up period of 12 years; children were in their 20s when HCM was diagnosed, and there were no cardiovascular events in G+/LVH− children [19]. Currently, our HCM program makes decisions on a case-by-case basis after extensive counseling of the family and the child, including psychological support and taking all the above considerations into account. As for cardiac evaluation, genetic testing is normally first offered once the child reaches the age of 10 years or shows signs of puberty [3].

Family Planning in HCM Families

Special attention should be paid to HCM patients and G+/LVH− family members with questions about family planning

regarding the risk of transmission of the disease to their offspring. These aspects should be part of the genetic counseling in subjects in the reproductive age, both male and female. When the underlying mutation is known, prenatal screening or preimplantation genetic testing is theoretically possible. These are not routinely performed due to the variable disease expression, the fact that disease manifestation usually occurs later in life, the fact that there are treatment options available, and the fact that longevity is maintained in these patients when viewed as a group [3, 20].

In both children and adults who have been counseled before they underwent genetic or cardiac testing in screening for HCM, no psychological harm or negative effect on quality of life has been observed [21–23]. Long-term impact on quality of life however requires further research.

Cardiac Evaluation in Family Screening for HCM

Cardiac evaluation should be offered to family members of HCM families in which no pathogenic mutation is found, G+ family members identified during predictive genetic testing, and family members refusing predictive genetic testing. In addition, in cases where the proband has died, and no gene testing was performed, cardiac evaluation is oftentimes the only remaining screening modality prior to the identification of a new proband within the family. It is important that counseling is provided to family members before they undergo cardiac evaluation, since the possible consequences as described before for genetic testing remain for clinical testing.

Because the expression of HCM is highly age dependent, overt cardiac hypertrophy often does not emerge until late adolescence or beyond; guidelines therefore recommend longitudinal screening with variable intervals according to age (Table 14.1). G+/LVH− subjects and family members with unknown genetic status should be evaluated clinically and by ECG and TTE at period intervals of 12–18 months in asymptomatic children and adolescents and about every 5 years in asymptomatic adults (Table 14.1). In case of pre-phenotypic features on TTE and/or ECG, the current ESC guidelines advise to have a repeated cardiac evaluation at 6 to 12 months. In case of new cardiac symptoms, family members should be re-evaluated promptly [3].

The AHA/ACC guidelines advise to start with cardiac evaluation at the age of 12 years (although some advocate for beginning when signs of puberty are noted), while the more recent ESC guideline advises screening from 10 years of age. Screening at even younger ages can be considered in families with a malignant family history, if the child is a competitive athlete, or when there are other signs or symptoms of early HCM [2, 3].

Table 14.1 Proposed clinical screening strategies in family members of HCM patients

Age	History, clinical examination, ECG, and echo
<10 years	Optional unless
	Malignant family history
	Competitive athlete
	Symptoms or signs of possible HCM
10 to 18–21 years	Every 1–2 years
> 18–21 years	At least every 5 years

Based on current guidelines by Gersh et al. [2] and Elliott et. al [3] (*ECG* electrocardiogram, *echo* echocardiogram, and *LVH* left ventricular hypertrophy)

Electrocardiogram

The ECG is abnormal in the vast majority (75–95%) of HCM patients [24, 25]. Abnormalities mainly consist of Q waves, repolarization abnormalities, and isolated voltage criteria for LVH or left atrial enlargement and can be present before there is hypertrophy on TTE [25]. The severity of ECG abnormalities is directly related to both the degree of hypertrophy and the prevalence of fibrosis expressed as late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) [24]. The ECG is therefore recommended as a screening tool to raise the suspicion of HCM in family members of HCM patients [2, 3].

In a recent study, the presence of Q waves and/or repolarization abnormalities was highly specific (98%) for the presence of a sarcomeric mutation in family members without LVH; unfortunately ECG abnormalities had a low sensitivity (25%), and therefore a normal ECG is non-informative and does not reliably indicate the absence of a sarcomeric mutation [26, 27]. A normal ECG however excludes severe phenotypic expression of HCM [24]. In G+ individuals without LVH at first evaluation, ECG abnormalities are predictors of developing LVH during follow-up [28].

Transthoracic Echocardiogram

The diagnosis of HCM is conventionally made by cardiac imaging, with at present a TTE most often used. A combination of ECG and TTE is recommended as a clinical screening algorithm in family members of HCM patients [2, 3].

The diagnosis of HCM is typically made when the maximal wall thickness is ≥15 mm; in affected family members with HCM, the degree of hypertrophy may be below this diagnostic threshold, and different criteria combining ECG and echo data have been proposed to diagnose HCM in 50% risk carriers [29]. In the latest ESC guideline, the threshold to diagnose HCM is lowered to ≥13 mm in first-degree relatives [3]. Although HCM is predominantly characterized by the presence of hypertrophy, other features, like mitral valve

or papillary muscle abnormalities or diastolic dysfunction, have been described. Presence of these features in 50% risk carriers should raise the suspicion of an early manifestation of HCM [30–32].

Especially in patients with suboptimal echo windows, TTE can fail to identify focal areas of myocardial hypertrophy, mainly at the inferoseptum, apex, or free wall of the left – or right – ventricle. In these patients other imaging techniques like CMR should be performed [33]. CMR may also show patchy LGE consistent with HCM.

In animal models of HCM, it has been shown that diastolic dysfunction can precede the development of HCM [34]. Tissue Doppler imaging studies in humans revealed differences in different mitral annular velocities; decreased Sm and Em velocities have been described, and one study found increased Am velocities [30–32]. Because of the discrepancies seen in the tissue Doppler imaging and speckle-tracking echocardiography in G+/LVH− subjects, the identification of G+/LVH− family members with echocardiography remains challenging. However, as alluded to above, the presence of diastolic dysfunction in the absence of overt LVH that meets anatomic criteria for HCM may be a sign of preclinical disease.

Cardiac Magnetic Resonance

Although the current clinical guidelines do not mention CMR in the screening algorithm for family members of HCM patients, it can be a useful adjunct in HCM family screening in selected patients. With CMR, the wall thickness of any segment of the ventricle can be accurately assessed, and the use of gadolinium contrast allows tissue characterization, including scar location, distribution, and burden. In a paper by Valente et al., the diagnostic agreement between TTE and CMR was 90%; however CMR detected mild hypertrophy in 10% of patients, which was missed by TTE [33].

CMR studies in G+/LVH− subjects revealed the presence of myocardial crypts, mitral valve abnormalities, and diastolic abnormalities [35, 36]. Myocardial crypts occur particularly in the septum and inferior (posterior) right ventricular insertion point [37]. These crypts are present in a subset of the G+/LVH− subjects, and their presence may be a pre-phenotypic marker of HCM; however their prognostic value needs to be determined [38].

The presence of LGE is extremely rare in G+/LVH− subjects. However, G+/LVH− subjects with LGE on CMR have been described; unfortunately no data on ECG were given in these patients [39]. The presence of an abnormal ECG may raise the suspicion of missed areas of focal hypertrophy or the presence of LGE. The latter is especially important, since sporadic cases of SCD have been described in G+/LVH− patients [40]. In the described patients, the ECG was abnormal, suggesting myocardial abnormalities. LGE is associated with an increased risk of heart failure, and recently special attention has been given to the extent of LGE as a possible risk factor for SCD and end-stage disease (systolic dysfunction) [41, 42].

Accordingly, CMR may especially be useful if TTE images are suboptimal or suggest borderline LVH and if there are unexplained ECG abnormalities or in the case of high-risk situations, i.e., high familial prevalence of SCD or G+/LVH− subjects engaging in competitive sports. Subtle findings on CMR may indicate a likely diagnosis of HCM and prompt more frequent monitoring and lifestyle modification or even solidify a diagnosis through the confluence of evidence, with resultant clinical implications.

Genotype-Positive/Phenotype-Negative Subjects

The penetration of genetic testing in clinical practice has revealed a new subset within the HCM spectrum, the G+/LVH− family members. Although this subset is very important for improving our understanding of how mutations cause disease, the identification of these individuals also leads to clinical decision-making dilemmas. The reported risk of adverse cardiac events in G+/LVH− is very low, and in the largest study thus far, no SCD occurred in mutation carriers without hypertrophy [43].

The precise proportion of the G+/LVH− subjects that will develop overt disease, and when, is still uncertain; this is due to the relatively short period of time that genetic testing has been available in clinical practice, with consequent limited follow-up duration. Disease progression is increasing with age but seems to be slow, both in children and adults [19, 44]. In a recent study, subtle HCM, without cardiac events, developed in 11% of G+/LVH− family members over a period of 6 years [28]. The family described in Fig. 14.2 shows that HCM can be absent until very advanced age.

The current guidelines recommend the intervals for cardiac evaluation as described in Table 14.1 [2, 3]. In G+/LVH− subjects with a family history indicating a high SCD risk, periodic assessment of arrhythmias, by exercise testing and/or Holter monitoring, may be appropriate. Until accurate penetrance data are available, it is prudent to extend standard HCM surveillance with cardiac imaging at least through midlife but perhaps even for the entirety of life.

Diastolic dysfunction, increased collagen synthesis, impaired energetics, expanded myocardial extracellular volume, myocardial crypts, and mitral valve abnormalities have been described in G+/LVH− subjects. These features are very interesting for further unraveling pathophysiology; however their clinical relevance is still unclear [30–33, 35–37, 45].

Whether or not G+/LVH− subjects should be excluded from sports has been subject to debate. At present, the reported

SCD rate in G+/LVH− subjects is extremely low, and therefore both the AHA/ACCF and ESC recommendations do not advise to routinely exclude G+/LVH− subjects from competitive sports [3, 46]. Instead, the G+/ LVH− subjects should be advised on an individual basis taking into account the type of sporting activity, the local legal framework, and the underlying mutation and the results of cardiac evaluation. Based on these recommendations, our HCM program usually allows G+/LVH− subjects to enroll in competitive sport activities but keeps them under close clinical surveillance with cardiac evaluations, including exercise testing and Holter monitoring every year and CMR at first evaluation and when changes in other examinations or symptoms occur.

Future Perspectives

The introduction of next-generation genetic testing with the possibility to test a large number of genes at the same time and the possibility of whole-exome sequencing will also most likely lead to an increased number of pathogenic mutations identified. This will enable predictive testing in a larger portion of the families. It will however also lead to even more complex genetic information to interpret.

Current guidelines suggest a "one-size-fits-all" approach to longitudinal cardiac follow-up for all unaffected family members, both G+ and those with unknown genetic status, regardless of family history. Further studies should aim at developing a more "tailor-made" approach, with intervals possibly based on the presence of pre-phenotypic markers of HCM, confirmed genetic status, and family history. The diagnostic algorithm, now consisting of ECG and TTE in all family members, most likely can also be adjusted to specific situations. Questions of whether or not it is safe to screen family members with ECG alone, as well as if and when to perform CMR, exercise testing, and Holter monitoring, should be answered, i.e., the study by Jensen et al. does not support the current guidelines regarding the short interval of performing serial cardiac evaluation in children [19].

Longitudinal follow-up studies of G+/LVH− subjects are necessary to get robust data on disease penetration, the prognostic value of pre-phenotypic signs, and the risks in these subjects. By studying this subset, we will hopefully be able to unravel the pathophysiology of disease development to the level that drugs to prevent disease development can be developed.

Conclusions

Family screening in HCM is important since HCM is an autosomal dominant disease and SCD can be the first presentation. In both children and adults who have been counseled before they underwent genetic or cardiac testing in screening for HCM, no psychological harm or negative effect on quality of life has been observed [21, 22]. It is important to realize that only truly pathogenic mutations can be used for predictive testing. Challenges of interpretation of genetic results are real and require careful review and are best done in the setting of a multidisciplinary approach to care. When gene testing is not available, or refused, serial cardiac evaluations of family members is the next best approach and likely should continue lifelong for all family members. G+/LVH− subjects are very interesting for research to unravel the pathophysiology of disease development, but the prognostic relevance of so-called signs of pre-phenotypic HCM remains unclear.

Clinical Pearls

- Disease development in G+/LVH− subjects is slow and may reflect the phenotypic variability of this disease even within a given family.
- G+/LVH− subjects should not routinely be denied to enroll in competitive sports, but a CMR to fully exclude the phenotype may be reasonable.
- Ramifications of gene testing, especially with regard to health and life insurance, must be explained to the patient prior to drawing blood for analysis.
- Clinical presentation and treatment in HCM are based on the phenotype, not on the genotype.
- Enabling affected family members to reach the remainder of their family, for example, by use of standardized letters describing the disease, inheritance pattern, and benefits of screening, is oftentimes helpful in raising awareness of HCM and identifying at-risk individuals.

Questions

1. At what age should family screening in hypertrophic cardiomyopathy in first-degree relatives be started?
   A. After birth
   B. At the age of 18 years
   C. At the age of 30 years
   D. At the age of 10 years
   E. At the age of 4 years

The correct answer is D:

Current European guidelines advise to start with family screening at the age of 10, earlier screening is only advised in special circumstances (malignant family history, if the child is a competitive athlete or when there are other signs or symptoms of early HCM).

2. Hypertrophic cardiomyopathy is an inheritable cardiac disease. What is the change of transmission of the disease to offspring?
   A. 10%
   B. 50%
   C. 25%
   D. 5%

The correct answer is B:
Hypertrophic cardiomyopathy is inherited in an autosomal dominant manner, this implicates that every child of a HCM patient has a 50% chance of inheriting the disease.

3. Is repeated cardiac evaluation advised in relatives at risk for HCM?
   A. Yes, cardiac evaluation is recommended with regular intervals until the age of 24 years.
   B. No, one cardiac evaluation is sufficient in adult relatives at risk if there are no abnormalities found.
   C. Yes, "lifelong" cardiac evaluation is recommended in at-risk relatives with regular intervals.
   D. Yes, cardiac evaluation is recommended with regular intervals between the age of 10 and 40 years old.

The correct answer is C:
HCM is characterized by age-related penetrance; this means that cardiac evaluation should be repeated with regular intervals until advanced age.

4. Which examinations are advised in the cardiac evaluation of all at-risk relatives?
   A. Transthoracic echocardiogram and electrocardiogram
   B. Transthoracic echocardiogram, electrocardiogram, and Holter monitoring
   C. Transthoracic echocardiogram and cardiac magnetic resonance imaging
   D. Cardiac magnetic resonance imaging, electrocardiogram, and Holter monitoring

The correct answer is A:
Cardiac evaluation of at-risk relatives starts with an electrocardiogram and echocardiogram; if (subtle) abnormalities are detected, further cardiac evaluation including cardiac magnetic resonance imaging, Holter monitoring, and exercise testing should be done.

5. What should you advise in a genotype-positive/phenotype-negative subject who wants to participate in competitive sport?
   A. Genotype-positive/phenotype-negative subjects should be excluded from all competitive sports.
   B. Genotype-positive/phenotype-negative subjects can only perform low-intensity sporting activities.
   C. Genotype-positive/phenotype-negative subjects can enroll in competitive sports after extensive negative cardiac investigation.

The correct answer is C:
At present, the reported SCD rate in G+/LVH− subjects is extremely low, and therefore both the AHA/ACC and ESC recommendations don't advise to routinely exclude G+/LVH− subjects from competitive sports. If the results of extensive cardiac investigations, including cardiac magnetic resonance imaging, Holter monitoring, and exercise testing are normal, subjects can enroll in competitive sports with regular, i.e., yearly, evaluation.

6. What are the advantages of presymptomatic genetic testing in first-degree relatives of a HCM patient with a definitive mutation?
   A. The advantages of presymptomatic genetic testing are identifying genotype-positive family members at risk of HCM and reassuring genotype-negative relatives.
   B. The advantages of presymptomatic genetic testing are identifying genotype-positive family members and prediction of the disease development and prognosis of HCM.
   C. There are no advantages of presymptomatic genetic testing.

The correct answer is A:
Currently, the power of HCM mutational analysis lies most prominently in identifying G+ family members who are at risk for developing disease and excluding unaffected, genotype-negative (G-) relatives of further cardiac evaluation; this is information not achievable otherwise. Given the extensive clinical heterogeneity of HCM, individual prognostic prediction is mainly based on the phenotype found.

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Medical Therapy: From Beta-Blockers to Disopyramide

15

Keith Mankowitz and Mark V. Sherrid

Key Points

- HCM is a heterogeneous disease with a significant clinical variation requiring individualized treatment for each patient.
- Many patients can be managed conservatively with few or even no medications.
- The history, physical examination, and baseline echocardiogram usually determine the need for, type of, and titration of medications.
- Coronary risk factors and other medical conditions should be appropriately treated, and coronary artery disease in particular should always be considered as a potential cause or contribution to the HCM patient's symptoms.
- Septal reduction therapy should generally only be considered once a patient has failed maximal medical treatment.
- HCM can present as apical or mid-ventricular HCM, including mid-ventricular obstruction and apical aneurysms.
- Beta-blockers are the first-line treatments for apical and mid-ventricular obstructive variants.
- Echocardiograms should be performed at least every 1–2 years in HCM patients to assess for apical aneurysms and left ventricular systolic dysfunction.
- Global left ventricular systolic dysfunction should be treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockade, beta-blockers, aldosterone antagonists, and diuretics.
- Patients without HCM can develop dynamic left ventricular outflow tract or mid-ventricular obstruction in conditions causing left ventricular volume depletion, hyperdynamic left ventricular contractibility, or focal left ventricular contractile disturbances.
- Intravenous fluids are the first-line treatment for hypotensive patients with HCM or LVOT obstruction. Beta-blockade is also administered. If patients remain hypotensive despite adequate volumes of IV fluids and beta-blocker, the pressor of choice for hypotension is phenylephrine.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease with diverse clinical manifestations. Many patients can maintain an active, healthy lifestyle and have few or no symptoms [1–12]. Most patients achieve a normal life expectancy without disability or the need for major therapeutic interventions [3, 4, 6–13].

Accordingly, patients with HCM should be counseled regarding the generally favorable natural history of HCM. Pathophysiology of HCM should be explained to the patient in lay terminology: diastolic impairment of filling should be contrasted with systolic contractile impairment, the concept of LV wall thickness and its normal range, and the concept of left ventricular outflow tract obstruction. An image or heart models are particularly useful as teaching aids. These discussions are imperative as part of the initial evaluation so that patients understand the need for medications and compliance to, usually, twice-daily dosing.

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General Considerations in HCM Patients

Comprehensive management aims are sudden death prevention, improving quality of life, advising patients about acceptable forms of exercise, recommending screening of family members and first-degree relatives for HCM by cardiologists experienced in diagnosing and managing HCM, anticoagulating patients with atrial fibrillation, and treating coronary risk factors including hypertension, obesity, diabetes mellitus, and hyperlipidemia. Patients should be advised about appropriate physical activity, eating a healthy diet, weight management, maintaining adequate hydration, and maintaining an ideal body weight. Smoking cessation should be strongly recommended, and a low-level aerobic exercise program should be recommended for all patients [14]. Patients should be assessed for coronary artery disease or other comorbid conditions, such as chronic obstructive pulmonary disease, if clinically indicated. The risk of sudden death should be explained to the patient and their family, as well as the need to perform periodic risk assessments to see if the patient needs an ICD. The prevention of sudden death is achieved by selecting the appropriate patients for implantation of a cardioverter-defibrillator (ICD) and advising patients to avoid competition and sudden bursts of physical exertion [14].

Patients with HCM should avoid dehydration, high doses of diuretics, pure vasodilators, and inotropes (Table 15.1). Caution should be used with decongestants such as pseudoephedrine and beta-stimulants such as bronchodilators, as they can aggravate palpitations and arrhythmias. Nonsteroidal anti-inflammatory drugs can cause fluid retention, increase blood pressure, interfere with renal function, and should be minimized or avoided.

The pathophysiology of hypertrophic cardiomyopathy is complex with many different processes contributing to symptoms including diastolic dysfunction, myocardial ischemia, outflow tract obstruction, mitral regurgitation, arrhythmias, and secondary pulmonary hypertension; a reduced cardiac output at rest or on exertion is almost universally present in symptomatic patients [1, 15, 16]. Left ventricular outflow tract obstruction which occurs in up to one third of patients at rest and another one third with physiological provocation like exercise causes an increase in left ventricular systolic pressure leading to a complex interplay of abnormalities including prolongation of ventricular relaxation, elevation of left ventricular diastolic pressure, mitral regurgitation, myocardial ischemia, and a decrease in the cardiac output [1, 15, 16]. There is a significant variability in a patient's symptoms from day to day, hence the classically "dynamic" nature of both the obstruction and the disease. There is often a large variation in the severity of the gradient in each patient during daily activities and in response to upright position, food, and alcohol, which can aggravate symptoms [17–22].

Table 15.1 Drugs to avoid in obstructive HCM

1. Nitrates
2. ACE, ARB (prils and sartans)
3. Dihydropyridine CaCB: Nifedipine, amlodipine (pines)
4. Alpha-blockers: Terazosin (Hytrin), tamsulosin (Flomax), doxazosin (Cardura) (sins)
5. PDE5 inhibitors: Sildenafil (Viagra), vardenafil (Levitra) (enafils)
6. Dobutamine, dopamine, digoxin
7. Sympathomimetics: Pseudoephedrine, methylphenidate (Ritalin, Concerta), amphetamine (Adderall)

The decision to begin medications should be based on the patient's symptoms. There are no conclusive data to support treating asymptomatic patients prophylactically with medications as they do not appear to protect patients from progression of their disease, nor do they prevent sudden death [15, 16, 23, 24]. The pediatric HCM population may be an exception to this rule. Also, because beta-blockers have been shown to decrease latent gradients, and because they are generally very well tolerated, some investigators have suggested that it is reasonable to beta-block even mildly or asymptomatic patients in an attempt to decrease the hemodynamic burden of dynamic obstruction.

The need for and response to pharmacologic therapy are best assessed by symptoms and findings on the physical examination and complemented by the echocardiogram. The physical examination is useful to assess the volume status and to auscultate for heart murmurs. The volume status is assessed by evaluating the jugular venous pressure and for signs of pulmonary and peripheral edema. Auscultation of the heart is useful to assess the presence of mitral regurgitation and roughly assess the severity of the left ventricular outflow tract obstruction, which correlates with the loudness, and length of the ejection systolic murmur. An echocardiogram and stress echocardiogram are useful to assess the ventricular and valve function, to rule out myocardial ischemia, and to assess for the presence, severity, and mechanism of the left ventricular outflow tract gradient. Exercise testing can quantify patient limitation in patients who have self-limited their exertion and hence complain of no symptoms. The ability to only walk <6 minutes of the Bruce protocol can convert a patient from a NYHA I to a NYHA II–III.

Medical therapy needs to be tailored to each individual patient with the initiation and adjustment of medications based on the clinical response and not only based on the echocardiogram or stress echocardiogram. In some cases an exercise treadmill test may help gauge symptoms and response to medical therapies.

There are no prospective randomized trials to guide medical therapy. Symptomatic patients with obstruction should generally be treated medically before considering septal reduction therapy such as septal myectomy or alcohol septal

ablation [25]. Septal reduction therapy should generally be reserved for eligible patients with severe drug refractory symptoms that interfere with daily activity or quality of life despite optimal medical therapy. An exception to this general tenet are patients who have such severe anatomic abnormalities like elongated slack mitral leaflets along with high resting gradients that they are deemed to have an anatomic abnormality that might never adequately respond to pharmacologic therapy. Another caveat, as alluded to above, is the childhood population, where symptoms may be difficult to gauge or the patient may present as a failure to thrive. In the adult population, invasive interventions to abolish the left ventricular outflow gradient are performed for the minority of patients who have both significant left ventricular outflow tract obstruction and severe symptoms unresponsive to medical therapy [15, 16, 24–26]. Higher rates of surgical myectomy will be observed in clinical series from dedicated HCM centers because of referral to these centers of sicker, more symptomatic and oftentimes younger patients with massive hypertrophy.

Infective endocarditis is uncommon within the overall HCM population, but it can have devastating effects on valvular and cardiac function and can cause systemic embolization. Virtually all reported cases of infective endocarditis in HCM occurred with left ventricular outflow tract obstruction. Vegetations can develop on the anterior mitral leaflet, aortic valve, or the adjacent proximal ventricular septum. Revisions to AHA guidelines state that HCM patients no longer require routine antibiotic prophylaxis. Others have contended that prophylaxis should be given [27, 28].

Obstruction in HCM

Systolic anterior motion (SAM) with mitral-septal contact is the most common cause of obstruction. SAM is caused by a physical overlap of early LV systolic flow and the mitral valve. The septal bulge displaces LV ejection flow so that it comes from a more posterior and lateral direction. As the flow sweeps around the septal bulge on its way to the outflow tract, it strikes the underside of the protruding mitral leaflets and sweeps them into the septum [29–31] (Fig. 15.1).

Once mitral-septal contact and an orifice are established, it is the resulting pressure gradient that continues to push the mitral valve into the septum, continuously narrowing the orifice and increasing the gradient, a classic amplification loop. This explains the scooped-out pattern observed on the CW Doppler tracing through the LVOT jet. Pharmacotherapic benefit can be understood as a *modulation* of this pathophysiology in which the severity of SAM and gradient is *modulated* by a tug-of-war between anteriorly displacing forces (the pushing force of flow) and restraining posterior forces (the chordae and papillary muscles). There is a dynamic equilibrium between these forces [32] (Fig. 15.2).

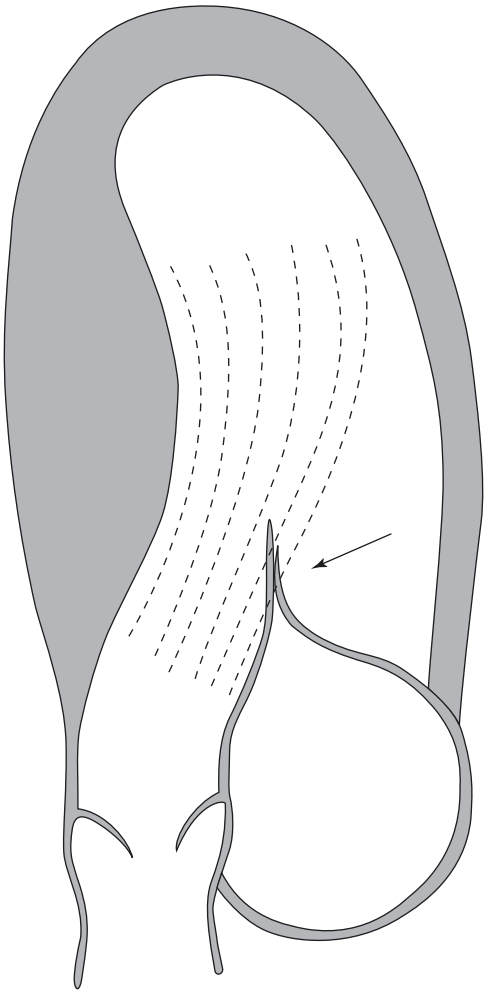

Fig. 15.1 The pushing force of flow. Intraventricular flow relative to the mitral valve in the apical five-chamber view. In obstructive HCM the mitral leaflet coaptation point is closer to the septum than normal. The protruding leaflets extend into the edge of the flowstream and are swept by the pushing force of flow toward the septum. Flow pushes the underside of the leaflets (**arrow**). Note that the midseptal bulge redirects flow so that it comes from a relatively lateral and posterior direction; on the five-chamber view, flow comes from "right field" or "one o'clock" direction. This contributes to the high angle of attack relative to the protruding leaflets. Also note that the posterior mitral leaflet is shielded and separated from outflow tract by the cowl of the anterior leaflet. Venturi flow in the outflow tract cannot be lifting the posterior leaflet because there is little or no area of this leaflet exposed to outflow tract flow. Venturi forces cannot be causing the anterior motion of the posterior leaflet. (Reproduced by permission from Sherrid et al. Systolic anterior motion begins at low left ventricular outflow tract velocities in obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol. 2000;36:1344–1354)

Negatively inotropic pharmacologic therapy decreases ejection acceleration; this displaces the equilibrium of forces on the mitral valve toward restraint [33]. Even small changes in ejection velocity yield large changes in the force on the valve, since the force on the mitral valve is proportional to the square of the velocity. A pharmacologic decrease in LV ejection acceleration correspondingly decreases the force on

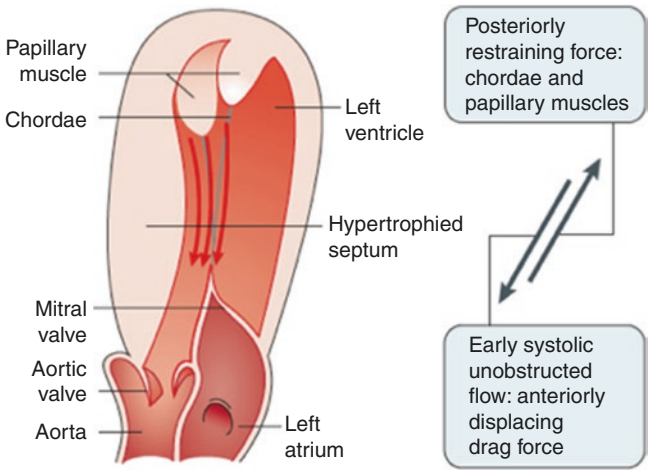

Fig. 15.2 Before mitral-septal contact, flow courses around the septal bulge and catches the anteriorly displaced mitral valve and sweeps it into the septum. The chordae and papillary muscles act to posteriorly restrain the mitral valve. There is a dynamic equilibrium between these forces that can be modulated by medications. (With permission from Ormerod et al. [32])

the mitral valve. The tonic chordal restraint delays mitral-septal contact and decreases the duration of mitral-septal contact, decreasing the duration of the amplifying loop and the final gradient (Fig. 15.3). This understanding explains how negative inotropes reduce or eliminate obstruction.

Medications for Hypertrophic Cardiomyopathy in 2017

There are no large randomized trials of efficacy and safety for any medications in HCM. No drug has been approved by the FDA; thus, reports of efficacy and safety depend on observational studies (Table 15.2).

Beta-Blockers

Beta-blockers are the first-line drugs to treat symptomatic obstructive hypertrophic cardiomyopathy [34–36].

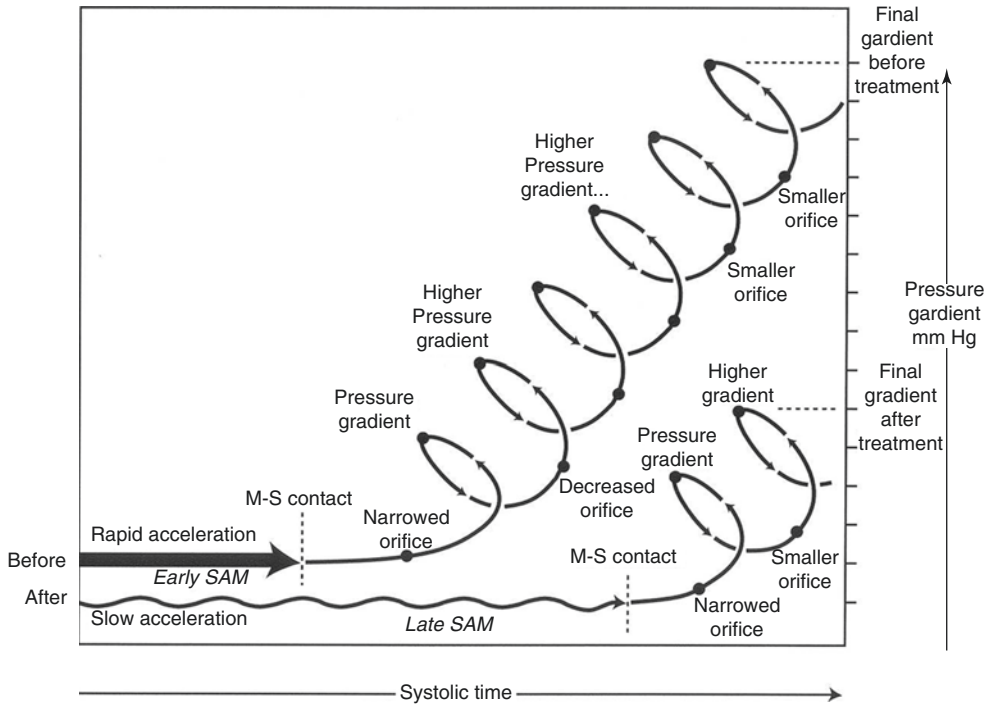

Fig. 15.3 Proposed explanation of pressure gradient development before and after treatment of obstruction. Before treatment (top tracing), rapid left ventricular acceleration apical of the mitral valve, shown as a horizontal thick arrow, triggers early systolic anterior motion (SAM) and early mitral-septal (M-S) contact. Once mitral-septal contact occurs, a narrowed orifice develops, and a pressure difference results. The pressure difference forces the leaflet against the septum, which decreases the orifice size and further increases the pressure difference. An amplifying feedback loop is established, shown as a rising spiral. The longer the leaflet is in contact with the septum, the higher the pressure gradient. After treatment (bottom tracing), negative inotropes slow early SAM (shown as a horizontal wavy arrow) and may thereby decrease the force on the mitral leaflet, delaying SAM. Mitral-septal contact would occur later, leaving less time in systole for the feedback loop to narrow the orifice. This would reduce the final pressure difference. Delaying SAM may also allow more time for papillary muscle shortening to provide countertraction. In the figure, for clarity, the "before" arrow is positioned above the "after" arrow, although at the beginning of systole they both actually begin with a pressure gradient of 0 mmHg. (Reproduced by permission from Sherrid et al. [33])

Table 15.2 Pharmacologic therapy for symptoms in patients with hypertrophic cardiomyopathy

Class and drug	Reduces resting gradient	Reduces exercise gradient	Improves symptoms	Initial daily	Max daily	Side effects
Beta-blockers						
Metoprolol	+	+++	+++	25 mg bid	200 mg	Bradycardia, hypotension, fatigue, depression, asthma
Atenolol	+	+++	+++	25 qd	200 mg	
Bisoprolol	+	+++	+++	2.5 mg qd	10–15 mg	
Propranolol	+	+++	+++	10 mg bid	320 mg	
Calcium channel blockers						
Verapamil	+	+++	++	40 mg tid	480 mg	Bradycardia, hypotension, constipation, Edema
Diltiazem (nonobstructive HCM)			++			
Disopyramide	+++	+++	+++	100 mg tid	600 mg	Dry mouth, constipation, urinary hesitancy
Diuretics						
HCTZ				12.5 mg qd	50 mg	Hypokalemia, hyponatremia, dehydration
Furosemide			+++	20 mg	100 mg	
Torsemide			+++	50 mg	100 mg	
Spironolactone			+/++	12.5 mg	100 mg	
HCTZ/triamterene			++	25 mg/37.5 mg	25 mg/37.5 mg	
Nitrates (predominantly nonobstructive HCM)						Headache
			Improves CP	Initial	Max	Headaches, hypotension
Nitropaste			++	1 inch prn	2 inch prn	
Nitropatch			++	0.1 mg/h	0.4 mg/h	
Isosorbide dinitrate			++	10 mg tid	40 mg tid	

Beta-blockers result in an improvement in angina, exercise tolerance, and syncope in 60–80% of patients. Sustained symptomatic improvement occurs in about 40% of patients [34, 35]. Beta-blockers reduce provocable obstruction but have a little effect on resting obstruction. They should be used with caution in patients with reactive airways disease, and in this setting, metoprolol and bisoprolol are the beta-blockers of choice because of their cardioselectivity. Beta-blockers should be used cautiously in patients with bradycardia and when systolic blood pressure is <90 mmHg.

The dose of beta-blockers should be titrated carefully to improve symptoms while minimizing side effects, especially those of fatigue, depression, and impotence. In general, long-acting formulations given in once- or twice-daily format are best. Propranolol and metoprolol are the best-studied beta-blockers. Metoprolol tartrate twice daily or metoprolol succinate once daily is usually well tolerated, although many experts elect to utilize the succinate formulation as a twice-daily dosing strategy. Doses range from low 12.5 mg daily to as high as 200–400 mg daily, depending on the clinical response of the patient. Propranolol can be started at 10 mg twice a day and titrated as tolerated. Bisoprolol from 2.5 mg to 10 mg/day is highly beta-1 selective and has, perhaps, a lower incidence of fatigue. Carvedilol and labetalol have alpha-blocking activity and are not generally used in patients with significant LVOT obstruction where they can aggravate the LVOT gradient. When hypertension occurs with obstructive HCM, one might consider adding low-dose verapamil or clonidine. Nebivolol, a relatively new beta-blocker with nitric oxide potentiating vasodilatory effect, also could exacerbate obstruction and therefore is to be avoided.

Calcium Channel Blockers

If beta-blockers are ineffective or produce unsatisfactory side effects, then verapamil can be used to control symptoms with certain precautions [37–40]. The use of verapamil as first-line therapy for nonobstructive HCM may be reasonable. In patients with atrial fibrillation, maintaining a low dose of a beta-blocker as a combination therapy may aid in control of rate of arrhythmias. Dihydropyridine calcium channel blockers, such as nifedipine and amlodipine, are generally contraindicated in patients with obstructive HCM, due to their vasodilating, afterload-reducing properties. Similar to beta-blockers, calcium channel blockers primarily ameliorate provocable, as opposed to resting, gradients.

Non-dihydropyridine calcium channel blockers utilized in HCM have vasodilating properties and can worsen left ventricular outflow tract obstruction when used at high doses [41]. Sudden death has been reported when verapamil was used in patients with severe resting obstruction and advanced heart failure. Accordingly, calcium channel blockers should not be used in patients with overt congestive heart failure or those with elevated filling pressures, and they should be avoided in patients with severe resting left ventricular outflow tract obstruction.

Verapamil starting at low doses such as 40 mg three times a day or verapamil ER 120 mg daily can be titrated as needed up as high as 480 mg a day and may provide symptomatic relief of angina or shortness of breath by its negative inotropic and rate-lowering effects. The lowest effective dose should always be used, and doses over 240 mg daily should be used with caution, with careful attention to whether such higher doses might exacerbate or alleviate obstruction in a given patient. If patients have side effects from verapamil, especially constipation, then diltiazem can be used in similar doses to verapamil. Diltiazem has not been as well studied as verapamil in patients with HCM but is a potential option.

There are no data to show that the combination of a beta-blocker with a calcium channel blocker is better than one drug alone. However, this combination may be useful in patients in whom uptitration of beta-blockers is not possible, such as asthmatics, and in atrial fibrillation to control rate.

Disopyramide

Disopyramide is a class I antiarrhythmic drug that has negative inotropic properties, making it a useful drug to treat patients with symptomatic obstructive HCM [42–52]. As opposed to beta-blockers and calcium channel blockers, disopyramide can reduce both resting and provocable obstruction. As a more potent negative inotrope, disopyramide is often effective when beta-blockade or verapamil is not (Fig. 15.4). As a matter of practice preference for heart failure symptoms due to obstruction, some clinicians start disopyramide as a second-line drug after beta-blockade instead of verapamil, because disopyramide is not a vasodilator and because of observations such as that shown in Fig. 15.4. Disopyramide should be used in combination with either a beta-blocker or a calcium channel blocker and for this reason is always a second-line agent.

Disopyramide can successfully ameliorate symptoms of exertional shortness of breath, presyncope, and syncope in up to two thirds of patients with hypertrophic obstructive cardiomyopathy [42–44]. Disopyramide ameliorates angina, dizziness, and shortness of breath by reducing the LVOT gradients by its negative inotropic properties. Disopyramide is usually given in combination with β-blockade to blunt the exercise-related rise in gradient and for synergistic negative inotropic effect and to provide AV delay should atrial fibrillation occur.

In the United States, disopyramide is available as regular-release capsules in 100 mg and 150 mg dosage given three to four times per day. In the United States, manufacturing shortages have rendered the time-release twice-daily dosing unavailable in the second half of 2017. It is scheduled to return to wholesalers and pharmacy shelves in early 2018. It is available in a controlled release preparation in Europe as a 250 mg tablet with twice-daily dosing. The dose of disopyramide ranges from 100 mg twice a day to 600 mg a day in divided doses three to four times/day depending on the preparation prescribed. The lowest effective dose that affords symptomatic relief should be used.

In the United States, this drug has often been started in the hospital after admission with telemetry monitoring for 48–72 h and daily ECG monitoring, although outpatient initiation is advocated by some. In Canada and the United Kingdom, it is begun routinely in outpatients at low-dose

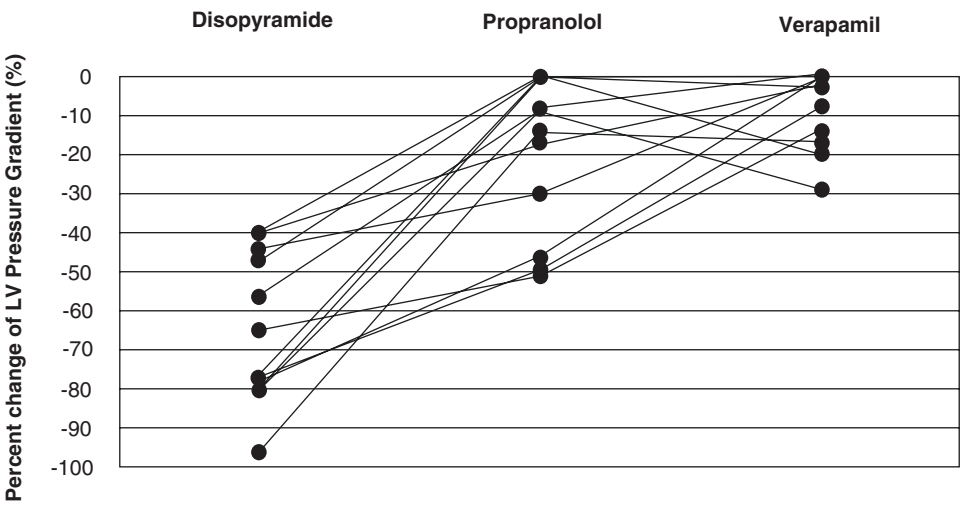

Fig. 15.4 Individual percentage of changes in LV pressure gradient at rest after intravenous administration of disopyramide, propranolol, or verapamil. (Reproduced by permission from Kajimoto et al. [51])

100 mg 3×/day and titrated upward as needed. Recently published data from Canada has shown the safety of outpatient initiation of disopyramide. Patients will usually notice an improvement in breathing and chest discomfort within 24–48 h. A maximum dose of 150 mg 4x/day of regular-release disopyramide and 300 mg twice a day of the control release preparation can be safely prescribed [52].

A multicenter non-randomized study showed no proarrhythmia and a lower mortality in disopyramide-treated patients [42]. There should be a consideration of inpatient initiation of disopyramide when there is bundle branch block, prolonged QTc at rest, or unavoidable administration of concomitant QT-prolonging drugs. Patients should be instructed to avoid other QT-prolonging drugs, and they should be stopped before initiation. This is almost always possible if, for example, macrolides, quinolones, and SSRIs are not given. Other antibiotics are preferred, and non-QT-prolonging antidepressants may be prescribed (duloxetine, bupropion). If a short course of concomitant QTc-prolonging drugs must be given (e.g., a short course of macrolide or quinolone antibiotic), disopyramide can be stopped for this interval [52].

An ECG should be performed at every outpatient visit to assess the conduction intervals especially the QT interval. We continue dosing with disopyramide unless the QTc is >525 msec in patients with underlying normal QRS duration and > 560 msec in patients with wide QRS from bundle branch block and pacing. Safety data has been published using these criteria [44]. An echocardiogram should assess the effectiveness of disopyramide in reducing the LVOT gradient but should only be ordered after several weeks of therapy to allow disopyramide to reach its maximal effectiveness.

Disopyramide is well tolerated although its anticholinergic side effects can limit the tolerability of the drug. The commonest side effect is a dry mouth. Urinary hesitancy, dribbling, or retention can occur in both males and females. Pyridostigmine has been used in select patients to reverse these side effects. Disopyramide should usually be given together with metoprolol or verapamil as the anticholinergic effects may enhance ventricular conduction and increase the ventricular rate during episodes of atrial fibrillation. Organ toxicity from disopyramide is very rare. We have observed no hematologic, central nervous system, renal, hepatic, or adverse effects; this makes it suitable for long-term use [52].

Disopyramide has a IIa recommendation from the 2011 AHA/ACCF guidelines and a Ib recommendation from the European Society Guidelines [25, 47]. Recent large patient experiences have been reported showing how disopyramide can effectively figure in the overall care of obstructive HCM patients refractory to beta-blockers or verapamil [43, 44]. Figure 15.5 is an example of one pathway of how pharmacologic therapy is often started and its relation to interventional therapy.

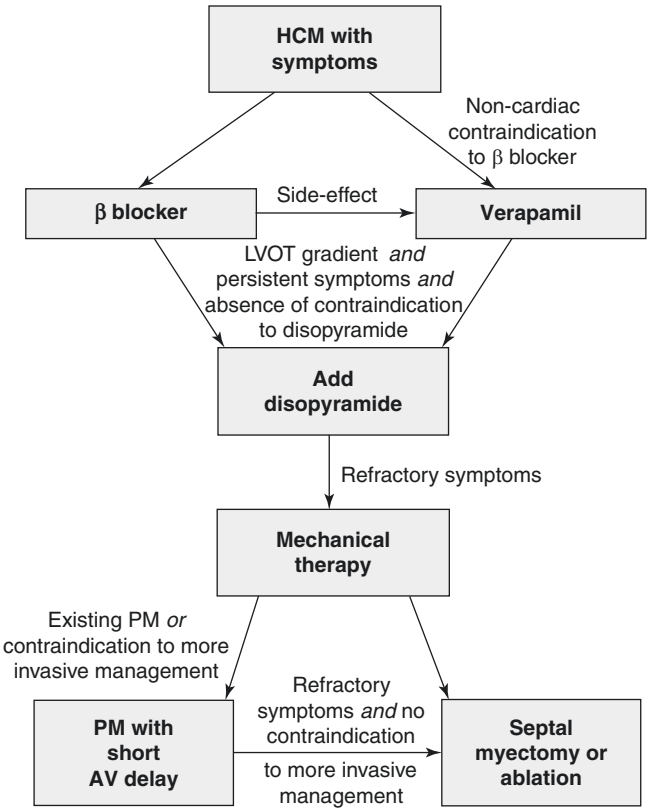

Fig. 15.5 Proposed treatment path for patients with obstructive hypertrophic cardiomyopathy. Note that patients generally should receive aggressive pharmacologic therapy before referral to invasive therapy. Patients resistant to beta-blockade or verapamil form a discrete patient group who are candidates for advanced care: treatments available include disopyramide, surgical septal myectomy, alcohol septal ablation, and DDD pacing with short AV delay. (Reproduced by permission Fifer and Vlahakes [45])

Diuretics

Diuretics are useful to treat the volume-overloaded patient especially those with nonobstructive HCM. Patients with long-standing HCM oftentimes are fluid overloaded, despite a relatively normal physical examination. By the time a patient with obstruction requires diuretics for heart failure symptoms, septal reduction therapy is the preferred long-term choice.

Diuretics ranging from low-dose thiazides to potent loop diuretics should be carefully chosen based on the patient's volume status, blood pressure, left ventricular outflow tract obstruction, and clinical response. For the volume-overloaded patient with borderline blood pressure or a left ventricular outflow tract gradient above 50 mmHg, a low-dose thiazide diuretic such as hydrochlorothiazide 12.5–25 mg should be the first-line diuretic given with oral potassium. Aldosterone antagonists such as spironolactone and eplerenone may restore euvolemia and are valued for their potassium-sparing effect. For patients with more severe volume overload or

after poor response to low-dose thiazides, combinations such as triamterene/HCTZ or escalating doses of loop diuretics such as furosemide should be titrated according to patient's needs. Torsemide is better absorbed and more potent than furosemide and can be used if more aggressive diuresis is needed. The addition of metolazone to furosemide or torsemide can significantly augment the effects of loop diuretics. However, HCM patients are sensitive to hypovolemia, so these more powerful diuretic combinations are rarely used. Sodium, potassium, and magnesium should always be closely monitored and should be kept at safe levels to prevent proarrhythmia. It is difficult to overemphasize the importance of maintaining normal potassium levels.

Nitrates

Nitrates, which are commonly used to treat angina in patients with epicardial coronary artery diseases, may be useful to treat angina in patients with nonobstructive HCM. There has always been a concern that nitrates could aggravate left ventricular outflow obstruction and worsen hemodynamics in HCM patients; however if used sensibly, nitrates can provide significant symptomatic benefit predominantly for nonobstructive HCM patients with angina. Caution should be used especially in treating patients with moderate-to-high LVOT gradients and/or patients with low blood pressures. Topical nitrates such as nitropaste or nitropatches are useful in patients with HCM and angina as they produce a small, somewhat controlled release of nitrates into the systemic circulation. Nitrates should be titrated according to patient's response and tolerance. It is important to note the geographic variation in the use of nitrates in clinical practice and that many HCM experts do not use nitrates in obstructive HCM patients due to the aforementioned risks.

Adverse Effects of Medications

One should always consider the possibility that the patient's symptoms may be due to the side effects of their medications and not due to HCM. Patients may develop significant side effects from medications, especially from beta-blockers, where it may be difficult to differentiate whether fatigue is from medication or the HCM. A careful comprehensive premedication assessment of symptoms before beginning treatment is thus essential. Uptitration of beta-blockade may alleviate obstructive physiology but increase symptoms of diminished cardiac output or reserve caused by chronotropic incompetence, prolongation of the PR interval with impairment of LV filling, or high-degree heart block. Contributions from beta-blocker-induced fatigue and depression should also be considered. Careful adjustment of the doses of drugs or switching to a different beta-blocker or to a calcium channel blocker or disopyramide can result in significant improvement in breathing and well-being [53, 54].

Treatment of Specific Symptoms

Chest Pain

Chest discomfort is a common symptom in patients with HCM and is usually due to the unique pathophysiology of HCM. Hypertrophic cardiomyopathy patients have increased oxygen demand caused by left ventricular hypertrophy and increased afterload from gradient. Both nonobstructed and obstructed patients also have compromised coronary blood flow due to medial hypertrophy of the coronary arteries and arterioles resulting in luminal narrowing and increased myocardial resistance to flow and due to impaired coronary flow reserve [55]. Severe myocardial ischemia and infarction may occur in HCM due to the supply-demand mismatch [56, 57].

Atherosclerotic epicardial coronary artery disease should always be ruled out before one attributes chest pain or angina to HCM, especially in older patients or those with cardiovascular risk factors. In this regard, coronary CT angiography has been a recent significant advance. Systolic myocardial bridging in which a segment of the left anterior descending coronary artery courses within the myocardium may be considered a potential cause for angina when the constriction persists into diastole; this etiology is controversial because of the other substantial causes for chest pain in HCM patients. To attribute angina to a bridge, one would need to demonstrate impaired flow reserve in just the subtended myocardium.

Beta-blockers should be the first-line treatment for HCM patients with chest pain or angina. These agents, when given in adequate dose to lower resting and exercise heart rates, improve oxygen supply-demand imbalance and reduce ischemia. If a beta-blocker does not control the chest discomfort or angina, it should be weaned and discontinued. Verapamil starting at low doses and titrated as needed up to 480 mg a day may provide symptomatic relief of angina by its negative inotropic and rate-lowering effects; caution should be exercised in doses over 240 mg daily, as provocation of outflow tract obstruction may occur. If patients have side effects from verapamil, especially constipation, then diltiazem can be tried in a similar dose as verapamil.

Patients with significant left ventricular outflow tract (LVOT) obstruction (resting or provocable gradient above 30 mm) who continue to complain of angina despite therapeutic doses of beta-blockers or calcium channel blockers may also respond to disopyramide. Disopyramide ameliorates angina by reducing the LVOT gradient through its potent negative inotropic properties. Patients will usually

notice an improvement in breathing and chest discomfort within 24–48 h.

Nitrates, especially topical nitrates such as nitropaste or nitropatches, may be useful to treat angina in patients with HCM. Caution should be used especially in treating patients with LVOT gradients and/or low blood pressures. Nitrates should be titrated according to patient's response and tolerance. There is no convincing data regarding the use of ranolazine in patients with HCM.

Shortness of Breath

Shortness of breath usually manifests as exertional dyspnea and can be caused by diastolic dysfunction, dynamic LVOT obstruction, mitral regurgitation, atrial fibrillation, myocardial ischemia, and pulmonary hypertension [15, 16]. Symptoms of diastolic heart failure, i.e., exertional shortness of breath, most frequently present themselves in middle-aged adults [1, 2, 16, 25, 58, 59]. The minority of patients, approximately 10–20%, will develop severe heart failure symptoms [1, 2, 16, 25, 59]. Functional limitation is usually gradual with long periods of stability and day-to-day variability. Women usually have more severe symptoms of heart failure, which often occur later in life [60]. The most favorable relief of dyspnea is often experienced in patients with LVOT obstruction who have gradient reduction by the methods described in Fig. 15.5.

There is no pharmacologic therapy that has been shown to improve primary diastolic dysfunction [61–63]. Relief of obstruction with disopyramide decreases LV filling pressures by relieving contraction loading in systole that can impair relaxation [63]. However, it has not been shown to be helpful in nonobstructive HCM.

Judicious use of diuretics is appropriate for patients with elevated filling pressures and volume overload. Diuretics should be carefully adjusted according to each patient's needs from cardiac history and physical examination, aided by invasive cardiac catheterization when needed for confirmation. Symptoms of shortness of breath, orthopnea, PND, and edema, and clinical signs of elevated filling pressures require especially careful assessment of the jugular venous pressure that will allow the clinician to titrate the appropriate diuretics. The BNP is often elevated in HCM patients, but the level of BNP is usually lower than in systolic heart failure and should not be relied upon to adjust diuretics.

Specific diuretics should be carefully chosen based on the severity of the volume overload, the blood pressure, the degree of left ventricular outflow tract obstruction, and the renal function. For any patient who is severely volume overloaded regardless of the underlying pathophysiology, diuretics should be started along with specific HCM pharmacotherapy. One should always consider the possibility that the patient's symptoms may be due to the side effects of their medications and not due to HCM. In particular, careful attention should be paid to over-diuresis, as this can stimulate obstruction and/or reduce cardiac output further.

Heart Failure Symptoms Due to LVOT Obstruction

LVOT gradients are dynamic, characterized by spontaneous variability on a day-to-day (or even hourly) basis, and are affected by various factors including dehydration, alcohol, or heavy meals [18–22]. Beta-blockers may improve shortness of breath by reducing LVOT obstruction, especially the obstruction that may occur with exertion, by improving oxygen-demand imbalance, by prolonging the diastolic filling period, and by allowing more efficient inactivation of myocardial contractile proteins [64–66]. Beta-blockers can mitigate exercise-provoked LVOT gradients thereby improving exertional dyspnea [18, 67]. The lowest effective dose of a beta-blocker should be used.

If beta-blockers are ineffective or cause significant side effects, then verapamil can be used or added to treat shortness of breath. Verapamil and diltiazem should be used cautiously in patients with LVOT gradient above 50 mmHg at rest and/or bradycardic patients. Calcium channel blockers have a similar negative inotropic and rate-lowering effect as beta-blockers [68–72]. Verapamil and diltiazem can improve diastolic dysfunction by slowing the heart rate to allow for better atrial emptying. Verapamil and diltiazem have vasodilating properties and can worsen LVOT obstruction, especially at doses > 240 mg daily. They should be used cautiously in patients with congestive heart failure or elevated filling pressures, and they should be avoided in patients with severe resting left ventricular outflow tract obstruction. They can aggravate congestive heart failure and cause sudden death [41]. Because of this potential, many HCM physicians prefer adding disopyramide to beta-blocker as the second drug in patients with severe resting obstruction.

Patients with resting or latent LVOT gradients may experience a significant improvement in shortness of breath with disopyramide. Disopyramide is the only drug with the potential for reducing LVOT gradients at rest. Disopyramide by its negative inotropic effects will reduce the LVOT gradient thereby improving diastolic dysfunction, reducing mitral regurgitation, and improving shortness of breath. Up to 70% of patients will have a significant improvement in their symptoms with disopyramide [42–44]. Disopyramide should usually be given together with metoprolol or verapamil as the anticholinergic effects may enhance ventricular conduction and increase the ventricular rate if the patient develops atrial fibrillation. Figure 15.5 describes our overall approach to pharmacologic treatment in obstruction. Figure 15.6

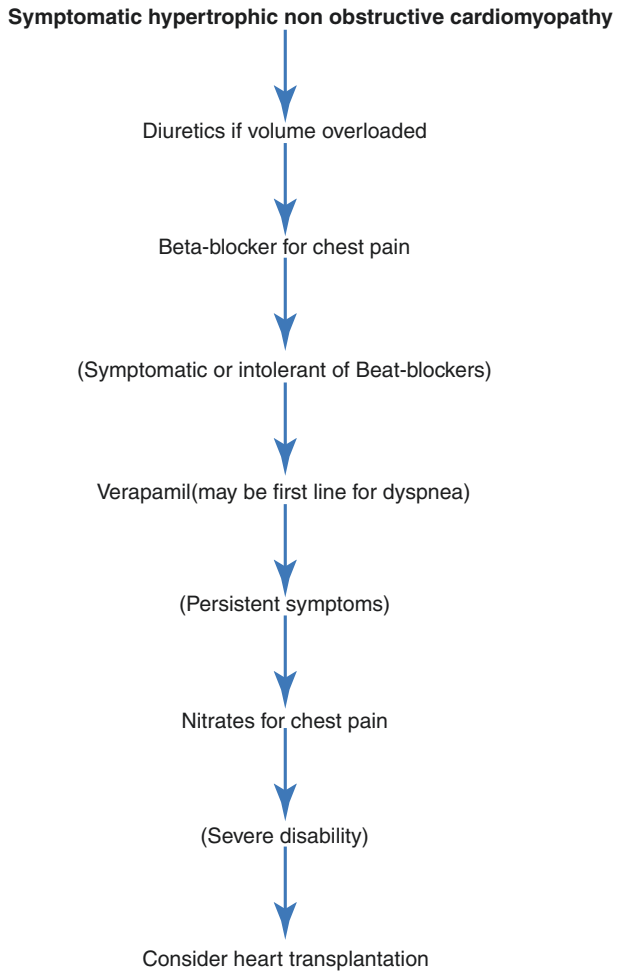

Fig. 15.6 Treatment of symptomatic hypertrophic nonobstructive cardiomyopathy

describes our approach to symptoms in nonobstructive HCM patients.

Pulmonary hypertension may develop in HCM patients due to severe obstruction, diastolic dysfunction, or mitral regurgitation. In long-standing HCM, partially irreversible pulmonary hypertension may develop. Medications for pulmonary hypertension have not been studied in the HCM population; vasodilators should be avoided. Patients with severe pulmonary hypertension may benefit from pulmonary evaluation.

Dizziness, Presyncope, and Syncope

Dizziness, presyncope, and syncope have numerous possible causes in HCM patients similar to patients without HCM. Brady- and tachyarrhythmias should always be excluded. If dizziness, presyncope, or syncope is felt to be due to LVOT obstruction, then a trial of beta-blockers should be initiated. Beta-blockers can reduce the LVOT obstruction especially the obstruction that may occur with exertion [67]. If beta-blockers are not helpful, then calcium channel blockers and/or disopyramide should be added. Disopyramide can improve dizziness, presyncope, and syncope that is due to a high LVOT gradient by its negative inotropic effects that reduce LVOT gradients [42]. Many patients with syncope from obstruction will come to septal reduction therapy over a period of years. Dizziness, presyncope, and syncope may also be due to autonomic instability in a subset of patients; such patients may benefit from adequate hydration and other conservative measures and medications. More information may be found within the chapter on syncope. Clinicians should recognize that unexplained syncope is often an indication for ICD insertion. However, syncope from obstruction would not be considered unexplained and is often best addressed by relief of obstruction.

Atrial Fibrillation

Atrial fibrillation occurs in about 20–25% of HCM patients and can cause significant morbidity, including precipitation or aggravation of heart failure and stroke [7, 8, 15, 16, 73–76]. Paroxysmal atrial fibrillation can cause rapid clinical deterioration by reducing diastolic filling and cardiac output in the patient dependent on atrial component of filling due to profound diastolic dysfunction, such as those with HCM. Chronic atrial fibrillation is often better tolerated especially if the heart rate is controlled. Atrial fibrillation that precipitates acute heart failure requires aggressive treatment including anticoagulation, rate control, and urgent rhythm control. The risk of stroke for patients with HCM who develop atrial fibrillation is quite high, at 4%/year, and is more common in patients with LVOT obstruction [77–81]. Susceptibility to atrial fibrillation is linked to aging and left atrial enlargement, usually > 50 mm [77, 78, 81]. There is no evidence that atrial fibrillation is an independent determinant of sudden death in HCM patients [2, 78, 82]. Disopyramide can be used for both its ability to reduce the LVOT gradient and to maintain sinus rhythm. Amiodarone is the most effective drug for controlling recurrences of atrial fibrillation but has more organ toxicity [25, 78].

The CHADS2 score ignores hypertrophic cardiomyopathy as a risk factor for stroke and should not be used in these patients as it has no relevance [83]. Anticoagulation should be considered even in patients with only one episode of atrial fibrillation because of the high risk of recurrent atrial fibrillation and the high risk of embolic stroke [73, 77, 78, 80, 81]. Aspirin is reserved for patients who refuse to take warfarin or other anticoagulants, but any efficacy in HCM is unproven. Left atrial appendage closure devices should be considered in these patients for those who cannot take long-term anticoagulation.

Anticoagulation with vitamin K antagonists, i.e., warfarin adjusted to an INR of 2.0–3.0, is indicated in HCM patients with paroxysmal, persistent, or chronic atrial fibrillation. Anticoagulation with direct thrombin inhibitors such as dabigatran is an alternative to warfarin, but data for HCM patients is not available [84]. Anticoagulation with factor Xa inhibitors such as rivaroxaban and apixaban is also an alternative, but data for HCM patients are not available. Anecdotal evidence in >100 patients treated by us has shown that the novel oral anticoagulants are safe and effective for preventing emboli in hypertrophic cardiomyopathy patients.

Specific Subtypes of HCM: Apical and Mid ventricular HCM, HCM with Hypertension, HCM with Depressed Ejection Fraction, and HCM with Takotsubo LV Ballooning

Apical Hypertrophic Cardiomyopathy

Apical hypertrophic cardiomyopathy is a phenotypic variant with thickening predominantly affecting the cardiac apex. Patients with apical HCM comprise approximately 25% of HCM patients in Asian populations and 1–10% in non-Asian populations. Apical hypertrophic cardiomyopathy can cause chest pain, myocardial infarction, atrial fibrillation, strokes, and sudden death. Although many afflicted patients have mild symptoms, some patients are severely debilitated due to profound diastolic dysfunction. It may be associated with apical pouches or apical aneurysms. In rare cases, concomitant abnormalities of the papillary muscles or extension of hypertrophic myocardium to the mid-cavity can cause mid-LV LVOT obstruction and a murmur. The treatment of apical HCM patients in general should include beta-blockers or verapamil for chest pain. Anticoagulation is indicated for apical aneurysms with thrombi, though their administration to all aneurysm patients has not been proven in a clinical trial. Currently this decision would be based on clinical judgment given the known hemorrhagic risk of warfarin. Important clinical concerns include appropriate management of atrial fibrillation and risk stratification to determine the need for an ICD [85–90]. Care must be taken to avoid clinically relevant chronotropic incompetence in apical variants, where filling is perturbed to such a degree that higher heart rates on exertion are required to maintain cardiac output.

Hypertrophic Cardiomyopathy Associated with Mid-ventricular Obstruction

Mid-ventricular obstruction is a distinct phenotype of HCM and occurs due to segmental midseptal hypertrophy and hypercontractility of the lateral ventricular wall along with misplacement and hypertrophy of the papillary muscles. It causes a mid-cavity gradient. Mid-cavity obstruction occurs in 9–13% of HCM cohorts and appears to be more symptomatic than other phenotypes of HCM. Dyspnea is the most common symptom. Left ventricular apical aneurysm can develop in up to one quarter of patients with mid-ventricular obstruction. The aneurysm is thought to develop due to the increased pressure load on the apical myocardium, increased metabolic demand, and reduced oxygen supply from small vessel disease and possibly by extravascular compression of the penetrating intramural coronary arteries. Progression to end-stage HCM occurs more frequently than other HCM phenotypes. Mid-ventricular obstruction may be associated with a high risk of arrhythmias and sudden death. Treatment should include beta-blockers or verapamil to reduce the mid-ventricular obstruction and thus improve shortness of breath. The benefits and risks of anticoagulation should be considered for apical aneurysms. Patients should be monitored closely to detect ventricular arrhythmias and the need for an ICD. Yearly echocardiograms should be done to monitor for apical aneurysms, ventricular dilation, and progression to a dilated cardiomyopathy [91–98].

HCM and Hypertension

Hypertension is common in the American population, with an estimated prevalence of 30%. By coincidence alone one might expect that close to a third of HCM patients may have hypertension. Potent vasodilator medications cannot be prescribed in obstructive HCM. However, they can be given without restriction in nonobstructive HCM. In an investigation in which obstructive HCM and hypertension were confirmed by strict criteria, judicious administration of pharmacotherapy could control both problems in the majority of cases [99]. If symptoms and elevated gradients persisted after β-blockade or non-dihydropyridine calcium channel blocker, disopyramide was generally added. A combination of all three negatively inotropic agents was generally avoided unless the patient had a permanent pacemaker. Patients with heart failure symptoms refractory to pharmacologic management and resting or provoked gradients greater than 50 mmHg should be referred for septal reduction. In patients with persistent hypertension after the initial therapy with beta-blocker and verapamil, clonidine 0.1 mg once or twice per day or a clonidine patch may be given. Spironolactone is a useful adjunct. Hydrochlorothiazide (HCTZ) 12.5–25 mg can be given with triamterene without worsening of symptoms (Fig. 15.7). More information on managing concomitant HTN is found elsewhere in this textbook.

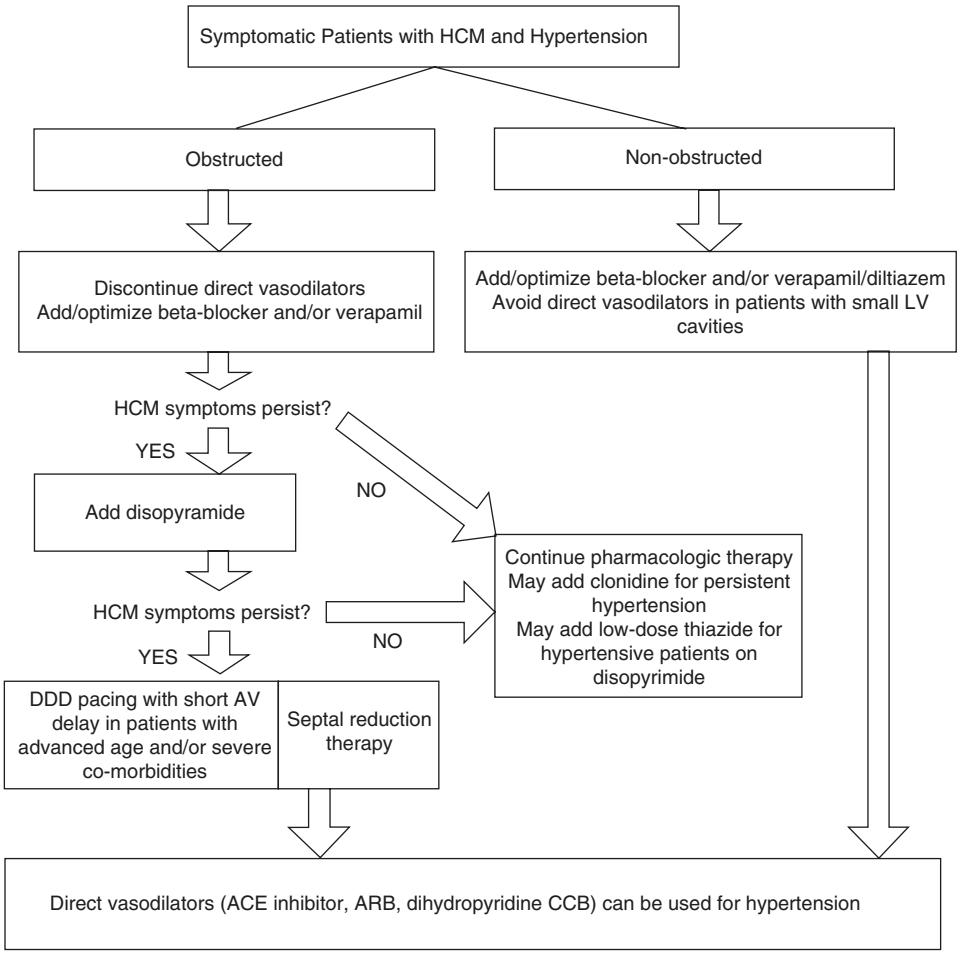

Fig. 15.7 General approach to patients with symptomatic HCM and hypertension. (ACE angiotensin-converting enzyme, ARB angiotensin receptor blocker, CCB calcium channel blocker, HCM hypertrophic cardiomyopathy, LV left ventricle. Reproduced from Argulian et al. [99])

HCM with Depressed Ejection Fraction: End-Stage Heart Failure

The discovery of a reduced ejection fraction occurs in approximately 3% of HCM patients. Before attributing the reduced ejection fraction to the hypokinetic transformation phase of HCM, other causes of left ventricular dysfunction should be evaluated such as coronary artery disease, valvular heart disease, and metabolic disorders [58, 100]. The hypokinetic stage is attributable to an irreversible process of extensive replacement scarring due to genetically mediated fibroblast activation or to microvascular ischemia [56, 100–105]. It is characterized by left ventricular remodeling with progressive wall thinning (due to myocardial necrosis), cavity enlargement, and systolic dysfunction [100, 101]. A substantial portion has a significant scar burden by MRI often totaling over 25% with late gadolinium enhancement.

The only known predictor of hypokinetic transformation of HCM is a family history of this transformation. The clinical course of HCM is variable and unpredictable. Some patients remain well compensated for many years [100]. Treatment should be changed to standard therapeutic agents for systolic heart failure including diuretics, angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers), beta-blockers, digoxin, and aldosterone inhibitors. Verapamil and disopyramide should be discontinued. Right atrial and right ventricular sequential pacing with short atrioventricular delay that had been applied for gradient should be discontinued. Patients who fail to respond to treatment with beta-blockers, diuretics, afterload-reducing agents, and ICDs with biventricular pacing should be considered for heart transplantation, depending on age and suitability [103–105].

A small percentage of patients who develop systolic heart failure may revert back to the original phenotype with normal systolic function and left ventricular outflow tract obstruction. Medications will need to be readjusted to treat symptomatic hemodynamics that may redevelop. Thus, careful attention to the physical examination and serial echocardiograms, especially for changes in the exam or clinical status, is paramount [103–105].

Takotsubo Cardiomyopathy in Obstructive HCM

Patients with hypertrophic cardiomyopathy may develop an acute takotsubo cardiomyopathy similar to patients

with normal hearts. Excessive sympathetic stimulation, vascular abnormalities, and metabolic disturbances have been suggested to be responsible [106]. Patients may develop transient acute severe systolic dysfunction, congestive heart failure, or cardiogenic shock [107]. These patients may need temporary hemodynamic support and will usually normalize their ventricular function within days to weeks. If they develop hypotension and left ventricular outflow tract obstruction, they should be treated with phenylephrine for blood pressure support. Dobutamine and inotropes (including digoxin) should always be avoided in patients with dynamic left ventricular outflow tract obstruction. In rare cases, placement of ventricular assist device may prove necessary; due to its ability to assist in ejection of blood directly from the LV to the aorta, the Impella device may be ideal. An intra-aortic balloon pump, in contrast, is contraindicated due to the worsening of outflow tract obstruction produced by the drop in systolic afterload.

Takotsubo Cardiomyopathy with LV Outflow Obstruction

There are a series of patients without HCM that present with takotsubo cardiomyopathy and develop transient left ventricular outflow tract obstruction or dynamic intraventricular pressure gradients [108, 109]. These patients resemble hypertrophic obstructive cardiomyopathy patients because of their similar obstructive pathophysiology. The mechanism of obstruction in these patients is uncertain; it may develop as a result of LV outflow tract obliteration secondary to mid and distal LV dyskinesis and compensatory basal wall hyperkinesia [109, 110]. It is imperative to recognize dynamic LV gradients because they require a different treatment approach than patients with acute systolic dysfunction alone. These patients are best treated by augmenting left ventricular (LV) volume, reducing LV ejection velocity, and supporting the blood pressure with a combination of intravenous fluids, beta-blockers, and phenylephrine as indicated. Again, inotropes and digoxin are contraindicated. As with patients with HCM and secondary takotsubo cardiomyopathy, patients with continued hypotension despite the above measures may benefit from Impella ventricular assist device and avoidance of the intra-aortic balloon pump.

Novel Pharmacotherapy for HCM

New approaches to medical therapy have accelerated in recent years including industry-sponsored trials. More information can be found in the chapter on novel therapies.

Perhexiline The energy needs of the heart are prodigious. The daily turnover of cardiac ATP, 6–35 kg, is many times the mass of the heart itself and its myocardial ATP pool. In light of this exceedingly high demand, subtle variations in the efficiency of energy generation by a switch in fuel type may have a major impact on cellular energy levels.
Inefficient use of intracellular energy has been identified as a potential pathophysiologic link between mutations and development of the HCM phenotype and symptoms. The development of metabolic magnetic resonance imaging now allows in vivo assay of myocardial energetics, comparison of patients and normals, and objective assessment of therapeutic efficacy [111].

In HCM phosphocreatine/ATP ratios are decreased [112]. Energy depletion in HCM may contribute to inability to increase cardiac output with exercise. The inability of the LV to maintain mid-systolic ejection in the face of severe obstruction, the echocardiographic finding of a mid-systolic drop in LV ejection velocities, is almost certainly a manifestation of energy depletion.

In HCM patients, investigators from the United Kingdom administered perhexiline 100 mg/day adjusted to keep serum level from 0.15 to 0.6 mg per liter to avoid drug toxicity. Perhexiline improved the myocardial ratios of phosphocreatine to ATP from 1.27 to 1.73 compared to no change in placebo groups. There was an improvement in the primary endpoint, peak oxygen consumption, with VO2 increasing from 22 ± 0.2 to 24 ± 0.2 vs. no change in the placebo treated patients. An improvement in exercise-related diastolic function was shown by New York Heart Association, and the quality of life improved in parallel.

Perhexiline toxicity is related to drug serum levels. It is now appreciated that with appropriate dosing based on genotype and drug concentration assays that the incidence of toxicity can be greatly reduced or eliminated [113]. A randomized clinical trial of perhexiline in hypertrophic cardiomyopathy is ongoing.

Late Sodium Current Blockade Abnormally prolonged action potential has been shown in isolated HCM cardiomyocytes harvested at myectomy. This abnormality has been related to an increase in the late sodium current (not observed in normals) and prolonged calcium transients with diastolic calcium overload and myocyte tension development. These abnormalities in turn lead to prolonged action duration, early afterdepolarizations, and enhanced arrhythmogenicity. A randomized placebo controlled trial of late Na current blockade has recently been stopped prematurely after there were increased arrhythmias and ICD discharges in the active agent arm of a parallel, non-HCM study. The outcome of the primary HCM endpoint, exercise capacity as assessed by maximum oxygen consumption, has not yet been analyzed.

Fibrotardive Therapy Fibrosis in HCM is an important cause of diastolic dysfunction and is thought to contribute to arrhythmic burden and sudden death. Fibrosis can be interstitial, replacement, and perivascular [114]; its presence and extent can now be imaged with CMR. Preventing fibrosis or reversing fibrosis has emerged as important goals in HCM patients. Mouse models have indicated that sarcomeric mutations promote trophic mediators of fibrosis especially Tgf-β. Animal models have indicated the potential of angiotensin receptor blockade to prevent fibrosis in mouse HCM; these effects appear mediated by blockade of angiotensin II and decreased expression of transforming growth factor β. Preliminary small trials in humans have suggested benefit though they cannot be considered conclusive [115]. A 2-year multicenter clinical trial of genotype positive, phenotype negative, or mild HCM, comparing valsartan-treated and placebo-treated individuals, is recruiting patients. Sarcomere mutation carriers with asymptomatic or mildly symptomatic overt disease (NYHA class I–II) and mutation carriers without left ventricular hypertrophy (LVH) are included.

The effect of aldosterone blockade with spironolactone has been evaluated and shown to be ineffective [116]. Maron randomized 53 HCM patients to 50 mg of spironolactone or placebo for 1 year and found no difference in serum markers of collagen synthesis, fibrosis by CMR, peak VO2, diastolic function by echo, and heart failure symptoms. Whether spironolactone or similar aldosterone blockade might prevent HCM has not been determined.

Small-Molecule Inhibitors of Myosin Activity

A small-molecule inhibitor of sarcomeric contractility (MYK-461) suppresses HCM phenotype development in mice with a gain-of-function mutation in myosin, in parallel with reductions in fractional shortening and ATPase activity [117]. It is a potent negative inotrope and will first be tested in obstructive HCM to decrease gradient. Data in animals demonstrated that correction of gain of function at the myofilament level resulted in a normalized cellular metabolic state and improvement in developmental abnormalities on light microscopy. These improvements might stem directly from the correction of the myofilament gain of function from more efficient energy utilization and less substrate depletion.

Conclusions

Medical therapy for HCM is a complex interplay, guided by the exam, echocardiographic findings, and patient symptoms and requires a significant experience treating hundreds if not thousands of patients. This chapter has reviewed the current thoughts on medications, how to initiate and titrate them, and what sequence to utilize them in for the different subtypes of HCM, including obstructive and nonobstructive, apical, and mid-ventricular obstruction phenotypes. This being said, because of the unique and individualized pathophysiology, and lack of randomized controlled data, medical therapy for HCM is an art and not entirely a science.

Clinical Pearls

- Reassure patients that most patients with HCM have a normal life expectancy. This will relieve a significant emotional burden.
- The history and examination, aided by echocardiography, should be relied on to determine the appropriate use of medications.
- Cardiac auscultation is useful to assess the severity of the left ventricular outflow tract gradient. The loudness and length of the murmur correlate roughly with the severity of the left ventricular outflow tract gradient.
- Utilizing a heart model helps patients understand HCM.
- A patient information sheet is recommended to explain exercise recommendations, screening for arrhythmias with Holter monitoring, gene testing, family screening, coronary risk management, reporting symptoms, follow-up, and suggested web sites. Letting patients know that this is a long-term relationship and that their understanding of the disease will grow over time is oftentimes helpful.
- Beta-blockers are a first-line therapy and are most effective for management of mildly affected patients. But, they are not expected to decrease resting gradients.
- Verapamil is useful if beta-blockers are ineffective or cause significant side effects. They may be particularly useful in nonobstructive HCM.
- Combining beta-blockers and calcium channel blockers is not generally more effective than either drug. The combination may be useful when there is concomitant hypertension. One must beware of severe bradycardia in the elderly.
- Diuretics are useful to relieve pulmonary or systemic congestion. HCTZ or combinations with triamterene can usually be tried first in those with mild hypervolemia; slower diuresis is in order to avoid dramatic shifts in filling pressure and provocation of outflow tract obstruction.

- Nitrates must be used cautiously due to the propensity to provoke outflow tract obstruction but may be useful drugs to treat angina in nonobstructive cases.
- Many patients, whose refractory symptoms are due to the effects of left ventricular outflow tract obstruction, will have a significant clinical improvement with disopyramide. The benefits are seen early.
- Anticoagulation for atrial fibrillation is indicated. Although warfarin is the gold standard, newer agents may be reasonable alternatives.
- For heart failure symptoms and angina, use the lowest effective dose of a medication, and assess the response after several weeks before titrating medications.
- Consider the possibility that medications are causing the patients symptoms. Shortness of breath, fatigue, dizziness, and syncope can be side effects of beta-blockers and calcium channel blockers.
- Many clinicians believe that disopyramide is the most potent agent currently available for control of LVOT gradients and disabling symptoms. Disopyramide may cause a dry mouth and/or urinary retention. Lowering the dose may help minimize the side effects. Pyridostigmine has been used to counteract these side effects.
- Nitroglycerin patches can be adjusted by patients and can be applied and removed according to complaints of chest pain and the development of side effects. Patches can be applied for as little as 30 min or as long as 12 h. Nitrates are usually well tolerated by most HCM patients, but many experts avoid nitrates altogether and prefer other agents for angina.
- The jugular venous pressure and abdominal jugular reflux are very useful for assessing elevated cardiac filling pressures, as well as the need for and the titration of diuretics.
- HCM patients with volume overload tolerate diuretics very well, including high doses of intravenous diuretics to achieve euvolemia.
- Patients with fluid retention should be taught how to titrate their oral diuretics at home. Daily weight recordings are often helpful.
- Beta-blockers, anticoagulants, and contemplation of rhythm control methods should be the first-line treatments for atrial fibrillation.
- Exertional syncope and/or dizziness determined to be due to a significant left ventricular outflow tract gradient respond well to beta-blockers alone or beta-blockers with disopyramide (Fig. 15.5). However, unexplained syncope may be due to an arrhythmic cause. Unexplained syncope should prompt a discussion with the patient of sudden death prevention strategies including ICD and/or surgery.
- The clinical evaluation combined with detailed echocardiography is useful to diagnose unusual presentations of HCM and conditions mimicking HCM.
- Dobutamine can produce hemodynamic disturbances including left ventricular outflow tract obstruction and mid-ventricular obstruction in normal patients. These patients should not be labeled as HCM patients unless they also have exercise-induced LV outflow obstruction.
- Treatments of choice for patients without HCM who develop left ventricular or mid-ventricular obstruction are avoiding inotropes, increasing fluid administration, and initiating a beta-blocker.
- Phenylephrine is a drug of choice for treating HCM patients with hypotension that is unresponsive to intravenous fluids. The use of ventricular assist devices that sit across the outflow tract may be considered. The IABP should be avoided in these settings.
- HCM patients who develop acute or chronic left ventricular systolic dysfunction can improve and normalize their systolic function.
- HCM patients who have persistent severe left ventricular systolic dysfunction and disabling symptoms after 1 year of appropriate medical treatment have a poor prognosis, and cardiac transplantation should be considered.

Questions

Hypertrophic Cardiomyopathy Medications: Questions and Answers

1. What medications can prevent adverse remodeling, especially worsening left ventricular hypertrophy in patients with hypertrophic cardiomyopathy?
   A. Beta blockers.
   B. Amiodarone.
   C. Calcium channel blockers.
   D. Disopyramide.
   E. Spironolactone.
   F. No medication prevents adverse remodeling.

Answer: F
No medication has been shown to prevent worsening/progression of left ventricular hypertrophy or the development of symptoms.

2. What is the best management strategy for patients with left ventricular outflow tract gradients that are above 50 mm?
   A. Beta blockers
   B. Myectomy
   C. Calcium channel blockers
   D. Disopyramide
   E. Alcohol septal ablation
   F. Symptoms guided

   Answer: F
   Treatment should be guided by symptoms and not by the echocardiogram or cardiac catheterization results especially the severity of the left ventricular outflow tract gradient. Asymptomatic patients do not need any treatment, although patients with severe gradients should be objectively followed. Symptomatic patients should always be started on medical management prior to considering septal reduction therapy. Beta blockers are the initial first-line medication unless they are contraindicated.

3. When is it appropriate to refer patients for septal reduction therapy such as myectomy or alcohol septal ablation?
   A. Left ventricular outflow tract gradient above 50 mm
   B. Anatomy suitable for myectomy or alcohol septal ablation
   C. Symptoms refractory to medical treatment
   D. Expertise of the institution
   E. Need all of the above

   Answer: E
   Patients who have symptoms related to hypertrophic obstructive cardiomyopathy such as shortness of breath, chest pain, or exertional syncope related to the outflow tract obstruction should always be treated with medications prior to considering invasive treatment such as myectomy or alcohol septal ablation. Anatomy must be suitable for one or the other procedure, and peak gradients should be at least 50 mm Hg. Septal reduction therapy should only be performed at institutions that have performed over 50 procedures or by operators who have performed more than 20.

4. What is the first-line drug to prescribe patients with symptomatic hypertrophic obstructive cardiomyopathy, and how should these drugs be titrated?
   A. Beta blockers
   B. Amiodarone
   C. Calcium channel blockers
   D. Disopyramide
   E. Spironolactone

   Answer: A
   Beta blockers should always be started prior to other medications as they have an excellent track record in treating patients with dilated cardiomyopathy and coronary artery disease. The lowest effective dose should be used and should be guided according to the patient's clinical response. Each patient will require a different dose based on the blood pressure, pulse rate, and the patient's tolerance of beta blockers. The left ventricular outflow tract gradient on the echocardiogram or cardiac catheterization should not be used to determine the ineffectiveness of medications, but instead one should rely on the clinical response of the patient and treat them according to how they feel.

5. What is the role of calcium channel blockers in the treatment of hypertrophic obstructive cardiomyopathy?
   A. Improve diastolic dysfunction.
   B. Reduce left ventricular outflow tract gradient.
   C. Treat angina.
   D. Improve survival.
   E. Reduce left ventricular hypertrophy.

   Answer: C
   Non-dihydropyridine calcium channel blocker such as verapamil and diltiazem are useful medications to treat patients with hypertrophic obstructive cardiomyopathy if patients fail beta blockers. Verapamil and diltiazem should generally not be combined with a beta blocker in elderly patients as the combination can cause significant bradycardia and/or hypotension and do not appear to be more effective than using the drug without a beta blocker. Calcium channel blockers should be avoided in patients with volume overload manifested by jugular venous distention, significant shortness of breath, and edema as they can aggravate congestive heart failure and cause hypotension and possibly death. Calcium channel blockers do not improve diastolic dysfunction and should never be given to patients who are volume overloaded. Calcium channel blockers in high doses should be avoided in patients with significant resting left ventricular outflow tract obstruction with gradients above 50 mm as they can worsen left ventricular outflow tract obstruction due to their vasodilator properties and cause hypotension. Calcium channel blockers are useful medications for treating chest pain and shortness of breath in patients with nonobstructive forms of hypertrophic cardiomyopathy.

6. Which is the best medication to reduce the left ventricular outflow tract obstruction in symptomatic patients with hypertrophic obstructive cardiomyopathy?

A. Beta blockers
B. Amiodarone
C. Non-dihydropyridine calcium channel blockers
D. Disopyramide
E. Spironolactone

Answer: D
Disopyramide is the most useful medication to treat patients whose symptoms are related to significant left ventricular outflow tract obstruction, as it lowers both the resting and provocable left ventricular outflow tract gradient. Disopyramide should be used in combination with a beta blocker to provide AV delay should atrial fibrillation occur, due to their anticholinergic effects.

7. How should hypertrophic cardiomyopathy patients with frank congestive heart failure and fluid retention be treated?
A. Beta blockers
B. Diuretics
C. Calcium channel blockers
D. Disopyramide
E. Myectomy

Answer: B
Patients with hypertrophic cardiomyopathy may have significant diastolic dysfunction causing fluid retention. The best medications for fluid retention are diuretics. Diuretics should be used cautiously in patients with hypertrophic obstructive cardiomyopathy to avoid causing hypotension and worsening of the left ventricular outflow tract gradient. The lowest effective dose of the diuretic should be used to achieve euvolemia. Mild diuretics such as thiazides should be tried first, moving to loop diuretics such as furosemide for more significant volume overload. Right heart catheterization may be needed to confirm the degree of fluid overload and guide choice of diuretic.

8. How should patients with hypertrophic cardiomyopathy and angina be treated?
A. Beta blockers
B. Amiodarone
C. Ranexa (ranolazine)
D. Disopyramide
E. Plavix

Answer: A
One should always rule out coronary artery disease as a cause for chest pain and angina in patients with hypertrophic cardiomyopathy. Calcium channel blockers and beta blockers are the first-line drugs for treating patients with angina due to hypertrophic cardiomyopathy. In patients with obstruction at rest or after exercise, an effort should be made to decrease LVOT gradient with medication, with beta blocker and disopyramide being the most effective combination. In nonobstructive hypertrophic cardiomyopathy patients who fail to respond to beta blockers or calcium channel blockers, a trial of low-dose nitrates such as a nitroglycerin patch may be useful.

9. When is an anticoagulant indicated for hypertrophic cardiomyopathy patients who develop atrial fibrillation?
A. CHADS score above 2
B. CHA2DS2-Vasc above 2
C. History of stroke
D. Significant left atrial enlargement
E. Presence of atrial fibrillation or atrial flutter

Answer: E
The CHADS and CHAD2DS2-Vasc scores are not applicable in HCM patients with Afib. Patients with hypertrophic cardiomyopathy and atrial fibrillation/flutter are at high risk of embolic stroke and should be started on warfarin, a direct thrombin inhibitor or a novel oral anticoagulant (NOAC).

10. If a symptomatic obstructive patient has dry mouth or constipation after beginning oral disopyramide. What would be the best therapeutic strategy?
A. Decrease the dose till side effects abate.
B. Administer with pyridostigmine sustained release to relieve vagolytic side effects, and continue a therapeutic dose of disopyramide.
C. Stop disopyramide.
D. Add 500 ccs of electrolyte-repleted oral fluids daily.

Answer: B
Pyridostigmine sustained release through its cholinesterase inhibition restores vagal tone. Lowering the dose or stopping disopyramide completely might preclude disopyramide benefit for this patient.

11. A symptomatic obstructive HCM patient has been started on disopyramide 500mg/day in divided doses. ECG 3 days after beginning therapy shows that the QTc has increased from 455 msec to 490 msec. What is the most appropriate response?
A. Continue therapy and observe for symptom relief. Everyone responds this way.
B. Administer an ampule of calcium gluconate.
C. Hold one dose of disopyramide, and repeat the ECG, and restart disopyramide at lower dose.
D. Transfer to an ICU bed for close monitoring.

Answer: A

Disopyramide predictably prolongs the QTc. However, as with some other agents like amiodarone that widen QTc, pro-arrhythmic complications do not appear to occur. It is recommended to avoid co-administering other drugs that prolong the QTc like macrolides, quinolones, and certain SSRIs. Also it is advisable to avoid hypokalemia. If a patient on disopyramide must be given one of the above-mentioned antibiotics, one should hold the disopyramide till the course of medication is completed.

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Hypertension and Hypertrophic Cardiomyopathy

16

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Key Points

- Hypertension is present in approximately half of patients with hypertrophic cardiomyopathy.
- Hypertension is associated with higher incidence of atrial fibrillation and worse outcome in patients with hypertrophic cardiomyopathy.
- Similar structural abnormalities in the left ventricular myocardium are found in patients with hypertrophic cardiomyopathy and hypertensive heart disease but more prominent in hypertrophic cardiomyopathy.
- There are no randomized studies of antihypertensive drugs that show reduction in cardiovascular events in patients with hypertrophic cardiomyopathy.
- Guidelines for the management of hypertrophic cardiomyopathy caution against the use of several types of blood pressure-lowering medications because of the potential of worsening left ventricular outflow tract obstruction.

Introduction

Hypertension (HTN), defined as systolic blood pressure (BP) ≥140 mm Hg or diastolic BP ≥90 mm Hg or antihypertensive medication use, has a prevalence of over 1/3 adults ≥20 years old in the United States [1]. The prevalence increases with age, and >60% of adults in the United States above the age of 60 have HTN [1]. Approximately 15% of persons with HTN are unaware of their condition, and 11% of patients have resistant HTN, requiring treatment with at least three antihypertensive medications from different drug classes [2]. The prevalence of HTN has increased across recent years, with projections for continued increase in the next decade [1].

In addition to high prevalence of HTN in the general population, HTN is present in 30–50% of patients diagnosed with hypertrophic cardiomyopathy (HCM) [3–5]. The high prevalence of HTN in adults as well as HCM patients emphasizes the clinical relevance of this condition to patients with HCM. In this chapter, the overlap between HCM and HTN will be discussed. Specifically, the objectives of this chapter are to (1) describe the many similarities between HTN and HCM myocardial changes, (2) discuss differentiation between hypertensive cardiomyopathy and HCM, and (3) describe the management of HTN in patients with obstructive or nonobstructive HCM.

Comparison of Structural Changes in HCM and Hypertensive Heart Disease

Left ventricular hypertrophy (LVH) is a primary, often genetically caused abnormality in patients with HCM, yet hypertrophy is a secondary process in hypertensive heart disease in response to chronically elevated afterload. Despite differences in the pathogenesis of LVH, there are surprising similarities in the structural myocardial changes in both these conditions that seem counterintuitive based on a number of misconceptions. Cardiomyocyte hypertrophy, alterations in the extracellular matrix with fibrosis, and abnormalities of the intramyocardial coronary vasculature are common myocardial abnormalities in both HCM and hypertensive heart disease. Although myocyte disarray is a more specific, pathologic finding in HCM, the use of this

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criterion to differentiate the conditions clinically is very limited and impractical.

Left ventricular mass is increased in both HCM and hypertensive heart disease. Approximately 60% of patients with mild to moderate HTN have been found to have LVH by echocardiography [6]. Because LVH in hypertensive heart disease is secondary to a global increase in afterload, the pattern of hypertrophy is expected to be more concentric than asymmetric as in HCM. In hypertensive heart disease, either global concentric or eccentric hypertrophy may occur. The ratio of LV wall thickness to diastolic diameter, termed the relative wall thickness, is increased (>0.42) in concentric LVH and less than this degree in eccentric hypertrophy [7]. Hypertensive heart disease may be associated with both patterns of LVH. Patients with concentric LVH have been found to have higher systolic blood pressures and total peripheral resistance than patients with eccentric LVH [8]. In addition, patients with concentric LVH have significantly higher ambulatory BP measurement [9], suggesting a longer duration of exposure to increased afterload may stimulate a concentric response.

In HCM patients, the anterior ventricular septum is the most frequently hypertrophied segment (96%), followed by the inferior septum (66%) and lateral free wall (42%) [10]. The posterior free wall is often spared in HCM and is thickened in less than 20% of patients [10]. As a result, the pattern of LVH is asymmetric, defined as ratio of basal septal wall thickness to posterior wall thickness ≥1.3 by transthoracic echocardiography (parasternal long axis view). However, in HCM patients with concomitant hypertension, posterior wall thickness has been found to be mildly hypertrophied in over half of patients compared with HCM patients without hypertension [6]; yet because the mean septal wall thickness in HCM cohorts is generally >20 mm, asymmetric hypertrophy persists in HCM patients with HTN. Even when severe LVH occurs in the setting of hypertensive heart disease, the pattern of LVH remains concentric [4], and less than 5% of patients with hypertensive heart disease met criteria for asymmetric septal hypertrophy [6]. However, a racial difference in pattern of LVH has been recognized, as black patients with HCM more commonly have a concentric pattern of hypertrophy compared with white HCM patients (9.3 vs. 1.5%, respectively), possibly related to a higher prevalence of hypertension (58% vs. 32%, respectively) [11]. As a corollary to asymmetric septal hypertrophy, different patterns of septal hypertrophy have been described, including sigmoid, reverse sigmoid, neutral, and apical [12]. Among these, the reverse sigmoid morphology was associated with a high prevalence of pathogenic myofilament mutation (89%) compared with other morphologies, and sigmoid septal curvature had a very low prevalence (8%) [12].

Although the clinical diagnostic criteria for HCM generally is based on left ventricular wall thickness 15 mm or more, this value represents two standard deviations greater than normal wall thickness in the general population and is not specific to HCM. In early studies of echocardiographic comparisons between HCM and hypertensive heart disease, mean wall thickness in patients with hypertensive heart disease was 19 mm [4]. In a more recent study of cardiovascular MRI comparing HCM to HTN, both groups of patients had similar left ventricular mass index, even though half of HCM patients had resting left ventricular outflow obstruction [13].

Myocardial fibrosis, as visualized by late gadolinium enhancement with magnetic resonance imaging, is found in 60–70% of HCM patients [13, 14]. The most commonly involved regions are the right ventricular insertion sites as seen on a short axis view. In hypertensive heart disease, extracellular volume is also increased due to fibrosis, which has been found in half of patients by cardiovascular MRI, but the amount of late gadolinium enhancement as a percentage of left ventricular mass is significantly lower than in HCM patients (5% vs. 12%, $p < 0.001$) [13]. Because late gadolinium enhancement is dependent on more concentrated areas of fibrosis and the relative contrast of diffuse fibrosis compared to normal myocardium, native (non-contrasted) T1 mapping has been used to assess extracellular volume. In HCM, native T1 values are higher than patients with hypertension, with or without left ventricular systolic dysfunction [15]. Furthermore, HCM patients with late gadolinium enhancement had the highest T1 values; and higher T1 values were associated with reduced peak systolic circumferential strain and early diastolic strain rates [15].

In summary, given the similar structural changes in both HCM and HTN, a number of findings may be used as a composite to differentiate these two conditions. By history, a family history of HCM, particularly in an immediate family member, suggests HCM as the cause of LVH. Conversely, a negative family history but long-standing, refractory HTN supports HTN as the cause. Per the 2011 American Heart Association and American College of Cardiology guideline for the *Diagnosis and Management of Hypertrophic Cardiomyopathy*, "genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy is recommended in patients with an atypical clinical presentation of HCM or when another genetic condition is suspected" [16]. Yet the yield of genetic testing for pathogenic HCM mutation is low among patients without family history of HCM (50% or less) and so may not clarify the cause of LVH. As described above, an asymmetric pattern of septal hypertrophy and non-sigmoidal septal curvature is strongly associated with HCM. Cardiac MRI finding of late gadolinium enhancement, particularly at right ventricular insertion sites, also is consistent with HCM (Table 16.1).

The combination of asymmetric septal hypertrophy and reduced global left ventricular systolic strain has been found to have high specificity for differentiating HCM from HTN [17, 18]. In a small study of 20 patients with HCM and 14 patients with HTN evaluated with transthoracic echocardiog-

Table 16.1 Differentiation of HCM and hypertensive heart disease

Clinical variable	HCM	HTN
Family history of HCM	+	–
Long-standing, refractory or resistant HTN	–	+
Asymmetric septal hypertrophy	+	–
Non-sigmoidal septal hypertrophy	+	–
Hyperdynamic left ventricular function (high ejection fraction)	+	–
Increased left ventricular volume or end-diastolic dimension	–	+
Mid-septal late gadolinium enhancement (right ventricular insertion sites)	+	–
Late gadolinium enhancement >5% of LV mass	+	–
Reduced left ventricular systolic strain	+	–
Regression of LVH after treatment of HTN	–	+

+ feature present, – feature absent

raphy, global left ventricular systolic strain value of −10.6% discriminated between HCM and HTN with a sensitivity of 85.0%, specificity of 100.0%, and predictive accuracy of 91.2%; the combination of the septum/posterior wall thickness ratio and reduced strain discriminated HCM from H-LVH with a predictive accuracy of 96.1% [18].

Prognostic Implications of HTN in HCM Patients

In patients with HCM, concomitant HTN is associated with increased symptoms by NYHA class in younger patients, but the severity of symptoms was similar in older adults [19]. Hypertension is independently associated with incidence of atrial fibrillation in long-term follow-up of HCM patients [5], likely related to its influence on left atrial volume. In addition, HTN has been found to be independently associated with a higher risk of cardiovascular death, cardiac arrest, or appropriate device therapy in HCM [11].

Management of HTN in HCM Patients

According to the Eighth Joint National Committee recommendations for the management of HTN, a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) should be the initial treatment of HTN in the general, nonblack population, including patients with diabetes mellitus [20]. In the black population, initial treatment with a thiazide-type diuretic or CCB is recommended [20]. Although multiple drugs have been evaluated to treat HCM-related symptoms, there are few data to inform the appropriate treatment of HTN in HCM patients. In the following section, the effects of various antihypertensive drug classes will be discussed.

Beta-Blocking Drugs

Beta-blockers are the recommended class of drugs in the treatment of symptomatic HCM, including both obstructive and nonobstructive forms [16]. For the treatment of HTN, multiple randomized clinical trials have evaluated the effects of beta-blockers on cardiovascular events (stroke and myocardial infarction) and overall mortality. Atenolol was the beta-blocker most commonly studied. A review of the trial results in HTN showed that initiating treatment with beta-blockers leads to modest reductions in cardiovascular disease, but little or no reduction in overall mortality [21]. In general, beta-blocker reductions in cardiovascular events and mortality were found to be inferior to other antihypertensive drugs [21]. However, in the losartan intervention for endpoint reduction in hypertension (LIFE) study, atenolol therapy (50–100 mg daily) reduced systolic blood pressure by a mean of 29 mm Hg, similar to losartan [22]. Beta-blocking drugs with vasodilator effects may be associated with greater reduction in blood pressure but are not generally recommended in patients with obstructive HCM owing to concern for exacerbation of outflow tract obstruction [23].

Calcium Channel Antagonists

Verapamil therapy is recommended for the treatment of HCM-related symptoms in patients who do not respond to beta-blocking drugs or who have side effects or contraindications to beta-blocking drugs [16]. Diltiazem has not been as well studied as verapamil for symptomatic HCM but has been reported to improve left ventricular diastolic function in one small study (n = 16) but with significant worsening of left ventricular outflow obstruction in one patient [24]. In HCM patients on maximally tolerated beta-blocking drugs and persistently elevated blood pressure, the safety of combination treatment with verapamil is unknown and potentially may result in high degree atrioventricular block or significant bradycardia [25]. Nifedipine or other dihydropyridine CCB are generally not recommended in HCM patients with resting or provocable left ventricular outflow tract obstruction due to the potential of increasing dynamic obstruction [16].

Renin-Angiotensin-Aldosterone System Antagonists

Losartan has been studied in a randomized, placebo-controlled trial of obstructive and nonobstructive HCM patients for left ventricular mass regression by cardiac MRI. In this study, the mean reduction in systolic blood pressure was 6 mm Hg in the losartan-treated patients [26]. Although there was no difference in left ventricular mass

endpoint, losartan was well tolerated in both obstructive and nonobstructive HCM patients [26]. Based on this study, it is reasonable to consider losartan for the treatment of HTN in HCM patients on maximally tolerated dose of either beta-blocking drugs or CCB.

Spironolactone has been found to reduce the expression of a pathogenic HCM mutation in a mouse model, including inhibiting myocardial fibrosis and improving left ventricular diastolic function [27]. However, this agent has not been studied in human HCM. Spironolactone, at doses from 12.5 to 100 mg daily, is a very effective therapy for resistant hypertension, associated with reduction in systolic blood pressure of 22 mm Hg [28]. In general, a lower dosage (≤50 mg daily) has less natriuretic properties and may not lower preload or worsen dynamic outflow tract obstruction.

Diuretics

Diuretics should be used cautiously in patients with HCM, including patients with nonobstructive (IIa recommendation) or obstructive HCM (IIb), with persistent dyspnea despite treatment with beta-blocking drugs or CCB [16]. In a small study of 13 patients with HCM, including 7 patients with resting left ventricular outflow tract gradient >30 mm Hg, furosemide 20 mg intravenously was not associated with worsening systemic blood pressure, cardiac index, systemic vascular resistance index, or overall exercise capacity during upright, bicycle exercise [29]. Milder diuretics such as thiazide-type diuretics may be better tolerated in the HCM patient with mild signs of hypervolemia, with loop diuretics reserved for patients with frank pulmonary edema and significant volume overload.

Refractory HTN

Some patients with HCM, either obstructive or nonobstructive, may have resistant HTN. This becomes a particular challenge in obstructive patients, where the available medications may be limited out of fear or worsening obstructive physiology. Most experts advise escalation of beta-blockers and then addition of non-dihydropyridine calcium channel blockers if there are no limitations by bradycardia or conduction disease. If this fails to sufficiently improve the blood pressure, then a mild diuretic may be added, such as spironolactone or hydrochlorothiazide. If patients continue to have refractory HTN, then additional medications such as clonidine or amlodipine may be attempted cautiously. Most patients can be controlled with the combination of these medications. However, on rare occasions, the best approach may be to proceed with septal reduction therapy to eliminate the obstruction and then utilize standard guideline-based HTN therapies. Although HCM guidelines do not support septal reduction for this indication, anecdotally it has worked quite well and is reasonable to consider in the rare patient.

Clinical Pearls

- The pattern of hypertrophy in HCM is typically asymmetric with greater septal than posterior wall thickness, even when concomitant hypertension is present.
- In addition, noninvasive imaging findings of hyperdynamic left ventricular ejection, reduced global left ventricular strain, and late gadolinium enhancement at right ventricular insertion sites differentiate HCM from hypertensive heart disease.
- Although HTN in HCM patients has been associated with worse prognosis, it is not known whether effective treatment of HTN improves outcome.
- Beta-blocking drugs or verapamil should be used as the initial treatment of HTN in HCM patients, regardless of whether the patient has HCM-related symptoms.
- An angiotensin receptor blocker (ARB) can safely be used as a secondary antihypertensive agent in patients with obstructive or nonobstructive HCM, although the patient should be monitored for worsening obstructive symptoms.
- If hypertension is resistant, consideration of an aldosterone antagonist at low dose for additional blood pressure lowering is reasonable; other mild diuretics may be considered in the hypervolemic patient. Renal function and potassium level should be monitored after its initiation, especially if used in conjunction with an ARB.
- Clonidine is perhaps the final medication that may be tried in refractory, severe HTN. However, in a subset of patients the best approach may be to eliminate obstruction via septal reduction therapy, thereby allowing for guideline-directed HTN management.

Questions

Multiple-Choice Questions

1. A 58-year-old man is referred for evaluation of mild dyspnea on exertion and abnormal EKG, which shows left ventricular hypertrophy with repolarization abnormality. His family history is negative for hypertrophic cardiomyopathy (HCM) or sudden death. He has a history of hypertension (HTN) for 10 years, treated with lisinopril

with good control. Transthoracic echocardiogram shows left ventricular ejection fraction 60%, septal wall thickness 15 mm, and posterior wall thickness 13 mm, with mild mitral regurgitation. There is grade 1 diastolic dysfunction but no systolic anterior motion of the mitral valve or dynamic left ventricular outflow obstruction.

Which of the following tests would be most useful to differentiate HCM from hypertensive heart disease?
A. Genetic testing for sarcomeric protein mutation.
B. Cardiac magnetic resonance imaging.
C. 48-hour Holter monitor
D. Stress echocardiogram.

Answer: The correct answer is **B**. HCM is typically diagnosed when there is left ventricular hypertrophy >14 mm in any region that is not secondary to another condition. This patient has a history of HTN of long duration but controlled with single drug. The finding of left ventricular hypertrophy may be due to HTN or HCM, and mild dyspnea on exertion may be related to left ventricular diastolic dysfunction. Cardiac MRI has been shown to identify left ventricular hypertrophy that is increased in degree compared with echocardiography owing to its better spatial resolution, particularly in the anterolateral wall. In addition, cardiac MRI may identify other findings suggesting of HCM, such as late gadolinium enhancement (myocardial fibrosis) and abnormal mitral valve anatomy. Genetic testing (answer A) is incorrect because the yield for genetic testing is low (approximately 50%) in patients diagnosed with HCM without a family history of HCM. Although Holter monitoring (answer C) may be helpful for risk stratification in patients with diagnosis of HCM, the results are not diagnostic for HCM. A stress echocardiogram (answer C) similarly does not provide diagnostic information for HCM over resting transthoracic echocardiogram but may help to identify causes of symptoms in HCM such as provocable, dynamic left ventricular outflow obstruction.

2. A 45-year-old woman with HTN for 5 years present for evaluation of dyspnea on exertion. She has been treated with amlodipine 5 mg daily and hydrochlorothiazide 25 mg daily, but her blood pressure has remained elevated (systolic BP range 15–160 mm Hg on home measurements). She has had gradual worsening of dyspnea on exertion for 1 year, now with dyspnea walking up two flights of stairs. She has no history of angina or syncope. Family history is notable for HTN in both parents. Electrocardiogram shows sinus rhythm, left ventricular hypertrophy with repolarization abnormality. Transthoracic echocardiogram shows left ventricular ejection fraction 65%, septal wall thickness 18 mm, and posterior wall thickness 14 mm; mild chordal systolic anterior motion with resting left ventricular outflow tract velocity 1.5 m/sec; left atrial enlargement (area = 26 cm^2); and grade 1 diastolic dysfunction.

What diagnostic test would be most useful to further manage her condition?
A. 24-hour urine collection for metanephrines and VMA
B. Abdominal CT scan with contrast.
C. Stress echocardiogram.
D. Serum and urine protein electrophoresis and plasma free light chain measurement.

Answer: The correct answer is **C**. Although this patient has HTN that has not been adequately controlled, her degree of left ventricular hypertrophy and its asymmetry suggest possible HCM rather than hypertensive heart disease. She has NYHA 3 symptoms but only mild diastolic dysfunction by echocardiography. Stress echocardiography with exercise would provide information regarding her exercise capacity, blood pressure response, and outflow tract gradient at peak exercise. Approximately 30–40% of HCM patients have no significant outflow tract obstruction (<30 mm Hg) at rest but a provoked gradient (>50 mm Hg) at peak exercise. These patients are considered to have obstructive HCM, and medical therapy for outflow tract obstruction may improve her symptoms. Answers A and B are incorrect because this patient does not have refractory HTN (she is not on maximal doses of three antihypertensive drugs). Answer D is incorrect because she has no other clinical findings suggestive of an infiltrative cardiomyopathy such as AL amyloidosis.

3. A 36-year-old woman is referred for evaluation of a systolic murmur. She has a history of HTN for the past 5 years, which has been treated with amlodipine 10 mg daily, lisinopril 40 mg daily, and chlorthalidone 25 mg daily. She has no cardiac symptoms and exercises by walking 30 minutes 3–4 days a week. Her father died suddenly at age 65 of a "massive heart attack."

   On physical exam, blood pressure is 145/92 mm Hg, and heart rate is 78 bpm. There is a 2/6 systolic ejection murmur at the right upper sternal border without radiation. The murmur does not change from squat to stand position. There is a systolic abdominal bruit in epigastric area. There is no brachial-femoral artery pulse delay by palpation, and peripheral pulses are intact and symmetric in both feet. Basic metabolic panel shows potassium concentration 4.8 meq/L and serum creatinine 1.3 mg/dl. EKG shows sinus rhythm, left ventricular hypertrophy with repolarization abnormality. Transthoracic echocardiogram shows LVEF

60%, concentric left ventricular hypertrophy with septal and posterior wall thicknesses 15 mm, no outflow tract gradient, and normal aortic and mitral valves.

What test would be most appropriate to manage her condition?

A. Cardiac MRI.
B. Urine metanephrines and VMA.
C. Serum aldosterone level.
D. Duplex renal ultrasound.

Answer: The correct answer is **D**. This patient has had early-onset HTN which has required three drugs at maximum doses for treatment, and her blood pressure remains elevated. Her physical exam revealed a soft systolic ejection murmur but an abdominal bruit. Echocardiogram showed concentric left ventricular hypertrophy likely related to refractory hypertension. In a patient with early-onset, refractory HTN, evaluation for secondary causes of HTN is appropriate. The presence of an abdominal bruit suggests possible renal artery disease, specifically fibromuscular dysplasia, as a cause of HTN. Although a pheochromocytoma or hyperaldosteronism are other causes of refractory HTN, these causes are less likely than renal artery disease. Cardiac MRI (answer B) would not provide information about possible causes of HTN and would not change the clinical assessment that concentric left ventricular hypertrophy is due to refractory HTN.

4. A 57-year-old woman is referred for evaluation of heart murmur. She has a 15-year history of hypertension treated with atenolol initially, and losartan was added 3 years ago for additional blood pressure lowering. Her blood pressure has been well controlled. She walks her dogs for an hour most days and has not had angina, dyspnea, or lightheadedness. Her family history is notable for coronary artery disease and bypass surgery in her father and atrial fibrillation in her mother.

   On physical exam, her blood pressure is 130/78 mm Hg and heart rate 64 bpm. There is 2/6 systolic ejection murmur at the left lower sternal border which increases to 3/6 intensity from squat to stand position. Peripheral pulses are normal and symmetric in all extremities. EKG shows sinus rhythm and left ventricular hypertrophy. Transthoracic echocardiogram shows left ventricular ejection fraction 62%, septal wall thickness 17 mm and posterior wall thickness 12 mm and maximum wall thickness in mid-septum 19 mm, elongated anterior mitral valve leaflet with systolic anterior motion and resting left ventricular outflow tract gradient 20 mm Hg, and mild mitral regurgitation.

   What diagnostic testing would be most appropriate to manage her condition?

   A. Cardiac MRI.
   B. 24 hour Holter monitor
   C. Stress echocardiogram.
   D. Exercise treadmill test.
   E. A and C.
   F. B and D.

   Answer: The correct answer is **F**. The findings on her physical exam and transthoracic echocardiogram are consistent with hypertrophic cardiomyopathy. Although she does have a history of HTN for many years, her blood pressure has been well controlled, and the asymmetric hypertrophy is not consistent with hypertension as the cause. In this patient with probable hypertrophic cardiomyopathy, assessment of her risk for sudden cardiac death is appropriate. She does not have a family history of sudden death nor a personal history of syncope or extreme hypertrophy (maximum wall thickness > 30 mm) on echocardiography. She has not had ambulatory ECG (answer B) or exercise testing to assess her blood pressure response (answer D), so both these tests are recommended. In contrast, cardiac MRI (answer A) is not recommended routinely for sudden death risk assessment in HCM. Although stress echocardiography (answer C) may provide additional information about possible provoked left ventricular outflow obstruction during exercise, this finding would not likely change her treatment because she is currently asymptomatic and already prescribed a beta-blocker for HTN.

5. A 61-year-old man with obstructive hypertrophic cardiomyopathy returns for annual follow-up. He has a history of hypertension and has been treated with metoprolol succinate 200 mg daily. One year ago, he had mild dyspnea during moderate intensity exercise (30 min of walking on a treadmill 4 days a week). At that time, transthoracic echocardiogram showed left ventricular ejection fraction 65%; asymmetric septal hypertrophy with sigmoid septum and maximum wall thickness 19 mm; systolic anterior motion of the mitral valve with resting outflow tract velocity 2 m/sec which increased to 3.5 m/sec during Valsalva maneuver; and mild, posteriorly directed mitral regurgitation. Metoprolol was increased at that time from 100 mg daily to 200 mg daily. His dyspnea has improved, and he has not had any chest discomfort or pre-syncope with the same exercise regimen.

   On physical examination, his blood pressure is 148/92 mm Hg, and heart rate is 54 bpm and regular. His cardiac exam is notable for a regular rate and rhythm, normal heart sounds, and 2/6 systolic ejection murmur at the left lower sternal border which increases

in intensity from squat to stand position. EKG shows sinus bradycardia 52 bpm, left ventricular hypertrophy with repolarization abnormality, QRS duration 100 msec, and QTc duration 445 msec.

What is the best management for his condition?
A. Addition of verapamil sustained release 180 mg daily.
B. Addition of losartan 25 mg daily.
C. Addition of disopyramide 100 mg three times daily.
D. Surgical myectomy.

Answer: The correct answer is **B**. This patient has obstructive hypertrophic cardiomyopathy and hypertension. He has excellent functional status, which improved with higher dosage of metoprolol a year ago. His hypertension is not effectively treated with high dose beta-blocker, and his resting heart rate precludes higher dosage. Losartan is an antihypertensive drug which has been found to be safe and tolerated in patients with obstructive HCM (inherit clinical trial). Verapamil (answer A) is incorrect because this medication may result in worsening bradycardia or other conduction abnormalities in patients treated with beta-blocker. Disopyramide (answer C) does not have blood pressure-lowering effect and is not indicated in this patient without HCM-related symptoms on beta-blocker. Surgical myectomy (answer D) is not indicated because this patient does not have HCM-related symptoms refractory to medical therapy.

6. A 73-year-old woman with obstructive hypertrophic cardiomyopathy, hypertension, coronary artery disease status post-previous percutaneous coronary stent in right coronary artery, and chronic stage 2 kidney disease is admitted for severe shortness of breath and near syncope. She has had refractory hypertension. Despite adherence to her medical regimen including metoprolol tartrate 100 mg twice a day, losartan 50 mg daily, and furosemide 40 mg daily, her blood pressure has remained elevated. She reports that her blood pressure "spiked" last night to 220/100 mm Hg, and she took her husband's clonidine 0.1 mg tablet because she was scared of having a stroke.

   She awoke this morning with severe shortness of breath and called 911. Upon arrival to the emergency department, her blood pressure is 216/108 mm Hg, heart rate is 96 bpm and regular, and oxygen saturation 85% on high flow oxygen mask. Physical exam is notable for coarse breath sounds bilaterally with scattered expiratory wheezing and rapid, regular heart rhythm with a 3/6 systolic ejection murmur at the left lower sternal border. Stat EKG shows sinus tachycardia 104 bpm and left ventricular hypertrophy with 1 mm anterolateral ST depression. Chest radiograph shows cardiomegaly and pulmonary edema. Serum chemistries are notable for potassium concentration 3.5 mEq/l, blood urea nitrogen 42 mg/dl, and creatinine 2.0 mg/dl.

   What intravenous treatment do you recommend?
   A. Nitroprusside.
   B. Nitroglycerin.
   C. Esmolol.
   D. Diltiazem.

   Answer: The correct answer is **C**. This patient with HCM and HTN has a hypertensive emergency associated with pulmonary edema. Treatment of her severely elevated blood pressure in a controlled manner without worsening left ventricular outflow tract obstruction should be the acute care objective. Esmolol is an intravenous, selective, beta-blocking drug with very short half-life (9 min) that is indicated for the treatment of postoperative HTN. In this case, esmolol may ameliorate both the patient's elevated blood pressure and dynamic outflow tract obstruction with a lower risk of hypotension. Options A, B, and D are incorrect because these drugs may exacerbate left ventricular outflow obstruction by acutely reducing afterload (nitroprusside and diltiazem) or preload (nitroglycerin) and precipitate acute hypotension.

7. Which of these abnormalities differentiates hypertrophic cardiomyopathy from hypertensive heart disease?
   A. Cardiomyocyte hypertrophy.
   B. Increased extracellular volume and collagen.
   C. Arteriolar mural thickening.
   D. Asymmetric hypertrophy.

   Answer: The correct answer is **D**. Asymmetric septal hypertrophy, defined as septal/posterior wall thickness ratio > 1.3, is present in most patients with HCM but found in 10% or less of patients with hypertensive heart disease. The posterior left ventricular wall is the least commonly affected in HCM but may develop mild hypertrophy in the presence of concomitant HTN. Options A, B, and C are incorrect because all of these structural changes are found in both HCM and hypertensive heart disease.

8. A 68-year-old woman with nonobstructive hypertrophic cardiomyopathy is seen in outpatient clinic for presyncope. She has a history of hypertension treated with metoprolol succinate 200 mg daily and chlorthalidone 25 mg daily and paroxysmal atrial fibrillation, treated with amiodarone and apixaban. She reports that she has had several episodes of near syncope in the past 2 months, often when getting out of her car or when arising from bed or when walking in warmer temperatures. These are

not associated with palpitations and resolve after lying supine for 5 minutes. She walks about 20 min for exercise every day without angina or dyspnea.

Her physical examination shows supine blood pressure 96/58 mm Hg and heart rate 56 bpm and standing blood pressure 100/66 mm Hg and heart rate 72 bpm. Jugular venous pressure is not elevated. There is a regular rate and rhythm, normal heart sounds, and 2/6 systolic ejection murmur at the left lower sternal border, increasing in intensity from squat to stand position. Electrocardiogram shows sinus bradycardia, rate 54 bpm, and left ventricular hypertrophy with QTc 510 ms. Transthoracic echocardiogram shows left ventricular ejection fraction 75%; left ventricular end-diastolic dimension 4.8 cm and end-systolic diameter 2.3 cm; severe, asymmetric hypertrophy with maximum septal wall thickness 26 mm; no systolic anterior motion of the mitral valve but mid-cavitary outflow tract velocity 3 m/sec.

What is the appropriate management of this patient?
A. 30 day loop monitor
B. Stress echocardiogram.
C. Reduce metoprolol to 100 mg daily.
D. Discontinue chlorthalidone.
E. Discontinue amiodarone.

Answer: The correct answer is **D**. This patient with HCM has severe left ventricular hypertrophy with a small left ventricular volume and mid-cavitary obstruction. She has orthostatic light-headedness. Her blood pressure is well controlled on metoprolol and chlorthalidone. However, diuretic therapy may reduce her intravascular volume, increase dynamic mid-ventricular obstruction, and exacerbate her symptoms. If her blood pressure is abnormally high after discontinuing chlorthalidone, another medication such as an angiotensin receptor blocker may be better tolerated. Answer A is incorrect because her history is not consistent with an arrhythmic cause. Answer B is incorrect because this test is likely to confirm the previous echo results and shows greater degree of mid-cavitary obstruction during exercise. Answer C is incorrect because beta-blocker therapy is beneficial for her dynamic mid-ventricular obstruction, as well as her hypertension. Answer E is incorrect because amiodarone is not likely contributing to her symptoms.

9. A 54-year-old man with obstructive hypertrophic cardiomyopathy and hypertension presents for annual office visit. He has been treated with atenolol 100 mg daily and losartan 100 mg daily. He does not exercise regularly but is able to do his activities of daily living, including work as an automobile mechanic and yardwork, without any angina, dyspnea, or light-headedness. His home blood pressure measurements have been elevated in the last month (systolic blood pressure range 144–160 mm Hg) and heart rates 50–60 bpm. Transthoracic echocardiogram 1 year ago showed normal left ventricular ejection fraction 63%, asymmetric septal hypertrophy (2.2 cm) with systolic anterior motion of the mitral valve, and resting left ventricular outflow tract gradient 45 mm Hg which increased to 68 mm Hg during Valsalva maneuver. Basic metabolic panel shows potassium 3.7 mg/dl and serum creatinine 1.0 mg/dl.

What is the appropriate management of this patient?
A. Begin disopyramide 100 mg three times a day.
B. Begin hydrochlorothiazide 25 mg daily.
C. Begin amlodipine 5 mg daily.
D. Begin spironolactone 25 mg daily.
E. Begin lisinopril 10 mg daily.

Answer: The correct answer is **D**. In patients with refractory hypertension, spironolactone has been shown to reduce blood pressure more effectively than other agents. Spironolactone $\leq$50 mg daily has little natriuretic effect and therefore may not reduce preload or worsen left ventricular outflow tract obstruction as might other diuretics. Option A is incorrect because disopyramide does not have blood pressure-lowering effect. Dihydropyridine calcium channel blockers, such as amlodipine (option C), should be avoided in patients with obstructive HCM due to potential for worsening obstruction. Option D is incorrect because although the combination of an ACE inhibitor (lisinopril) with an angiotensin receptor blocker (losartan) is associated with greater blood pressure lowering than either agent alone, the combination has not been found to reduce clinical endpoints (death, stroke or myocardial infarction) and has been associated with greater decline in renal function and more hypotensive episodes.

10. A 58-year-old woman with a history of obstructive hypertrophic cardiomyopathy and hypertension presents for worsening dyspnea with exertion. Fifteen years ago, she had successful surgical myectomy for severe, dynamic left ventricular outflow obstruction. Postoperatively, she developed a left bundle branch block, and transthoracic echocardiography showed left ventricular ejection fraction 55%, maximum wall thickness 18 mm in mid-septum without systolic anterior motion of the mitral valve, resting left ventricular outflow velocity 1.9 m/sec, and mild mitral regurgitation. Her medical regimen is metoprolol succinate 50 mg daily and atorvastatin.

Over the past 6 months, she has had worsening dyspnea with normal activities such as housework

and gardening. She has not had angina, orthopnea, or edema. No palpitations or pre-syncope. She has noticed that her blood pressure has been elevated on multiple home measurements.

Her physical exam shows blood pressure 154/96 mm Hg, heart rate 82 bpm, and oxygen saturation 95% on room air. Her lungs are clear. Jugular venous pressure is approximately 10 cm H20. There is a regular rate and rhythm and normal heart sounds, with a 2/6 holosystolic murmur at the apex. Extremities are warm without edema. EKG shows sinus rhythm and left bundle branch block, QRS duration 152 ms. Echocardiogram shows left ventricular ejection fraction 40% with dyssynchronous septal motion, no outflow tract gradient, moderate mitral regurgitation, and left atrial enlargement.

What is the appropriate treatment?

A. Begin lisinopril 10 mg daily.
B. Increase metoprolol succinate to 200 mg daily.
C. Begin spironolactone 25 mg daily.
D. Begin furosemide 40 mg daily.
E. Refer for biventricular pacemaker.

Answer: The correct answer is **A**. This patient with hypertrophic cardiomyopathy has had successful surgical myectomy but now has developed left ventricular systolic dysfunction, possibly related to chronic left bundle branch block or "end-stage" HCM. In this patient with systolic dysfunction and hypertension, lisinopril is a guideline-directed medication. Increasing metoprolol to 200 mg daily (answer B) because the patient is currently on low dosage and a drastic increase in dosage may exacerbate her heart failure symptoms. Beta-blocker therapy should be titrated gradually over several weeks. This patient's ejection fraction is above 35%, so spironolactone (answer C) is not correct. Furosemide (answer D) may improve symptoms of heart failure, but does not offer survival benefit. Biventricular pacemaker (answer E) is not indicated for patients with left ventricular ejection fraction greater than 35%.

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17 Diagnosing and Managing Pulmonary and Right-Sided Heart Disease: Pulmonary Hypertension, Right Ventricular Outflow Pathology, and Sleep Apnea

M. Fuad Jan and A. Jamil Tajik

Key Points

- Hypertrophic cardiomyopathy (HCM) is a unique disease with a variable clinical course that may present during any stage of life.
- Pulmonary hypertension in HCM is primarily due to diastolic dysfunction resulting in elevated left ventricular pressures, left atrial hypertension, and, subsequently, elevated pulmonary artery pressures.
- Right ventricular hypertrophy is a known phenomenon in HCM, and right ventricular outflow obstruction is uncommon. However, significant RVOT obstruction may be present, especially in children and younger adults with HCM.
- Coexistence of HCM and obstructive sleep apnea is often reported.
- In the background of HCM, patients with obstructive sleep apnea tend to have a higher incidence of atrial fibrillation and its attendant complications.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease (1 in 500 people; 0.2%) [1]. It is characterized at the cellular level by disorganized hypertrophied cardiac myocytes that are separated by areas of interstitial fibrosis. At the anatomical level, it is expressed by a hypertrophied, non-dilated left ventricle (LV; usually asymmetric, with greatest predilection for hypertrophy of the interventricular septum) with an increased ejection fraction and impaired ventricular relaxation and filling. Dynamic LV outflow obstruction is an important pathophysiological component, present in approximately 75% of patients.

HCM is a unique and heterogenous disease with a variable clinical course that may present during any phase of life [2]. Although patients with HCM may remain stable over long periods of time and achieve normal longevity (>75 years), many patients have their natural course punctuated by sudden death, tachyarrhythmias, embolic stroke, and development of heart failure (HF) [3–8]. Atrial fibrillation (AF) is the most common sustained arrhythmia in HCM (20–25% of HCM patients) and is independently associated with HF-related death, occurrence of fatal and nonfatal stroke, long-term disease progression with HF symptoms, and severe functional disability [5, 9–15].

Pulmonary Hypertension and Right-Sided Heart Disease in HCM

HF in HCM (outside of the burnt-out phase) is primarily due to diastolic dysfunction (HF with preserved ejection fraction [HFpEF]) resulting in elevated LV pressures and left atrial hypertension. The coexistence of dynamic LV outflow tract (LVOT) obstruction, diastolic dysfunction secondary to intrinsic myocardial stiffness, mitral regurgitation, and LV hypertrophy in HCM eventually leads to the development of postcapillary pulmonary hypertension (PH), representing the cumulative downstream effect of the hemodynamic derangements (LVOT obstruction, mitral regurgitation, diastolic dysfunction) that cause left atrial hypertension.

The schematic in Fig. 17.1 displays the pathophysiologic processes (some putative and some proven) involved in the development of PH in HCM. The primary operators involved in the mechanistic considerations include:

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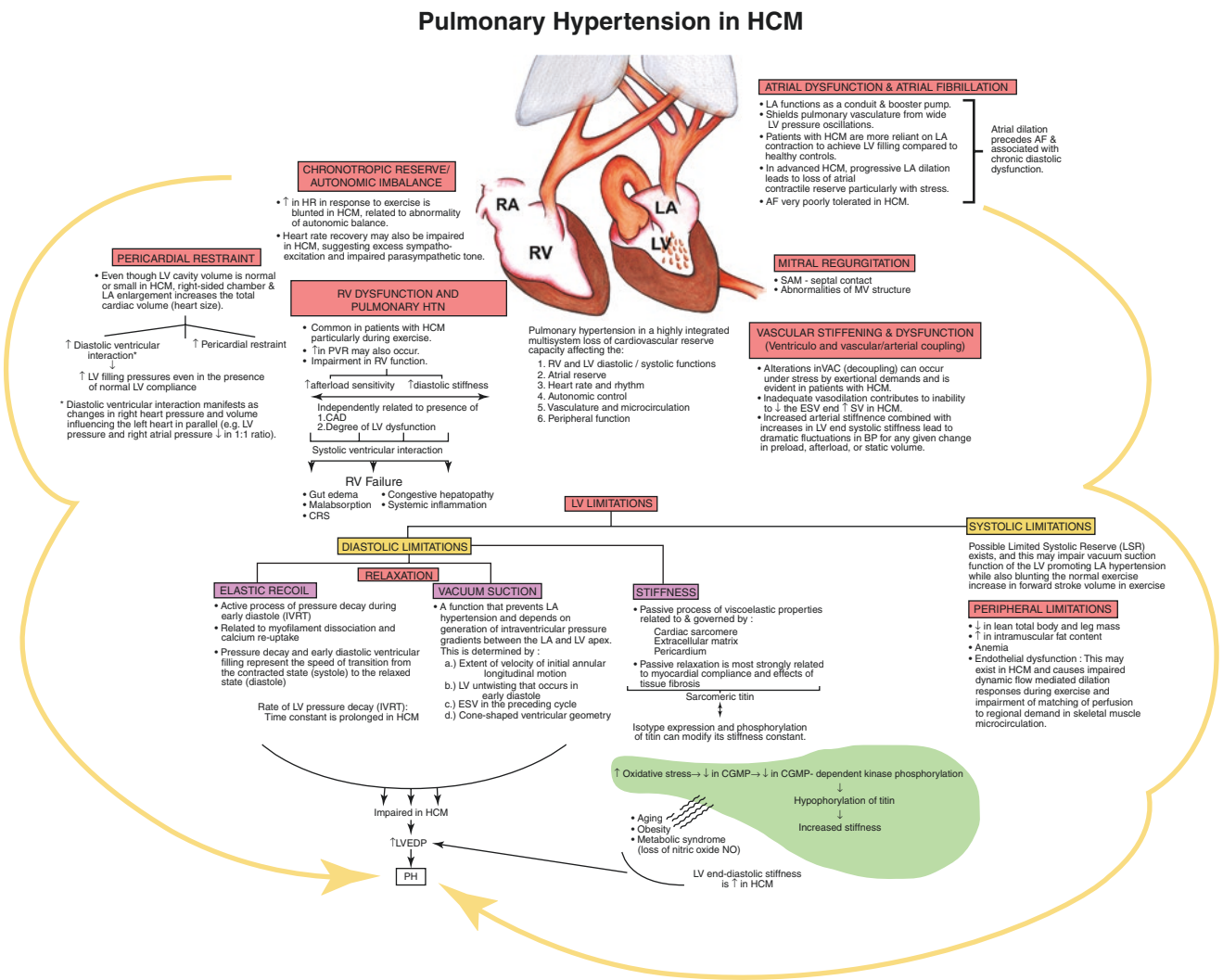

Fig. 17.1 Mechanistic considerations in the evolution of pulmonary hypertension in hypertrophic cardiomyopathy. Note that some of these considerations are well known and some are putative AF atrial fibrillation, BP blood pressure, CAD coronary artery disease, CGMP cyclic guanosine monophosphate, CRS cardiorenal syndrome, ESV end-systolic volume, HCM hypertrophic cardiomyopathy, HR heart rate, HTN hypertension, IVRT isovolumic relaxation time, LA left atrium, LSR limited systolic reserve, LV left ventricle, LVEDP left ventricular end-diastolic pressure, MV mitral valve, NO nitric oxide, PH pulmonary hypertension, PVR pulmonary vascular resistance, RA right atrium, RV right ventricle, SAM systolic anterior motion, SV stroke volume, VAC ventriculo- and vascular/arterial coupling

1. LV diastolic dysfunction (elastic recoil, vacuum suction, stiffness) and systolic limitations.
2. Left atrial dysfunction.
3. Vascular stiffening and dysfunction, which are not necessarily unique to HCM.
4. Issues with chronotropic reserve and autonomic imbalance.
5. Pericardial restraint.
6. Peripheral limitations.

In obstructive HCM, beside diastolic dysfunction, development of PH is predicated on dynamic LVOT obstruction leading to both mitral regurgitation from systolic anterior motion (SAM) of the mitral leaflets and impaired diastolic filling secondary to an increase in contractile load [16].

In nonobstructive HCM, diastolic dysfunction with restrictive filling is the primary player responsible for the increase in left atrial pressure that leads to PH. These mechanistic considerations are, by and large, operative in left-sided heart disease and may not be unique to HCM. Indeed, PH is a known complication of left-sided heart disease and is associated with a poor prognosis even with mild elevations in pulmonary pressures [17–22]. The prevalence of PH in HCM is reported to be similar to that in conditions such as aortic stenosis and HFpEF, which share similar hemodynamic traits with HCM [20, 23]. There is a dearth of literature on

the prevalence, clinical significance, management implications, and associated risk for adverse outcomes in patients with HCM and PH, with very few studies having investigated this association [24–28].

A recent (2016) large study cohort of HCM patients from the Mayo Clinic showed that PH was present in a significant proportion of HCM patients (38.2%), was moderate or severe in a small proportion (12.5%), and affected nonobstructive and obstructive HCM patients with similar frequency [26]. In this study, PH was associated with increased all-cause mortality in patients with nonobstructive or obstructive HCM who did not undergo septal reduction therapy. More recently (2017), a group of Italian investigators reported the prevalence at 18% at initial evaluation or during follow-up [27]. A smaller cohort of patients (n = 187) from the United States (Tufts Medical Center) was reported to have a high prevalence of PH (51%), including 18% with moderate-severe (mean pulmonary artery pressure ≥35 mmHg) — 34% of these also had increased pulmonary vascular resistance (>3.0 WU), with 11% meeting hemodynamic criteria for precapillary PH (mean pulmonary artery pressure ≥ 25 mmHg, pulmonary vascular resistance >3.0 WU, pulmonary artery wedge pressure ≤15 mmHg) [28]. In both the Mayo Clinic and Italian studies, PH was more prevalent in older patients and in females, and PH remained an independent predictor of HCM-related morbidity.

For the diagnosis of PH related to HFpEF in HCM, other potential causes of PH must be excluded. Heart catheterization is obligatory and will usually reveal an elevated pulmonary capillary wedge pressure and LV end-diastolic pressure, mean pulmonary artery pressure, and, in some patients, elevated pulmonary vascular resistance with an exaggerated trans-pulmonary gradient. Given the high frequency of PH in HCM (including moderate to severe levels), existence of precapillary PH, and inconsistent relation between pulmonary artery pressure and LVOT gradient or mitral regurgitation, the novel possibility that increased pulmonary pressures represent an intrinsic pulmonary vascular disease independent of mechanical left-sided obstruction and HF (HFpEF) in HCM remains an open issue [29]. Thus, the possibility of coexistent precapillary pulmonary hypertension or pulmonary arterial hypertension in some patients with HCM needs to be considered.

The ultimate construct in PH is the development of histopathologic lesions in the pulmonary vasculature with differing degrees of hypertrophy of the medial layer of the vessel wall, hyperplasia of the intimal layer, proliferation of the adventitial layer, and/or plexiform lesions [30]. These changes in the structure of the pulmonary arterial vascular bed lead to resistance to blood flow and, correspondingly, increased right ventricular (RV) pressures, often leading to RV pressure overload with eventual RV failure. The latter is uncharted territory in HCM underscoring the potential value of continued investigations.

Current literature suggests that, in an unselected HCM population, patients with PH have an increased risk of HCM-related mortality and that the increase of HCM-related mortality in patients with PH is driven by events occurring in a context of decompensated HF. Thus, PH represents mostly a marker of HF and, once identified, should raise awareness in guiding appropriate management. In general, identification of PH may prompt earlier consideration for septal reduction therapy to abolish LVOT gradient in obstructive HCM patients because relief of obstruction may negate the decreased survival effect observed in patients with PH who do not receive septal reduction therapy [26, 31]. It also may guide a more aggressive therapeutic management in nonobstructive HCM patients that includes a timely evaluation for heart transplantation in end-stage selected cases. It has been shown that the subgroup of patients with severe preoperative PH is no more likely to experience many clinically relevant adverse postoperative measures, including major surgical complications, prolonged use of intravenous inotropes, or extended duration of hospitalization, than patients with mild or moderate PH when subjected to surgical myectomy or alcohol septal ablation [28]. Therefore, although PH is an established risk factor for adverse outcome in patients undergoing most forms of cardiac surgery [32], septal myectomy may be somewhat of an exception in this regard [28]. Nonetheless, patients with severe, irreversible, or minimally reversible PH may reasonably opt for alcohol septal ablation to minimize perioperative risks. It is probably unnecessary to consider specific therapeutic pharmacological interventions to mitigate PH preoperatively in patients with HCM undergoing surgical or percutaneous interventions.

Although there are no guideline recommendations or clinical trial data regarding the management of PH in HCM, or for that matter PH in HFpEF, general guidance emphasizes the importance of control of systemic blood pressure, rate control for AF if present, and diuretic usage if needed to avoid hypervolemia. Certainly, patients with PH should have a closer clinical follow-up to reduce the risk of hemodynamic worsening or instability and arrhythmias and to assess for progression of disease.

RV Outflow Pathology

Although morphologic and pathophysiologic changes of the LV in HCM are well characterized, RV anatomy and pathology in HCM have not been well elucidated. This is primarily because conventional echocardiographic techniques do not allow a very accurate assessment of hemodynamics of the RV outflow tract (RVOT) due to its complex geometry and obscuration on conventional echocardiographic imaging [33]. However, RV hypertrophy is a known phenomenon in HCM and has been described, particularly in early reports

and in infants and children, with severe or massive hypertrophy extending into both ventricles [34–43].

In fact, the majority of young adults with asymmetric hypertrophy in Teare's original report of sudden death had both RV and LV hypertrophy [44]. More recent studies utilizing cardiac magnetic resonance imaging have demonstrated that RV wall thickness and/or mass is increased in patients with HCM, including about 10% with extreme RV wall hypertrophy (>10 mm) and most (53%) with diffuse RV hypertrophy involving all three segments of the RV [45].

The genetics of RV involvement has not been well characterized, although histological findings appear similar to those in the LV, suggesting similar pathogenesis [46]. Increased thickness of the RV free wall and interventricular septum may lead to RVOT obstruction, the reported incidence of which varies from 15% to 92% (15–20% in children and young adults) as documented by old cardiac catheterization studies [38, 47].

In a seminal paper published by Shimizu et al. [48], RV obstruction was present in 15% of 91 patients with HCM. This study involved a thorough use of echocardiography, the current gold standard for diagnosing HCM. Utilizing color flow mapping to define the sites of obstruction in the left and right ventricles, RV obstruction is considered to be present if the peak flow velocity is more than 2.0 m/s on continuous-wave Doppler, which, by simplified Bernoulli equation, amounts to more than 16 mmHg. The sites of RV obstruction may be in the outflow tract (the vast majority), the mid-base region at the level of the septal band, and the apical trabecular region (Fig. 17.2). Obstruction of the RVOT in HCM has been shown to be associated with massive hypertrophy of the LV musculature, which comprises the crista supraventricularis, moderator band, or trabeculae [36]. Combined RVOT and LVOT obstruction is more common than isolated RVOT obstruction, and triple intraventricular obstruction (RVOT, LVOT, and mid-ventricular) also is seen. Isolated RV obstruction has occasionally been described [37, 38, 40–42].

RV obstruction (subpulmonic) is more commonly reported in young children and infants than older adults, and explanations have been based on two reasons:

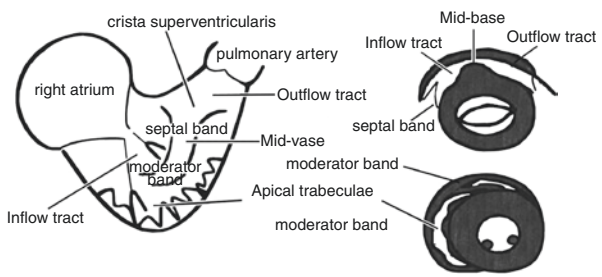

Fig. 17.2 Schematic diagrams of the right ventricular obstruction and its relation to the right ventricular structures. (From Shimizu et al [48]; with permission of The Japanese Circulation Society)

1. RVOT obstruction present in some infants with HCM may resolve with time because of growth and aging, owing in part to conformational changes in cardiac structure and function that increase the size of the RVOT.
2. Combined subaortic and subpulmonic obstruction may be particularly lethal in infants with HCM, predisposing them to premature death before they reach adulthood [43].

The Doppler flow velocity profile of RV obstruction appears relatively symmetric and dome-like, without the dagger-shaped profile characteristic of LVOT obstruction resulting from the dynamic obstruction caused by systolic anterior motion (SAM) of the mitral valve and SAM-septal contact. This suggests that RV obstruction is caused by a narrowing of the ventricular cavity as a result of muscle contraction during systole together with a hypertrophied RV free wall and protruding interventricular septum. There are important caveats that need to be understood during the echocardiographic examination of patients with RVOT obstruction. The tricuspid regurgitation jet velocity is usually high, and a diagnosis of PH may be entertained. Close examination reveals a normal pulmonary valve and normal-sized pulmonary artery, and obstruction on Doppler profile appears to be in the infundibular area and is often missed. In addition, the RV does not appear dilated and hypofunctioning but rather thickened and hyperfunctional. A short-axis view of the LV reveals a very thick septum and a crowded RV with severe muscle thickening. These are usually the echocardiographic clues to combined RV and LV obstruction.

Because the greatly hypertrophied musculature comprising crista supraventricularis, moderator band, or trabeculae is the morphologic basis for RV obstruction, operative resection of portions of this muscle relieves the outflow gradients and abolishes or substantially reduces the RV outflow gradient. Limited data are available on treatment approaches to biventricular obstruction [36, 49–51] because the optimal treatment for HCM patients with significant RV disease, simultaneous RVOT and LVOT obstruction, and severe hypertrophy is unknown. In fact, conventional surgical strategies such as the traditional Morrow procedure pose a particularly high risk to patients with severe hypertrophy and RV obstruction. For these patients, the most appropriate therapeutic approach has not yet been established.

The known surgical techniques to relieve obstruction in patients with severe hypertrophy and RV obstruction include [1] right ventriculotomy with resection of substantial portions of the greatly hypertrophied RV muscle, including the crista and moderator band; [2] excision of the hypertrophied tissue in the asymmetrical area of the interventricular septum, with access to the hypertrophied area achieved by entering through the conal part of the RV, leaving the moderator band alone [50, 52]; [3] extensive muscular resection of the RVOT, minimal resection of the LVOT, and interposition of a graft patch in the RVOT; and [4] transaortic extended septal

myectomy and/or a left apical ventriculotomy in pediatric patients [51].

Biventricular myectomy as a surgical treatment for HCM patients with biventricular obstruction and for patients with isolated RVOT obstruction is a high-risk procedure. Limitations of published research include the small number of patients in currently available studies. Thus, further investigation and a larger study population that includes HCM patients with RV involvement and RV obstruction will be required to establish treatment/surgical guidelines.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing and is characterized by recurrent episodes of either partial or complete upper airway obstruction during sleep, leading to episodes of interruption of respiration associated with fragmented sleep and intermittent hypoxia [53]. One in five individuals in the general population (9–12% of women and 27–35% of men) are believed to have OSA [54], making it a major public health problem. OSA is an acquired clinical condition, and it is considered an important, reversible cause of LV hypertrophy [55]. Moreover, both HCM and OSA are independently associated with an increased risk of morbidity and mortality [54, 56]. Recent studies have established a high prevalence of OSA in patients with metabolic and cardiovascular disease [57–60], including hypertension, AF, and metabolic syndrome, with ranges as high as 30–90% [61–65]. This high prevalence of OSA among patients with established cardiovascular disease may, in part, be explained by the fact that both share several common risk factors, such as increasing age, obesity, sedentary life, and male sex [66].

OSA and HCM: Combined Burden of Disease

The coexistence of HCM and OSA even in patients without the traditional risk factors for OSA, e.g., obesity, is suggested by recent studies [67, 68]. There is mounting evidence that OSA is not only a condition frequently associated with cardiovascular disease, including HCM, due to an overlap of risk factors, but that when present, it may causally participate in the development or aggravation of the underlying cardiovascular disease [69, 70]. Banno et al. in 2004 were the first to report an almost 50% prevalence (7 out of 15) of OSA in patients with HCM [67]. The group of patients with OSA had a higher mean body mass index compared with those who did not have sleep apnea (27.6 ± 3.8 versus 22.0 ± 4.0). Several other contemporary investigations also consistently have found a high prevalence of OSA among HCM patients, ranging from 32% to 71%, depending on the methodology and diagnostic criteria [68, 71–73]. Evidence suggests that the presence of OSA is independently associated with worse structural and functional impairment of the heart, including overdilation of the left atrium and aorta, higher prevalence of AF, worse New York Heart Association (NYHA) functional class, and reduced quality of life [67, 68, 71–74].

Poor sleep quality has been reported in patients with HCM and has been associated with poor quality of life. In a study of 126 patients, patients with HCM had higher Pittsburgh Sleep Quality Index scores (7 versus 4) denoting poor sleep than did controls [74].

Based on current literature, the general population of OSA patients is predominantly male and significantly older and more obese than patients without OSA, although patients with HCM and OSA are less obese than the typical OSA patient referred to a sleep laboratory, with the mean body mass index among patients with HCM and OSA ranging from 27 to 31 kg/m^2 [66]. The observation of relatively lean patients with OSA has also been reported in other populations, such as end-stage renal disease patients undergoing dialysis and patients with congestive HF [75, 76].

The rostral fluid hypothesis [77] of overnight rostral fluid shift to the neck is believed to help explain some of these phenomena, particularly among patients with an edematous state. Among patients with congestive HF, fluid displacement from the legs to the neck and lungs can help explain the genesis of both central and obstructive sleep apnea [78], whereas among patients with end-stage renal disease, nocturnal rostral fluid shift has been independently associated with the severity of OSA [79]. It also has recently been demonstrated that even in nonobese, healthy subjects, the shift of fluid into the nuchal structures may contribute to the increase of neck circumference and upper airway resistance [80]. Thus, the rostral fluid hypothesis may play a role in the genesis of OSA among patients with HCM.

Diagnosis of OSA in patients with HCM may, however, pose a challenge because consistent clinical predictors are lacking. In one study, the only significant predictors of OSA in patients with HCM were age ≥ 45 years (odds ratio 4.46, $p = 0.008$) and presence of AF (odds ratio 5.37, $p = 0.013$) [81]. Thus, sleep-disordered breathing in HCM, although common, is probably under-recognized. Given the potential morbidity and mortality associated with sleep apnea being left untreated and unrecognized, it is a feasible suggestion that objective sleep evaluations be considered in all HCM patients, especially if they have drug-refractory symptoms or other high-risk features.

OSA AND HCM: Genetic Links and Pathophysiologic Correlations

HCM is an archetypical monogenic disorder with an autosomal dominant pattern of inheritance [82] whereby a single mutation is usually sufficient to cause the disease, albeit with variable penetrance and expression. Among the known

causal genes, *MYH7* and *MYBPC3* (myosin-binding protein C) are the two most common, together being responsible for approximately half of the patients with familial HCM [83–86]. The spectrum of HCM-associated genes currently involves not only the myofilaments of the sarcomere, "sarcomeric HCM," but also additional subgroups (non-sarcomeric proteins) tentatively classified as "Z-disc HCM" and "calcium-binding HCM." The mutant proteins cause diverse structural and functional defects in the cardiac muscle sarcomere but converge into a common final pathway characterized by impaired myocyte function and increased myocyte stress accompanied by activation of stress-responsive intracellular signaling kinases. This activates the myocyte transcriptional machinery, producing compensatory hypertrophy, myocardial disarray, and fibrosis [87]. A large number of candidate gene studies have been performed in OSA, but to date no consistent genetic linkage for OSA has been found. Maternally inherited mutations in mitochondrial DNA have been reported in few patients with concomitant HCM and sleep-disordered breathing [88, 89]. Such patients also have been reported to suffer from deafness, diabetes, lactic acidosis, and encephalopathy. Of note, sleep apnea in such patients is usually of central type rather than obstructive. Thus, a definitive genetic linkage between HCM and OSA has not been determined. With rapid advances in the field of genetics as well as increased affordability of genotyping, it will be important to continue to search for any genetic linkage between these two entities. Such a linkage may well be the cornerstone for further elucidation of the pathophysiologic association of HCM and OSA, as well as for identifying areas of potential therapy [90].

Several pathophysiologic mechanisms help translate the link between these two disease states (Figs. 17.3 and 17.4). The most likely explanation is the altered adrenergic signaling seen in OSA, which is also one of the key features of HCM. In patients with OSA, hypoxemia and frequent arousals from sleep via the chemoreflexes result in increased sympathetic activation and elevated catecholamine levels,

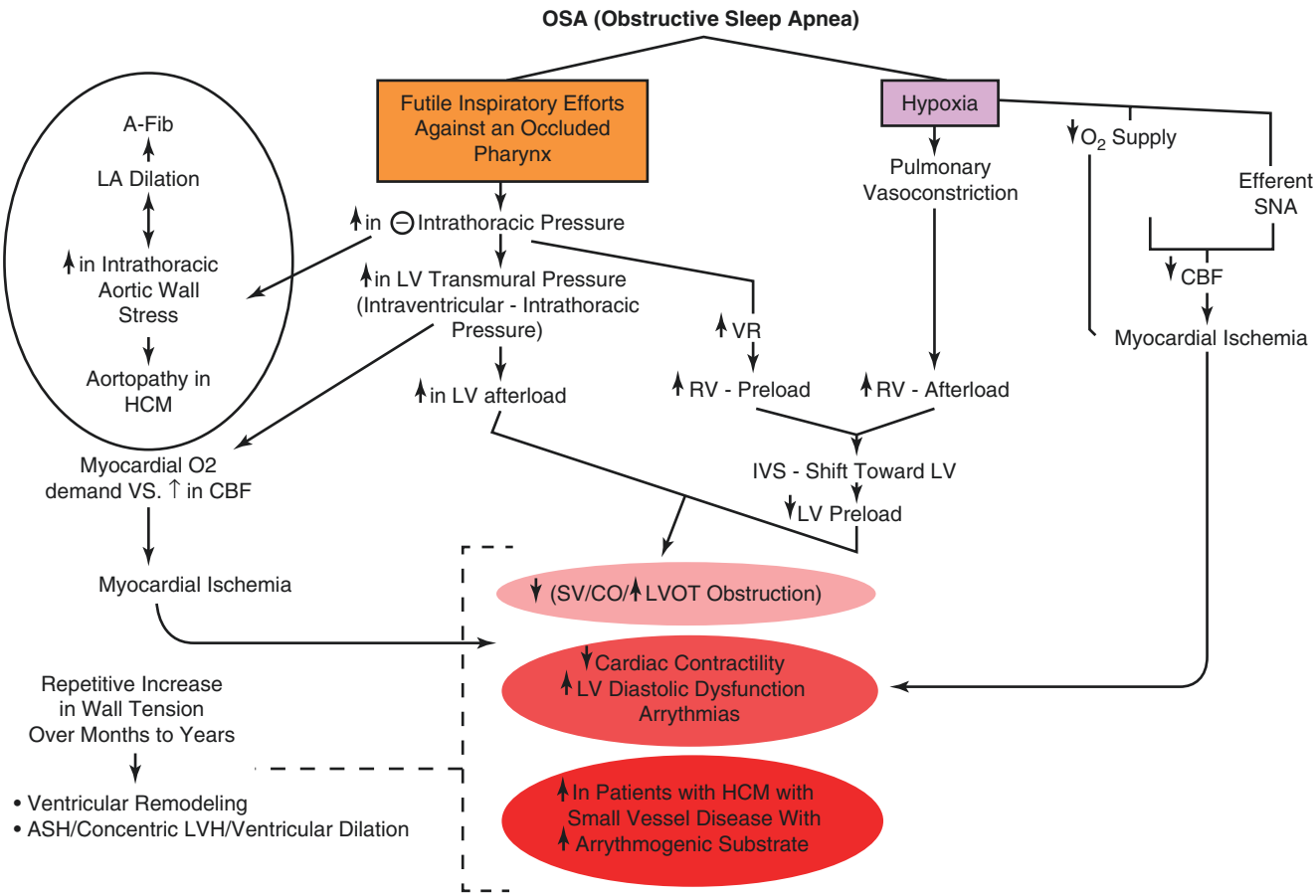

Fig. 17.3 Schematic illustrating the possible mechanisms underlying the cardiovascular effects of obstructive sleep apnea (OSA) in patients with hypertrophic cardiomyopathy (HCM). Also shown is the putative mechanism of development of atrial arrhythmia and aortopathy in patients with combined HCM and OSA. A-Fib Atrial fibrillation, ASH asymmetric septal hypertrophy, CBF coronary blood flow, CO cardiac output, IVS interventricular septum, LA left atrium, LV left ventricle, LVH left ventricular hypertrophy, LVOT left ventricular outflow tract, RV right ventricle, SNA sympathetic neuronal activity, SV stroke volume, VR venous return. (From Aggarwal et al. [90], with permission from Taylor & Francis)

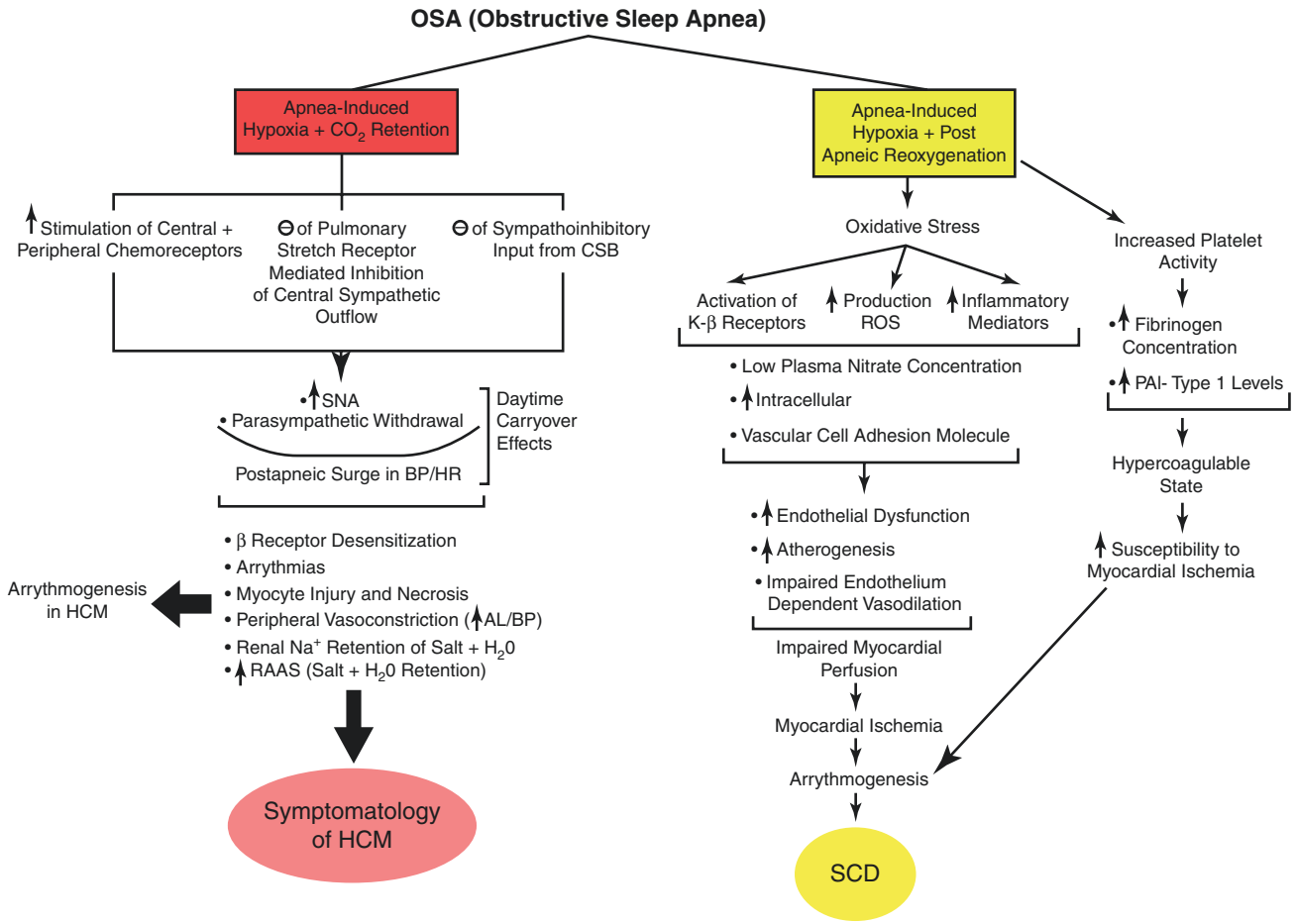

Fig. 17.4 Schematic outlining proposed elements of the pathophysiological fundamentals of OSA, activation of cardiovascular disease mechanisms, and consequent contribution to both the symptoms of hypertrophic cardiomyopathy (HCM) and risk development for sudden cardiac death (SCD) in patients with combined HCM and OSA. AL afterload, BP blood pressure, CSB carotid sinus baroreceptors, HR heart rate, PAI plasminogen activator inhibitor, RAAS Renin-angiotensin-aldosterone system, ROS reactive oxygen species, SNA sympathetic neuronal activity. (From Aggarwal et al. [90], with permission from Taylor & Francis)

which improve after continuous positive airway pressure (CPAP) therapy [91]. This high catecholamine state causes increased hypertrophy and LV filling pressures, decreased cardiac output, and initiation or worsening of LVOT obstruction, dyspnea, dizziness, and mitral regurgitation [69]. LV septal hypertrophy has been shown to be independently associated with OSA severity. It develops even in the setting of normal blood pressure, and it reverses after initiation of CPAP therapy [92, 93]. Therefore, factors other than hemodynamic overload have been proposed to contribute to hypertrophy. In addition to the increased sympathetic activity, several other possible mechanisms for the worsening of HCM in OSA patients include increased afterload during OSA owing to large negative intrathoracic pressures generated because of increased inspiratory efforts, impaired vagal activity, insulin resistance, and endothelial dysfunction with reduced endogenous nitric oxide production [94]. In addition, levels of leptin, a peptide hormone known to cause cardiac myocyte hypertrophy, have been seen to be elevated in patients with OSA and may further contribute to disease and symptom progression [95, 96]. Thus, there are several overlapping pathophysiologic alterations in patients with HCM and OSA that might explain the worsening of HCM symptoms in these patients. Interestingly, most of these mechanisms are reversible in OSA patients via CPAP therapy, which underscores the importance of early recognition and treatment of OSA in HCM patients before irreversible LV remodeling occurs [90].

OSA AND HCM: Clinical Implications in Obstruction

The morphologic and functional changes associated with HCM result in multiple complex and interrelated changes in cardiac physiology, including diastolic dysfunction, LVOT

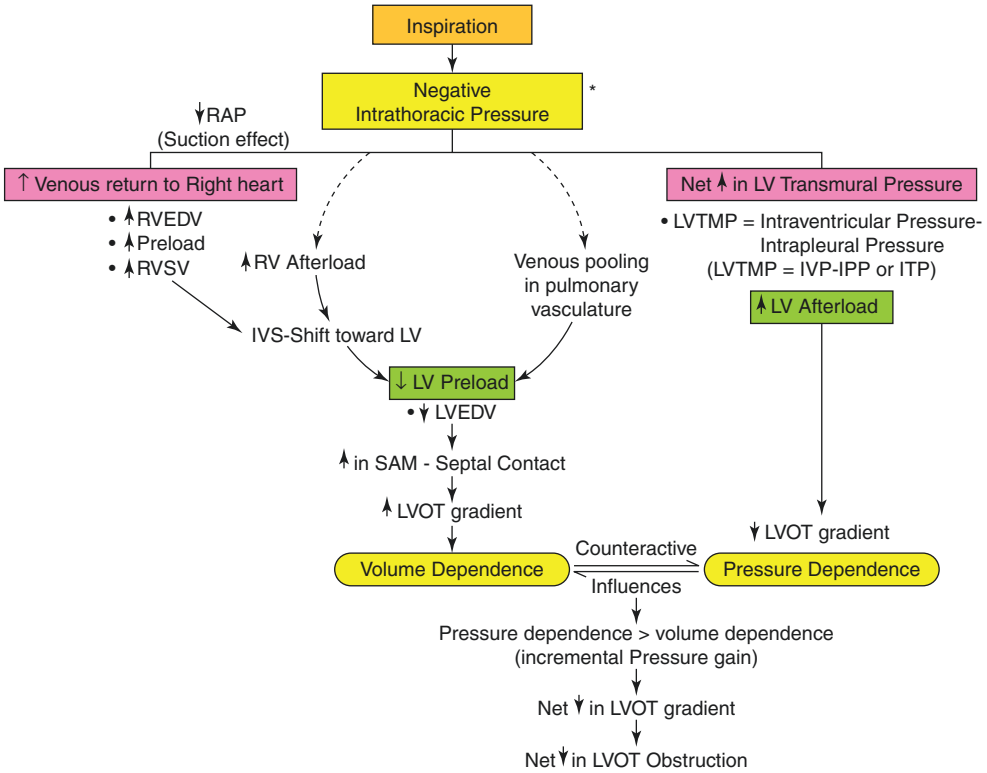

Fig. 17.5 Schematic of LVTMP. This schematic of the left ventricular transmural pressure shows the multifactorial effect of inspiration on the left and right ventricle. (From Jain et al. [97]; with permission of Oxford University Press)

obstruction, mitral regurgitation, myocardial ischemia, arrhythmias, and, in a minority of patients over time, overt systolic dysfunction [87]. The defining pathophysiologic abnormality of LVOT obstruction is complex, multifactorial, and defined by SAM of the mitral leaflet (Venturi effect and flow-drag phenomenon) with associated secondary mitral regurgitation. Drag forces on a portion of the mitral valve leaflets create a self-amplifying loop in which longer durations of SAM-septal contact lead to further increases in obstruction. Because septal hypertrophy can extend distally, obstruction also can occur in the midcavitary region because of a hypertrophied papillary muscle abutting a hypertrophied ventricular septum (mid-ventricular obstruction). Documentation of the dynamic nature of LVOT obstruction extends back more than a half century, and it is well known that changes in preload, afterload, and contractility can greatly affect the magnitude of LVOT obstruction.

Recent investigations have shown the important contribution of heightened sympathetic nerve activity in OSA to drug-refractory symptoms and worsening LVOT obstruction in HCM [68]. The generally stable state of cardiovascular quiescence in sleep is interrupted in patients with OSA by intermittent surges in sympathetic nerve activity, blood pressure, and heart rate. Recently, our group described phasic respiratory variation of LVOT obstruction in HCM patients, in whom the prevalence of OSA was 75% [97]. In this cohort of 20 patients, LVOT gradients varied widely during the respiratory cycle; peak gradients were uniformly lowest during inspiration (50.8 mmHg +25.6) and highest during expiration (90.1 mmHg +41.8). In 11 patients with mitral annulus inflow, LV inflow (preload) was decreased during inspiration, and in 16 patients with isovolumic relaxation time and ejection time measurements, decreased left atrial filling pressure was noted during inspiration, consistent with decreased LVOT obstruction. When compared with a control group of 20 HCM patients who did not have respiratory variation, the study group patients were more overweight (mean body mass index 35.1 ± 7.3 vs control group 29.1 ± 5.1, $p = 0.0045$) and more likely to have sleep-disordered breathing ($n = 15$ study group, $n = 5$ control group). This study describes counterintuitive respiratory-related fluctuations in LVOT gradients, challenging the traditional hemodynamic teaching and demonstrating the contribution of LV transmural pressure (LVTMP) to LVOT obstruction in certain HCM patients, where the preponderance of OSA was high (75%).

The most satisfactory explanation for these findings appears to be an increase in LVTMP with inspiration (Fig. 17.5). In addition to changes in LV preload, LVOT obstruction is well known to be sensitive to afterload changes [98]. It is believed that transmission of increased negative intrathoracic pressure results in an increase of LV afterload via LVTMP. This effective afterload increase results in reduced LVOT obstruction, analogous to a handgrip maneuver. LVTMP, the systolic pressure corrected for intrathoracic pressure (LVTMP = systolic pressure-intrapleural pressure) [98], is considered a more accurate representation of cardiac

afterload and is increased in inspiration [99–101]. During inspiration, the intrathoracic pressure becomes negative, and thus, even though systolic arterial pressure may decrease slightly, the net effect is a slight increase in LVTMP. In HCM patients, LVOT gradients can vary significantly based on loading conditions. As a result, the effect of reduced preload is negated by increased LV afterload (LVTMP), and obstructive gradients observed during inspiration are reduced. In the normal healthy heart, preload-mediated effects are predominant, whereas in HCM patients, afterload sensitivity can be profound.

Sleep-disordered breathing in patients with HCM is associated with an elevated mean heart rate on 24-h Holter monitoring when compared with those without sleep-disordered breathing (71 versus 67 bpm, adjusted $p < 0.001$) [102] despite the use of rate control medications [103]. More severe forms of sleep-disordered breathing are associated with a higher heart rate ($p = 0.008$), particularly during the night ($p < 0.001$), and subsequent tachycardia is noted to correlate with the drop in oxygen saturation [104]. While both HCM and sleep-disordered breathing are independently associated with increased risk of AF, the prevalence of AF is even higher when both disease states coexist (30–40% versus 5–10%) [71, 72].

Peak oxygen consumption, an accurate and reproducible measure of cardiopulmonary fitness, is decreased in HCM patients with sleep-disordered breathing compared with those who do not have sleep-disordered breathing (16 versus 21 $mlO_2/kg/min$, $p < 0.001$) [105]. The vast majority of HCM patients have impaired diastology, signifying that left atrial dysfunction, PH, and diastolic dysfunction may be the potential mechanisms by which sleep-disordered breathing decreases exercise tolerance in patients with HCM. Sleep-disordered breathing has been reported to be associated with significantly increased left atrial length (65 versus 58, $p = 0.0026$), left atrial volume index (58 versus 42 ml/m^2, $p = 0.0002$), and E/E' ratio (20 versus 14, $p < 0.042$) in patients with HCM [72]. An increase in the severity of sleep-disordered breathing has been associated with increases in left atrial volume index and LV end-diastolic diameter ($r = 0.3$, $p < 0.05$) [72, 106]. Conversely, patients with a larger left atrium on echocardiography had a greater severity of OSA than those without atrial dilatation (apnea–hypopnea index [AHI] 26.7/h versus 16.2/h, $p < 0.05$) [106]. No differences in LVOT gradient were noted in these studies in HCM patients with and without sleep-disordered breathing even though it has been suggested that LVOT obstruction could be worsened in such a setting due to increased LV filling pressures, reduction in cardiac output, and impaired hypertrophic remodeling [107]. In fact, improvements in exertional breathlessness and a reduction in resting LVOT gradients after CPAP treatment have been demonstrated previously, thus avoiding the need for a septal reduction surgery [69]. Patients with HCM and abnormal pulse oximetry also are more likely to have NYHA functional class II or III than patients with HCM and normal pulse oximetry (83% versus 62%, $p = 0.023$) [68]. OSA in HCM patients could be contributing significantly to drug-refractory symptoms and worsening LVOT obstruction, as a result of heightened sympathetic activity. Thus, the treatment options for patients with OSA and obstructive HCM should first focus on the recognition and appropriate management of OSA prior to labeling the patient drug-refractory and referring them for a septal reduction procedure [90].

OSA and HCM: CPAP Therapy

Currently, the data available are insufficient to allow us to draw a conclusion about the beneficial effects of CPAP in patients with HCM. However, anecdotal evidence based on some case reports and smaller studies is available. In the study by Banno et al., only one patient with HCM and OSA was treated with CPAP therapy, and the patient demonstrated marked improvement in AHI (from 49.3/h to 6.4/h) [67]. In a study of four patients referred for septal reduction therapy due to refractory medical symptoms, consistent and comparable reductions in LVOT gradients and consequent improvement in exertional breathlessness were noted in all four patients [69]. This also translated to improvement in blood pressure in two patients and reduction of LV hypertrophy in one patient. CPAP therapy also has been reported to terminate recurrent ventricular tachycardia in a patient with HCM and OSA [108]. As discussed above, patients with HCM demonstrate more severe sleep-disordered breathing, with a mean AHI of 23.0 ± 17.8/h compared with controls [109], and compliance with CPAP also has been shown to be higher in patients with a higher AHI [110]. Consequently, patients with HCM and a higher AHI are more likely to be compliant with CPAP than those without HCM; however, this has not been tested directly.

OSA and HCM: Risk Stratification for Sudden Death

Sudden death is unpredictable in HCM and is the most frequent mode of premature death. Precise risk stratification in HCM remains a challenge due to its clinical heterogeneity of presentation and expression, its relatively low prevalence in general cardiology practice, and the complexity of potential pathophysiologic mechanisms [1, 3, 111–114]. Nevertheless, it is possible to identify most high-risk patients by noninvasive clinical markers [115–117], and only a small minority of those HCM patients who die suddenly (about 3%) are without any of the currently acknowledged risk markers

Table 17.1 Low-risk cohort for sudden death in HCM

Asymptomatic patients
Mild symptomatic class (NYHA I and II)
No family history of sudden death
No syncope (HCM related)
No episodes of NSVT on ambulatory ECG monitoring
LVOT gradient at rest less than 30 mmHg
Normal or mildly increased left atrial size (<45 mm)
Normal blood pressure response to upright exercise
Left ventricle wall thickness < 20 mm
Absence of delayed hyperenhancement on CMR imaging
Absence of obstructive sleep apnea

CMR cardiac magnetic resonance, *ECG* electrocardiogram, *HCM* hypertrophy cardiomyopathy, *LVOT* left ventricular outflow tract, *NSVT* nonsustained ventricular tachycardia, *NYHA* New York Heart Association. (From Jan and Tajik [87], with permission of Jaypee Brothers Medical Publishers.)

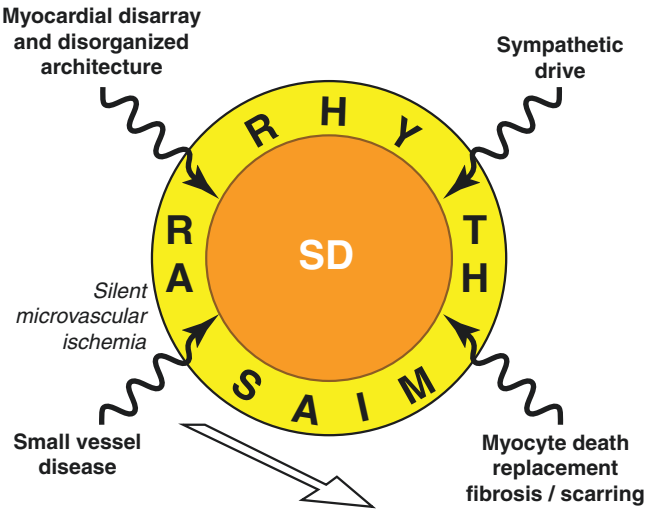

Fig. 17.6 Pathogenesis of sudden death (SD) in hypertrophic cardiomyopathy (HCM). Note the interplay of multiple factors involved in HCM-related SD. Eventually, the architectural disorganization and scarring (and possibly the expanded interstitial matrix), with contribution from small vessel disease and sympathetic tone, lead to an unstable electrophysiological substrate, which creates susceptibility to reentry arrhythmias. Data assembled from stored electrograms document that SD events in HCM are caused by sustained ventricular tachyarrhythmias [i.e., rapid ventricular tachycardia (VT) and/or ventricular fibrillation (VF)]. (From Jan and Tajik [87], with permission of Jaypee Brothers Medical Publishers)

(Fig. 17.4). Although most clinical markers of sudden death risk in HCM patients have a low positive predictive value (due to low event rates) [5, 116, 118–121], their negative predictive value is high (at least 90%), suggesting that the absence of these markers and certain other clinical features can be used to profile HCM patients into a low-likelihood cohort for sudden death or other adverse events (Table 17.1). The HCM-related sudden death events are caused by sustained ventricular tachycardia and/or ventricular fibrillation [122–124], and although the trigger for these potentially lethal rhythms is poorly understood, sinus tachycardia is identified as an initiating rhythm in some cases, suggesting that high sympathetic drive can be proarrhythmic [125]. The architectural disorganization and scarring (and possibly the expanded interstitial matrix) in addition to microvascular dysfunction and ischemia are believed to represent the unstable electrophysiologic substrate that creates susceptibility to reentry arrhythmias (Fig. 17.6).

In the background of this cardiovascular profile, when patients with HCM and OSA have obstructive apneic events that cause systemic hypoxemia (sometimes severe and prolonged), oxygen desaturations may cause enhanced ventricular ectopy (Figs. 17.3 and 17.4). OSA can prompt several mechanisms that can begin and sustain a cascade of pernicious stimuli that immediately and over time contribute to both general cardiovascular disease progression and repetitive arrhythmogenic potential in patients with HCM. Apnea-induced hypoxemia and carbon dioxide retention in OSA lead to autonomic dysregulation, precipitating increased sympathetic nerve activity, and parasympathetic withdrawal. These lead to peripheral vasoconstriction, myocyte injury and necrosis, renal retention of salt and water, and increased renin-angiotensin-aldosterone activity, all of which contribute to both arrhythmogenesis in HCM and its symptomatology. Furthermore, altered adrenergic signaling, a key feature of HCM, also is seen in OSA; indeed, beta-adrenergic receptor inhibition is the most common therapy for symptom relief. Apnea-induced hypoxemia also causes increased oxidative stress (increased reactive oxygen species) and platelet activation, which in turn propagate endothelial dysfunction and hypercoagulability. Both of these increase the susceptibility of the patient with HCM and small vessel disease to myocardial ischemia and its consequent attendant malignant ventricular rhythms. Recent studies involving patients with implantable cardioverter-defibrillators have shown that appropriate device discharge occurs two- to fourfold more frequently in those with OSA than in those without OSA [126].

Repetitive oxygen desaturation with associated hypercapnia also activates the chemoreflex, which increases vascular sympathetic nerve activity and serum catecholamines. Thus, tachycardia and surges in blood pressure at the end of apneas result in increased myocardial oxygen demand at a time when oxygen saturation is at its lowest, a situation that may lead to myocardial ischemia and potentially dysrhythmic consequences [127]. OSA also affects mechanisms mediating heart rate variability, including central nervous system coupling between cardiac and ventilatory parasympathetic inputs, the arterial baroreflex, and feedback from pulmonary stretch receptors, i.e., cardiac autonomic dysfunction [128]. Chronic sympathetic overdrive is another mechanism that can contribute to the elevated risk of sudden cardiac death in HCM patients with OSA [129].

In summary, there is evidence from observational and nonrandomized trial data suggesting a significant relationship (not necessarily a causal relationship) between OSA and HCM symptomatology. Mechanistic investigations also stimulate the proposition of a true arrhythmogenic role of OSA in HCM in susceptible patients. Thus, it has been argued among others in obiter dicta that integrating OSA into the risk stratification tool in the "pyramid profile" and arbitration assembly for sudden death in HCM would strengthen the current pyramid profile [70]. Furthermore, because the HCM risk factor algorithm remains incomplete [130, 131], additional relevant variables like OSA represent a significant contribution to disease management. Given its influence on clinical outcomes in a variety of cardiovascular diseases, OSA does warrant further investigation in this regard.

HCM and OSA: Double Jeopardy for AF

AF is the most common sustained arrhythmia in HCM (20–25% of HCM patients) [5, 9, 10, 12, 13] and is independently associated with HF-related death, occurrence of fatal and nonfatal stroke, long-term disease progression with HF symptoms, and severe functional disability [9, 10, 14, 15]. Although linked to left atrial enlargement and an increasing incidence with age [9], the mechanism is not completely understood. Both paroxysmal (PAF) and chronic AF occur in patients with HCM, and although AF is reasonably well tolerated by about one-third of patients [9] and is not a primary independent determinant of sudden death, it may be a trigger for life-threatening ventricular arrhythmias in some patients [132, 133]. Furthermore, episodes of PAF can result in acute clinical deterioration accompanied with syncope or HF owing to reduced diastolic filling and cardiac output in a hypertrophied LV with preexisting severe diastolic dysfunction.

A strong association between OSA and AF also has been consistently observed in both epidemiologic and clinical cohorts, and multiple studies have demonstrated that OSA is associated with an increased risk of AF recurrence following chemical or electrical cardioversion or pulmonary vein isolation by catheter ablation [64, 134–138].

The consistency of these observations in clinical cohorts contributes to a body of evidence that strongly implicates OSA as a cause, and not merely a correlate, of AF. Moreover, not only is OSA associated with an increased risk of incident AF; recurrence treatment with CPAP appears to eliminate this excess risk [139–141].

The effects of acute gas exchange abnormalities, changes in autonomic activity, or the mechanical effects of large intrathoracic pressure swings are believed to be involved in the mechanistic considerations of OSA and AF. Recent studies have suggested the importance of both cardiac sympathetic and parasympathetic autonomic systems in rendering the atria at increased risk of fibrillation following induced apneas [142, 143]. Of particular importance is the negative intrathoracic pressure in promoting AF through vagal activation, which results in a marked shortening of the atrial effective refractory period [143].

Thus in the background of HCM, patients with OSA tend to have a higher incidence of AF and its attendant complications. Because even one or two episodes of PAF have been associated with increased risk for systemic thromboembolization in HCM, the threshold for anticoagulation should be low and considered in patients even after one AF paroxysm [9].

OSA and HCM: Future Directions

The exact mechanisms by which OSA causes poorer outcomes in patients with HCM remain to be elucidated. More data are needed in regard to the occurrence of arrhythmias and mortality in such patients. Even though CPAP therapy appears favorable, larger studies are needed to confirm the benefit of CPAP in patients with HCM and OSA.

Both HCM and OSA have been associated with higher levels of serum heart-type fatty acid-binding protein (H-FABP) [144–146]. H-FABP mediates the passage of fatty acids from the plasma membrane to sites of lipid synthesis and has been postulated as a marker for atherosclerosis and myocardial injury in patients with metabolic syndrome [147]. Further research on this marker in patients with concomitant HCM and OSA may help in early identification of atherosclerosis in this population.

A consistent finding of trials on CPAP therapy in patients with heart disease has been a decrease in activity of the sympathetic nervous system, an important clinical marker of adverse outcome in cardiovascular disease in general and HCM in particular. Observational studies have consistently described an increased risk of fatal and nonfatal cardiovascular events associated with untreated OSA independent of other risk factors, as well as a decrease in this risk in patients treated with CPAP for OSA. Despite this substantial body of supportive evidence, large, long-term randomized trials are missing and therefore are needed to delineate definitively the role of diagnosing and treating OSA in decreasing the incidence of, and mortality from, cardiovascular diseases like HCM. Undertaking such studies and implementing findings in clinical practice will pose several challenges.

Another challenge in clinical practice is the complex logistics of screening patients for OSA (insurance claims, reluctance of primary care physicians, etc.). Simple and cost-effective methods to screen for OSA and subsequently treat such patients will therefore need to be developed and tested in unselected community samples, including the select group

of HCM patients. The combination of OSA and HCM will continue to represent a major challenge as knowledge and evidence evolve over the next several years.

Clinical Pearls

1. The coexistence of dynamic left ventricular outflow tract (LVOT) obstruction, diastolic dysfunction secondary to intrinsic myocardial stiffness, mitral regurgitation, and left ventricular hypertrophy in hypertrophic cardiomyopathy eventually leads to the development of postcapillary pulmonary hypertension, representing the cumulative downstream effect of the hemodynamic derangements (LVOT obstruction, mitral regurgitation, diastolic dysfunction) that cause left atrial hypertension.
2. The prevalence of pulmonary hypertension in hypertrophic cardiomyopathy is reported to be similar to that in conditions such as aortic stenosis and heart failure with preserved ejection fraction, which share similar hemodynamic traits with hypertrophic cardiomyopathy.
3. For the diagnosis of pulmonary hypertension related to heart failure with preserved ejection fraction in hypertrophic cardiomyopathy, other potential causes of pulmonary hypertension must be excluded, and right heart catheterization is obligatory.
4. Right ventricular obstruction may be present in up to 15% of patients with hypertrophic cardiomyopathy, most commonly in children and young adults.
5. The sites of right ventricular obstruction may be in the outflow tract (the vast majority), the mid-base region at the level of the septal band, and the apical trabecular region.
6. The Doppler flow velocity profile of right ventricular obstruction appears relatively symmetric and dome-like without the dagger-shaped profile characteristic of left ventricular outflow tract obstruction resulting from the dynamic obstruction caused by systolic anterior motion (SAM) of the mitral valve and SAM-septal contact.
7. Limited data are available on treatment approaches to biventricular obstruction.
8. The coexistence of hypertrophic cardiomyopathy and obstructive sleep apnea (OSA) even in patients without the traditional risk factors for OSA, such as obesity, is suggested by recent studies, and the rostral fluid hypothesis may play a role in the genesis of OSA among patients with hypertrophic cardiomyopathy.
9. Obstructive sleep apnea (OSA) in hypertrophic cardiomyopathy patients can contribute significantly to drug-refractory symptoms and worsening left ventricular outflow tract obstruction, as a result of heightened sympathetic activity. Thus, the treatment options for patients with OSA and obstructive hypertrophic cardiomyopathy should first focus on the recognition and appropriate management of OSA prior to labeling the patient drug-refractory and referring them for a septal reduction procedure.
10. Mechanistic investigations stimulate the proposition of a true arrhythmogenic role of obstructive sleep apnea (OSA) in hypertrophic cardiomyopathy in susceptible patients, and thus there is an argument that integrating OSA into the risk stratification tool in the "pyramid profile" and arbitration assembly for sudden death in hypertrophic cardiomyopathy may strengthen the current pyramid profile.

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Questions

1. The following are true about pulmonary hypertension (PH) in hypertrophic cardiomyopathy (HCM):
   A. Development of PH in HCM is a rare phenomenon and when it develops is primarily related to severe left ventricular outflow tract (LVOT) obstruction. Patients with PH in HCM are usually older and in their seventh decade of life and also usually have severe mitral regurgitation.
   B. PH is universal in HCM.
   C. PH in HCM is usually associated with irreversible changes in the pulmonary arterioles, and almost all patients have high pulmonary vascular resistance.
   D. PH in HCM is usually associated with syncope and is a high-risk marker for sudden death.
   E. None of the above.

   Answer: E
   Explanation:
   The prevalence of PH in HCM is reported to be similar to that in conditions like aortic stenosis and heart failure with preserved ejection fraction, which share similar hemodynamic traits with HCM. PH is neither rare nor universal in HCM. The pathophysiologic basis of PH in HCM is primarily due to diastolic dysfunction resulting in elevated left ventricular (LV) pressures and left atrial hypertension. The coexistence of dynamic LVOT obstruction, diastolic dysfunction secondary to intrinsic myocardial stiffness, mitral regurgitation, and LV hypertrophy in

HCM also eventually leads to the development of post-capillary PH, representing the cumulative downstream effect of the hemodynamic derangements (LVOT obstruction, mitral regurgitation, diastolic dysfunction) that cause left atrial hypertension. High pulmonary vascular resistance in PH associated with HCM is not common, and a small percentage of such patients may have elevated pulmonary vascular resistance. Currently, PH is not a high-risk marker for sudden death in HCM and is not used as a risk arbitrator for the implantation of an implantable cardioverter-defibrillator for primary prevention of sudden death.

2. Right ventricular (RV) hypertrophy is common in HCM and may pose management dilemmas in the routine care of patients with HCM. The following are true about RV obstructive pathology in HCM:
   A. The genetics of RV involvement in HCM has been well described in most modern reports.
   B. Reported incidence of RV obstructive pathology in HCM is miniscule and occurs in <1% of HCM patients when the interventricular septum is >18 mm thick.
   C. RV obstruction is present in up to 15% of patients with HCM.
   D. RV obstruction is only present when the interventricular septum is >35 mm in thickness.
   E. All of the above.

   Answer: C
   Explanation:
   The genetics of RV involvement has not been well characterized, although histological findings appear similar to those in the LV, suggesting a similar pathogenesis. The incidence of RV obstructive pathology has been reported to vary from 15% to 92% in older cardiac catheterization studies, while more modern data on echocardiography (the current gold standard for diagnosis) document it at 15%.

3. RV obstruction (subpulmonic) in HCM is more commonly reported in young children and infants than adults. The site of RV obstruction is fairly easy to localize with current imaging techniques. The following are true about this phenomenon:
   A. The sites of RV obstruction may be in the outflow tract (the vast majority), the mid-base region at the level of the septal band, and the apical trabecular region.
   B. Combined RV outflow tract (RVOT) and LVOT obstruction is less common than isolated RVOT obstruction.
   C. The Doppler flow velocity profile of RV obstruction shows the typical dagger-shaped profile characteristic of LVOT obstruction due to systolic anterior motion of the tricuspid valve.
   D. Echocardiography easily localizes the region of interest of obstruction in RVOT pathology in the same way as LVOT obstruction.
   E. None of the above.

   Answer: A
   Explanation:
   RV obstruction in HCM is caused by a narrowing of the ventricular cavity as a result of muscle contraction during systole together with a hypertrophied RV free wall and protruding interventricular septum. Obstruction of the RVOT in HCM has been shown to be associated with massive hypertrophy of the LV musculature, which comprises the crista supraventricularis, moderator band, or trabeculae. Combined RVOT and LVOT obstruction is more common than isolated RVOT obstruction, and triple intraventricular obstruction (RVOT, LVOT, and mid-ventricular) also is seen. Isolated RV obstruction has occasionally been described. The Doppler flow velocity profile of RV obstruction appears relatively symmetric and dome-like without the dagger-shaped profile characteristic of LVOT obstruction resulting from the dynamic obstruction caused by systolic anterior motion (SAM) of the mitral valve and SAM-septal contact. There are important caveats that need to be understood during the echocardiographic examination of patients with RVOT obstruction. A concerted effort is needed to investigate the obstructive process under Doppler echocardiography. A short-axis view of the LV that reveals a very thick septum and a crowded RV with severe muscle thickening is an early clue to investigate RVOT obstruction under Doppler.

4. The following are thus true about HCM and obstructive sleep apnea (OSA):
   A. Poor sleep quality may be reported in HCM, but OSA is rare.
   B. Non-sarcomeric mutations are frequent in patients with OSA and HCM.
   C. Patients with OSA and HCM usually have a syndromic association with other features such as deafness and lactic acidosis.
   D. OSA may help protect against the more severe forms of obstructive pathology in HCM.
   E. Several overlapping pathophysiologic alterations underlie the worsening of HCM symptoms in patients who have both HCM and OSA.

   Answer: E
   Explanation:
   The coexistence of HCM and OSA even in patients without the traditional risk factors for OSA is suggested

by recent studies, ranging from 32% to 71%, depending on the methodology and diagnostic criteria used. A large number of candidate gene studies have been performed in OSA, but to date no consistent genetic linkage for OSA has been found. Maternally inherited mutations in mitochondrial DNA have been reported in few patients with concomitant HCM and sleep-disordered breathing. Several pathophysiologic mechanisms help translate the link between these two disease states. The most likely explanation is the altered adrenergic signaling seen in OSA, which also is one of the key features of HCM. This high catecholamine state causes increased hypertrophy and LV filling pressures, decreased cardiac output, and initiation or worsening of LVOT obstruction, dyspnea, dizziness, and mitral regurgitation.

5. A 55-year-old man with a known history of nonobstructive HCM (diagnosed about 6 years ago), maintained on metoprolol 50 mg twice a day, sought attention for a syncopal episode while running. He does not have a history of sudden death in the family. Transthoracic echocardiography showed a septum of 20 mm in thickness. Treadmill exercise testing showed appropriate blood pressure response. A 24-hour, ambulatory electrocardiography monitor revealed short runs of atrial tachycardia but no episodes of non-sustained ventricular tachycardia. Cardiac magnetic resonance imaging revealed a < 5% area of the myocardium with delayed enhancement, and a sleep study showed evidence of severe obstructive sleep apnea-hypopnea syndrome. Which of the following would you use as a minor risk arbitrator for recommending an automatic implantable cardioverter-defibrillator (ICD) in this patient?
   A. LV wall thickness > 20 mm
   B. Genetic testing for sarcomere gene mutations
   C. Electrophysiologic testing (programmed ventricular stimulation)
   D. Sleep study
   E. None of the above

   Answer: E
   Explanation:
   This is a controversial question. In contemporary practice several risk markers have emerged from observational studies and have achieved a general acceptance in risk stratification for prophylactic use of ICDs in HCM patients. These are traditionally classified as ten conventional risk factors and potential or uncertain risk factors. The conventional risk markers include:
   1. Family history of one or more HCM-related sudden death or resuscitated sudden death
   2. One or more episodes of unexplained syncope
   3. LV wall thickness > 30 mm
   4. Non-sustained ventricular tachycardia on Holter monitor
   5. Hypotensive or attenuated blood pressure response on exercise stress testing

   The potential and uncertain risk markers include:
   1. Late gadolinium enhancement by cardiac magnetic resonance imaging
   2. LV apical aneurysm
   3. OSA
   4. LVOT obstruction with a resting gradient >30 mmHg
   5. Associated epicardial coronary artery disease
   6. Atrial fibrillation
   7. Malignant gene mutations (nonsarcomere LAMP 2 or double sarcomere mutations)
   8. Myocardial bridging
   9. Myocardial ischemia
   10. Troponin elevation

   Sudden death is unpredictable in HCM and is the most frequent mode of premature death. Precise risk stratification in HCM remains a challenge due to its clinical heterogeneity of presentation and expression, its relatively low prevalence in general cardiology practice, and the complexity of potential pathophysiologic mechanisms. It is possible that OSA – by affecting mechanisms mediating heart rate variability, including central nervous system coupling between cardiac and ventilatory parasympathetic inputs, the arterial baroreflex, and feedback from pulmonary stretch receptors, i.e., cardiac autonomic dysfunction – can contribute to an elevated risk of sudden death in HCM. Chronic sympathetic overdrive is another mechanism that can contribute to the elevated risk of sudden cardiac death in HCM patients with OSA. These are mechanistic considerations that can stimulate the proposition of a true arrhythmogenic role of OSA in HCM in susceptible patients, but not one that has been proven yet.

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Epiphenomena in Hypertrophic Cardiomyopathy: Acquired von Willebrand Syndrome

18

Joseph L. Blackshear

Key Points

- If asked, many patients with hypertrophic cardiomyopathy (HCM) will report spontaneous bleeding; the two most common types are epistaxis and gastrointestinal bleeding (GIB). GIB is often seen in elderly females with phenotypic HCM and left ventricular outflow tract obstruction.
- In patients with HCM and GIB, the most frequent endoscopic finding is gastrointestinal angiodysplasia, which has been associated with congenital and acquired von Willebrand syndrome.
- Hypertrophic cardiomyopathy with resting left ventricular outflow tract obstruction produces abnormalities of biochemical tests that approach the severity of derangement seen in patients with nonpulsatile left ventricular assist devices.
- In patients with hypertrophic cardiomyopathy and a significant bleeding history, laboratory tests for acquired von Willebrand syndrome should include platelet function analyzer 100, von Willebrand factor antigen and activity, and von Willebrand factor multimer analysis.
- Severe bleeding and laboratory tests of VWF function respond to interventions which reduce left ventricular outflow tract gradients; thus the expectation should be that septal reduction therapy will be curative of severe angiodysplasia-related GIB in HCM patients.

An Introduction to von Willebrand Factor

Biologically normal von Willebrand factor (VWF) is perturbed to cause acquired von Willebrand syndrome by shear stress in cardiac disorders or by immune mechanisms in hematologic disorders [1]. Normal VWF monomers are synthesized in the ribosome of endothelial cells and platelets and are dimerized in the endoplasmic reticulum, and multimers up to 20–40 monomers are assembled in the Golgi. Once secreted into plasma, passive elongation of the ultralarge multimers during passage through the microcirculation results in enzymatic degradation from ADAMTS 13, such that pre-secretion forms vary from 500 to 40,000 kDa but post-secretion sizes are 500–10,000 kDa. In normal physiology VWF multimers vary from 2 to 25 or so identical monomers, but sizes of >10 monomers represent only 4% of total protein, while 30% are dimers, and 24% are 5 monomer units or smaller [2]. The highest molecular weight species are required for effective hemostasis in high shear environments [3, 4]. Once secreted, re-multimerization does not occur, so that VWF multimers degraded by high shear cardiac lesions remain dysfunctional, and if measured, provide evidence of cardiac lesion severity. VWF has also been linked to angiogenesis, and so the much higher prevalence of intestinal angiodysplasia in von Willebrand diseases of all types is likely fostered by VWF dysfunction [5, 6]. In Fig. 18.1, gel electrophoresis of VWF in a patient with hypertrophic obstructive cardiomyopathy (top) and control plasma (bottom) shows the loss of multimers with repeat units > approximately 18.

There is no consensus on how to quantitate multimer loss, but both descriptions of which bands are lost and a comparison

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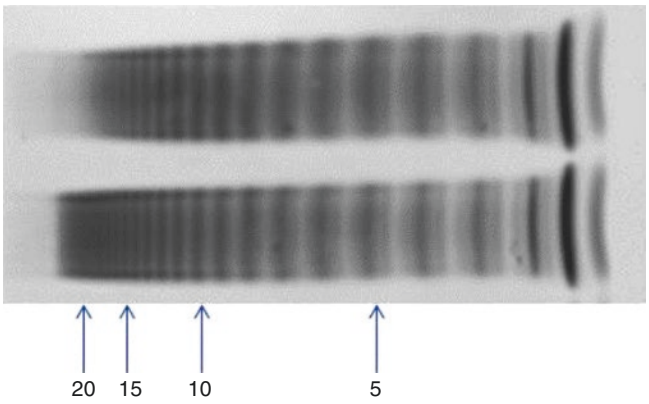

Fig. 18.1 Plasma from a patient with obstructive HCM, top and control plasma, bottom. The vertical line separates band 1 from band 2, and arrows indicate the larger bands

to normal plasma are relevant. We and others have introduced a "normalized multimer ratio," in which high molecular weight multimer (HMWM) bands >15 are divided by bands 2–15, constituting a HMW fraction, and can be divided by the same measure for normal plasma [7–10]. This normalization is required, since the absolute value of the HMW fraction of normal plasma is highly variable from electrophoretic run to run and from lab to lab. The normalized multimer ratio yields a value approximating unity for normal plasma, and between 0.40 and 0.50 for patients with the most severe loss of HMW multimers, such as left ventricular assist device (LVAD) patients. The point of care platelet function analyzer (PFA) closure time, normal <121 s, produces results which parallel to the findings from multimer analysis for most cardiac diagnoses and have the advantage of immediate results, as opposed to a week's turnaround for VWF multimers. However with the most severe loss of VWF function, as with LVAD, the vast majority of samples of PFA will not clot during the 300 s observation period, and so relative differences between LVAD types cannot be discerned by PFA. Ratios of VWF activity to antigen are less sensitive than either VWF multimers or PFA. For more on testing, see reference [11].

Historical Perspective: Bleeding and Hypertrophic Cardiomyopathy

Bleeding associated with severe aortic stenosis was initially reported in the 1950s, and for years the association with gastrointestinal angiodysplasia was debated [12]. An association of hypertrophic cardiomyopathy and gastrointestinal hemorrhage and angiodysplasia has been reported several times [13–19], and resolution of the bleeding disorder has also been reported with definitive therapies to reduce the outflow gradient including beta-blockade, alcohol septal ablation, and septal myectomy [13, 18, 19]. In one prior case report, a patient with hypertrophic cardiomyopathy and a history of bleeding had confirmation of loss of HMWM, with some qualitative improvement after intensification of medical therapy [20]. Bleeding has also been reported with organic mitral regurgitation, in which disruption of VWF multimers also correlates with the severity of mitral regurgitation [21], suggesting an additional mechanism by which VWF multimers may be disrupted in obstructive hypertrophic cardiomyopathy. Any residual doubt about the association of intravascular shear, bleeding, and gastrointestinal angiodysplasia has been dissipated by the experience with the continuous flow LVADs. Gastrointestinal bleeding complicates modern LVAD therapy in 20% of patients, and angiodysplasia has been the most common lesion found at endoscopy [22]. We will explore the relative severity of abnormalities of VWF between high shear entities later in this chapter.

VWF as a Biomarker of Lesion Severity and as a Treatment Biomarker

In aortic stenosis a correlation of gradient severity and relative reduction of high molecular weight VWF multimers has been noted by several investigators [23–27]. In 2008, LeTourneau and colleagues described 62 patients with hypertrophic cardiomyopathy, 28 of whom were considered to have subaortic obstruction. Loss of high molecular weight multimers of VWF closely correlated to the magnitude of left ventricular outflow obstruction [28]. This close relationship between pressure gradient and VWF degradation raises the possibility that functional VWF laboratory studies could be used as markers of disease severity, reflect progression of disease, and accurately indicate responses to intervention.

Our group studied a large cohort of patients before and after various clinically indicated treatments. As was noted by LeTourneau and colleagues, multiple tests of VWF function reflected the severity of the gradient (Tables 18.1 and 18.2). Peak left ventricular outflow tract gradient and peak velocity correlated more strongly with VWF indexes than BNP, while BNP correlated with septal thickness and mitral E/septal e' [8]. We presented an example of a patient with two pathologic mutations who experienced rapid hemodynamic progression of disease over 2 years with marked worsening of outflow gradient and VWF dysfunction and resolution of the changes with septal myectomy (Fig. 18.2). Finally, we evaluated VWF tests in demonstrating responses to medical or pacing interventions, alcohol septal ablation, and surgical septal myectomy. Myectomy was associated with normalization of VWF multimers in all patients, while responses to medical interventions and alcohol septal ablation were not uniformly able to improve VWF function (Fig. 18.3). This accords well with the current notion that septal myectomy is the preferred intervention for refractory symptoms of left ventricular outflow tract obstruction.

Table 18.1 Prevalence of abnormal von Willebrand factor activity measures and BNP in obstructive versus latent hypertrophic cardiomyopathy

Variable	Total group (n = 90)	Obstructive HC (n = 62)	P, obstructive versus latent HC	Latent HC (n = 28)	P, latent HC versus control	Control (n = 10)
Abnormal VWF multimers	64/87, 74%	53/61, 87%	0.0001	13/28, 48%	0.008	0/10
Abnormal PFA	64/88, 73%	50/61, 82%	0.0044	14/28, 50%	0.056	1/10, 10%
Abnormal VWF activity/antigen	41/82, 50%	36/58, 62%	0.0018	6/26, 23%	0.157	0/10
BNP abnormal	71/83, 86%	51/55, 93%	0.0001	13/27, 48%	0.007	0/10

Abbreviations: *BNP* brain natriuretic peptide, *HC* hypertrophic cardiomyopathy, *PFA* platelet function analyzer, *VWF* von Willebrand factor
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Table 18.2 Correlations (Spearman) of echocardiographic and Doppler indexes to von Willebrand factor (VWF) variables and brain natriuretic peptide (BNP) in hypertrophic cardiomyopathy

	Peak gradient	p=		Peak velocity	p=
PFA	0.51	<0.0001	PFA	0.51	<0.0001
VWF Ag	0.26	0.02	VWF Ag	0.26	0.02
VWF Act	0.14	0.21	VWF Act	0.13	0.24
Act/Ag	−0.57	<0.0001	Act/ag	−0.57	<0.0001
NMR 15	−0.57	<0.0001	NMR 15	−0.57	<0.0001
NMR 10	−0.61	<0.0001	NMR 10	−0.62	<0.0001
BNP	0.37	0.0005	BNP	0.38	0.0005
BNP/ULN	0.26	0.02	BNP/ULN	0.24	0.03
	Septal thickness	p=		LV mass index	p=
PFA	0.19	0.07	PFA	0.16	0.16
VWF Ag	−0.26	0.02	VWF Ag	−0.1	0.39
VWF Act	−0.29	0.01	VWF Act	−0.13	0.26
Act/Ag	−0.1	0.38	Act/Ag	−0.21	0.06
NMR 15	−0.15	0.16	NMR 15	−0.24	0.03
NMR 10	0.15	0.16	NMR 10	−0.29	0.009
BNP	0.26	0.02	BNP	0.29	0.01
BNP/ULN	0.44	<0.0001	BNP/ULN	0.37	0.001
	E/e'	p=		LA volume index	p=
PFA	0.29	0.008	PFA	0.23	<0.04
VWF Ag	0.36	0.001	VWF Ag	0.01	0.93
VWF Act	0.2	0.08	VWF Act	0.02	0.87
Act/Ag	−0.48	<0.0001	Act/Ag	−0.11	0.35
NMR 15	−0.37	0.0007	NMR 15	−0.29	0.008
NMR 10	−0.37	0.0007	NMR 10	−0.41	0.0001
BNP	0.52	<0.0001	BNP	0.34	0.002
BNP/ULN	0.34	0.002	BNP/ULN	0.35	0.002

Abbreviations: *Act* activity, *Ag* antigen, *BNP* brain natriuretic peptide, *E/e'* mitral Doppler E wave/septal tissue Doppler e' wave, *LA* left atrial; *LV* left ventricular, *NMR* normalized multimer ratio, *PFA* platelet function analyzer, *ULN* upper limit of normal, *VWF* von Willebrand factor
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VWF as One of Many Screening Biomarkers

Screening for disease phenotype is used in assessing safety for sports participation and for first-degree relatives of known patients with hypertrophic cardiomyopathy. Current guidelines for screening for phenotypic hypertrophic cardiomyopathy utilize clinical history and examination, electrocardiography, and echocardiography. Phenotypic blood biomarkers have not been widely exploited. Elevations of the ventricle-expressed B-type natriuretic peptides, which in the setting of myocyte disarray show elevations far in excess of those expected for ventricular hypertrophy alone [29–41], and abnormalities of von Willebrand factor activity are candidate biomarkers for screening. Screening with sensitive blood tests could allow more frequent testing for relatives of affected individuals and also prior to sports participation. We evaluated the potential for these biomarkers to be used individually and

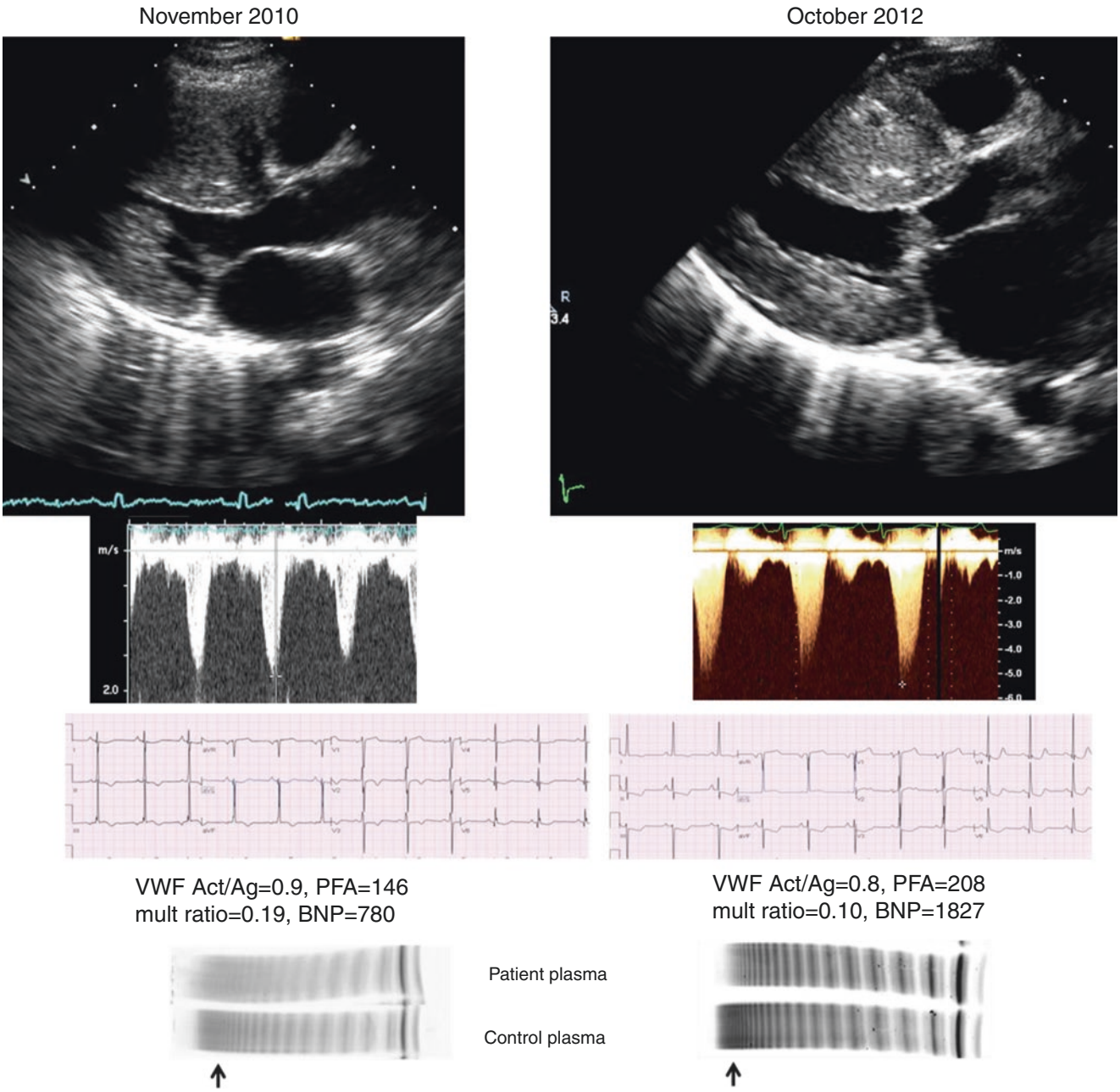

Fig. 18.2 A 19-year-old man with two myosin-binding protein C mutations experienced rapid progression of hypertrophy over 2 years with de novo development of left ventricular outflow obstruction. The change was associated with new von Willebrand factor dysfunction signaled by three independent laboratory parameters. Reproduced from Ref. [8] with permission

jointly in a screening context [42]. Given the prior extraordinary elevations of BNP reported and a high sensitivity of NT-proBNP in screening relatives of hypertrophic patients with identified sarcomere mutations [41], we also compared levels of BNP or NT-proBNP in functional class I patients who had undergone genetic testing.

Platelet function analyzer 100 (PFA, sample $n = 99$) and normalized brain natriuretic peptide or NT-proBNP (BNP/ULN, sample $n = 92$) were measured in 64 patients with hypertrophic cardiomyopathy (HC) compared to 29 normal controls (NC). To simulate a screening context, biomarker or estimated biomarker sensitivity and specificity versus ECG were assessed in a separate group of 189 functional class I HC patients without prior septal reduction therapy. For this group, PFA was estimated from the regression equation relating gradient to PFA in the prior patients and controls. Finally, BNP/ULN levels were compared in functional class I patients with known sarcomere mutations ($n = 28$) versus NC, mutation-negative hypertrophic cardiomyopathy patients ($n = 36$), hypertrophic cardiomyopathy patients

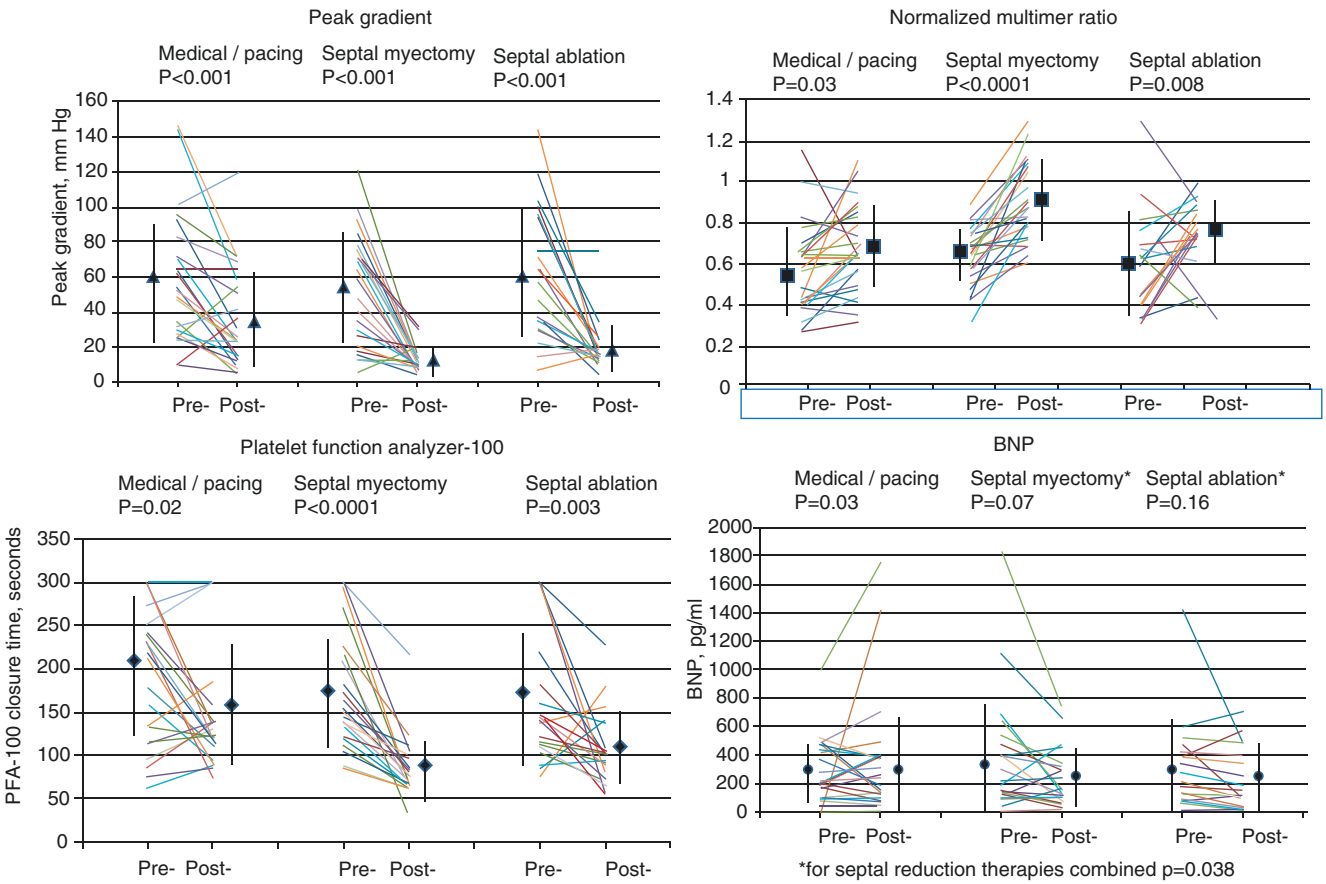

Fig. 18.3 Individual patient response to medical or pacing interventions or alcohol septal ablation or surgical septal myectomy. Reproduced from Ref. [8] with permission

with undefined mutation status (n = 124), and positive (n = 71) or negative (n = 109) family history.

In 42 obstructive patients versus normal controls, there was slight overlap of PFA, and BNP/ULN, but for the product of PFA-CADP X BNP/ULN, there was near-complete separation of values (Fig. 18.4). Among 37 separate class I obstructive patients, estimated PFA had a sensitivity of 92% and specificity of 100%, and BNP/ULN showed sensitivity of 89% and specificity of 100%. In the same patients, ECG showed a sensitivity of 70% and specificity of 93% (Table 18.3). Functional class I patients with and without sarcomere mutations and family history of hypertrophic cardiomyopathy had significant elevations of BNP/ULN versus controls, but among these class I groups, no differences were seen. While elevated over controls, BNP was not uniquely elevated in patients with familial versus non-familial or mutation positive versus mutation-negative hypertrophic cardiomyopathy (Fig. 18.5). These results suggest that BNP and PFA could be used to screen for hypertrophic cardiomyopathy, especially for the obstructive phenotype. Annual evaluation of relatively inexpensive tests might show trends earlier than the every 5-year echocardiographic evaluation recommended in guidelines.

Outcomes of Bleeding and Therapy for HCM

Our group first encountered a patient with hypertrophic cardiomyopathy and recurrent, transfusion-dependent gastrointestinal blood loss due to angiodysplasia in 2006. The initial laboratory screen, using VWF antigen and ristocetin cofactor activity, failed to identify acquired von Willebrand syndrome. Due to clinical suspicion, VWF multimer analysis was ordered and revealed a typical pattern of loss of high molecular weight multimers. After declining surgery for several months, the patient ultimately came to extended septal myectomy with cure of recurrent bleeding: a cure that has been durable for 9 years even when prescribed clopidogrel for a transient ischemic attack. The efficacy of myectomy in relieving bleeding and the abnormality of VWF multimer in this patient and in four additional patients were reported in 2011 [43].

We have continued to encounter patients with this entity. Fig. 18.6 illustrates how clinical suspicion, laboratory testing, and guideline-based intervention can result in favorable outcomes. A 70-year-old woman was referred for evaluation of a 4-year history of transfusion-dependent anemia and melena. Despite multiple enteroscopies, ablation of angiodysplastic lesions in the small bowel, and angiography-

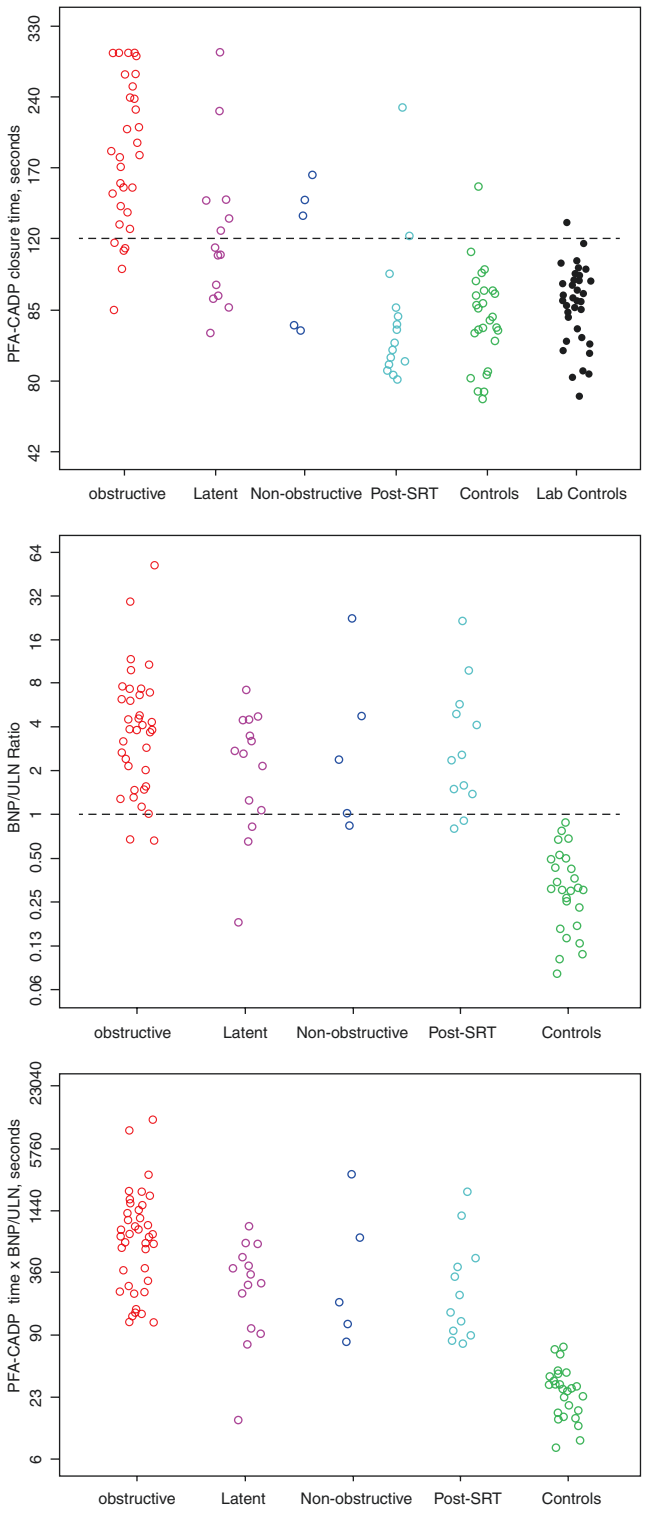

Fig. 18.4 Scatterplots of platelet function analyzer 100 closure time, adenosine diphosphate cartridge (PFA) (top), brain natriuretic peptide/upper limit of normal (BNP/ULN), (middle) and PFA X (BNP/ULN) (bottom) in 99 samples from 64 patients with obstructive, latent, nonobstructive HC patients, in 17 patients post septal reduction therapy (SRT) and 29 samples from individual controls. Reproduced from Ref. [42] with permission

directed surgical resection of the ileocolic junction, she had persistent melena and required transfusions every 2–3 weeks. She carried a diagnosis of mitral regurgitation, and she had a prominent systolic murmur on exam. However, echocardiography revealed hypertrophic cardiomyopathy with mitral regurgitation that was secondary to systolic anterior motion of the mitral valve and a left ventricular outflow tract (LVOT) peak instantaneous velocity of 4–5 meters per second. Laboratory analysis revealed loss of high molecular weight multimers of VWF. Despite the use of beta-blocker therapy, she continued to bleed, and alcohol septal ablation of two septal perforator vessels was performed. Six months after the procedure, her left ventricular outflow tract gradient had normalized, and her hemoglobin was 14 mg/dL. She has remained transfusion independent for 3 years.

We have reported that severe bleeding is unlikely to respond to medical therapy alone. Although the first patient from the 2011 series was male, the 4 additional cases in that initial report, and all 11 cases with transfusion dependence in a subsequent report were elderly women [44]. Lesser degrees of gastrointestinal bleeding and other bleeding occurred in men and women, and epistaxis was a frequent finding in patients in whom a bleeding questionnaire was prospectively employed. Although our population had skewed prevalence due to the referral bias of expertise in double-balloon enteroscopy, we found an overall prevalence of abnormal bleeding in 26%, with bleeding being more likely with advancing age and female gender. Data from this series, including interventions, gradients, and outcomes, is reproduced in Table 18.4 [44].

As mentioned previously, the LVAD population has the most severe loss of high molecular weight multimers of all patient groups that have been studied, as well as the highest rates of gastrointestinal bleeding and angiodysplasia. Using the normalized multimer ratio, we have been able to compare the severity of high molecular weight multimer loss in hypertrophic cardiomyopathy to other entities. As can be seen, hypertrophic cardiomyopathy patients overlap LVAD patients and, by three independent tests of acquired von Willebrand syndrome, namely, multimer analysis, PFA, and VWF activity to antigen ratio, show trends of more severe VWF abnormalities even than in patients with severe aortic stenosis (Fig. 18.7). Thus, questioning patients regarding bleeding and linking the findings of exam and echocardiography to appropriate laboratory tests for acquired von Willebrand disease especially in the setting of severe bleeding are required to comprehensively unify the diagnosis in some patients. Our general approach in evaluating patients who present with bleeding is shown in the following treatment algorithm.

Table 18.3 Sensitivity, specificity, positive and negative predictive value, and likelihood ratios for detection of HC versus controls by estimated PFA and by BNP/ULN

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Liklihood ratio
Estimated PFA					
Obstructive HC	88 (76–95)%	97 (80–100)%	98 (87–100)%	82 (65–93)%	25.7 (3.7–176)
Latent HC	56 (31–78)%	97 (80–100)%	91 (57–100)%	78 (60–89)%	16.1 (2.3–115)
Nonobstructive HC	45 (18–75)%	97 (80–100)%	83 (36–99)%	82 (64–93)%	13.2 (1.7–101)
BNP/ULN					
Obstructive HC	93 (80–98)%	100 (85–100)%	100 (89–100)%	91 (74–98)%	Infinity
Latent HC	61 (36–82)%	100 (85–100)%	100 (68–100)%	81 (63–91)%	Infinity
Nonobstructive HC	73 (39–93)%	100 (85–100)%	100 (60–100)%	91 (74–98)%	Infinity
Estimated PFA X BNP/ULN					
Obstructive HC	93 (80–98)%	100 (85–100)%	100 (89–100)%	91 (74–98)%	Infinity
Latent HC	61 (36–82)%	100 (85–100)%	100 (68–100)%	81 (63–91_%	Infinity
Nonobstructive HC	72 (39–93)%	100 (85–100)%	100 (60–100)%	91 (74–98)%	Infinity
Electrocardiography					
Obstructive HC	71 (53–84)%	93 (64–100)%	53 (39–67)%	47 (33–61)%	9.8 (1.47–66)
Latent HC	34 (19–53)%	93 (64–100)%	26 (15–41)%	74 (59–85)%	4.8 (0.7–4)
Nonobstructive HC	67 (57–75)%	93 (64–100)%	60 (52–69)%	40 (31–-48)%	9.3 (1.4–62)

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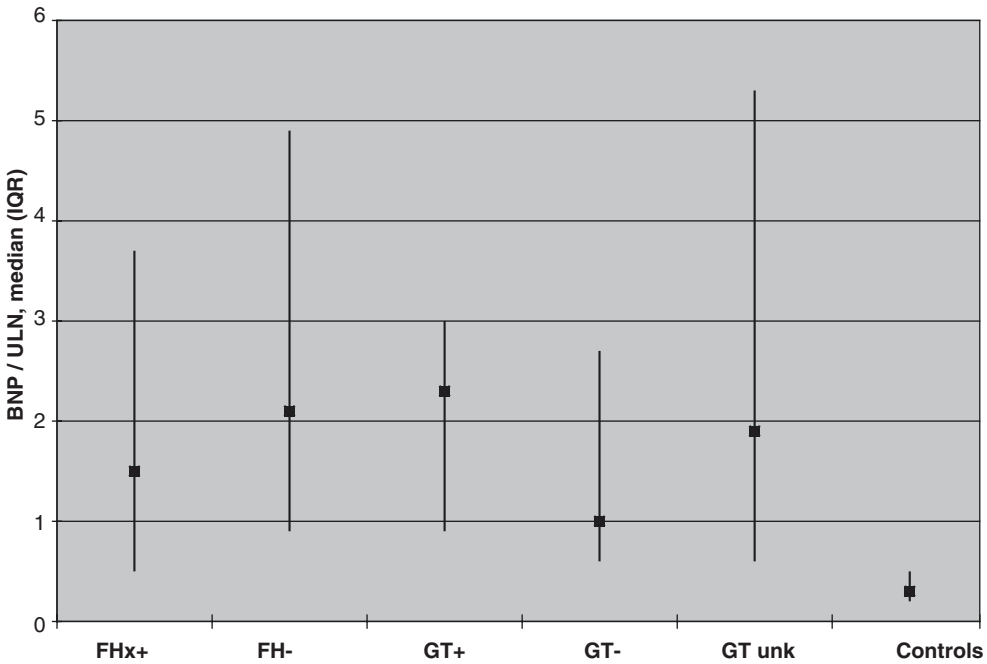


Fig. 18.5 Median and interquartile range for brain natriuretic peptide/upper limit of normal (BNP/ULN) in 189 functional class I hypertrophic cardiomyopathy (HC) patients with a positive family history (FHx+) of HC, negative family history of HC (FHx-), positive genetic test for sarcomere mutation (GT+), negative genetic test for sarcomere mutation (GT-), and no genetic test performed (GT unk) compared to 29 controls. $P < 0.002$ for all comparisons to controls. No significant differences in tests of the means between the other groups

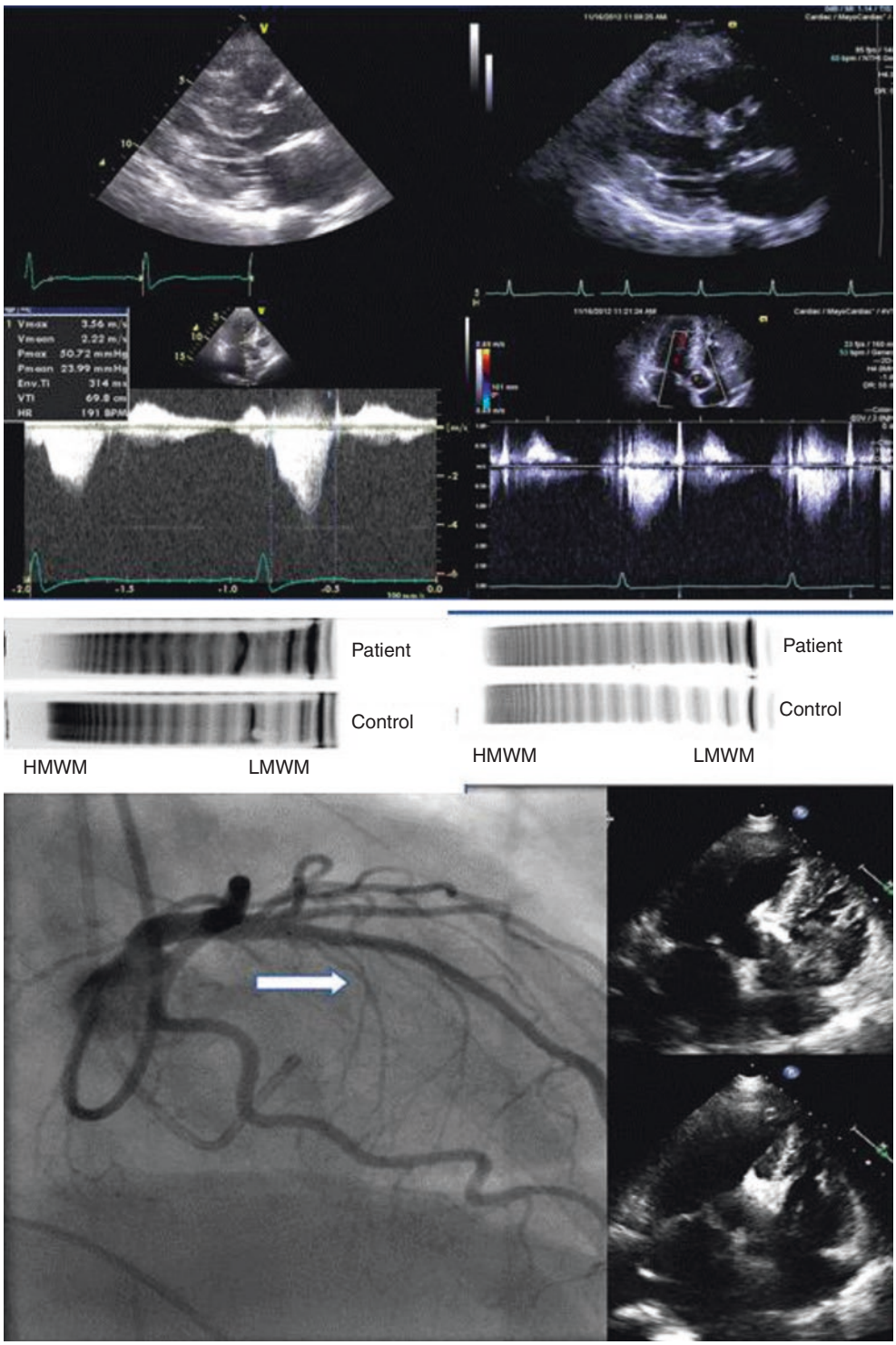


Fig. 18.6 Top left, prior to septal ablation, and top right, after alcohol septal ablation. Mid-systolic 2-D echo and continuous wave Doppler signals show left ventricular outflow tract obstruction. High molecular weight multimer loss corrected after ablation. Still frame coronary angiography and perflutren contrast echo show regions of ablation in two septal perforator vessels

Table 18.4 Bleeding and response to intervention in hypertrophic cardiomyopathy. Reproduced from Ref. [44] with permission

Age, gender	Rest (provoked) gradient mm Hg	MR severity	VWF multimers	Endoscopic findings	Intervention	Freedom from bleeding, months
Transfusion-dependent GI bleeding						
63, F	64	++	abn	None	Myect	29
73, F	57	unk	abn	AVM	SA	42
72, F	100	++	abn	AVM[a]	SA	21
78, F	71	+	abn	None	SA	5
77, F	75	++	abn	None	Myect	29
81, F	36 (100)	+++	abn	AVM[a]	SA	11[b]
81, F	40	++	abn	AVM	BB	9.6[b]
82, F	44	++	abn	AVM	BB	8.4[b]
69, F	92	++	abn	AVM	SA X 2	5
75, F	19 (64)	+	nl	None	SA	2
74, F	29 (84)	++	abn	AVM	BB	3
Other GI bleeding‡						
80, F	55	++	abn	AVM	BB	69
63, M	95	++	abn	None	Myect	99
65, M	29 (112)	+	abn	None	BB	105
63, M	46	++	abn	None	BB	103
72, F	121	+	abn	None	Myect	77
46, F	95	+	abn	None	Myect	47
66, F	144	+	abn	None	SA	41
75, F	74	++	abn	None	BB	37
35, M	12 (91)	+	nl	Polyps	Myect	12
Epistaxis						
74, F	34 (104)	++	nl		Diso	
54, F	85	++	abn		Myect	
59, M	101	++	abn		SA	
53, M	77	+	abn		Myect	
65, F	62	+	abn		Diso	
Other§						
73, M	44	++	abn		BB	
55, F	74	+	abn		SA	

‡Other types of GI bleeding included recurrent rectal outlet bleeding [4], one or more episodes of melena with one hospitalization and transfusion [3], and iron deficiency with episodic anemia and positive fecal occult blood test results [2].

§'Other' patients included one patient who bled twice after angiography and once after orthopedic surgery, and a second patient with menorrhagia requiring uterine ablation and a history of bleeding from trivial cuts and easy bruising.

Abbreviations: *MR* mitral regurgitation, *VWF* von Willebrand factor, *GI* gastrointestinal, +, ++, +++ indicating mild, moderate, or severe mitral regurgitation, *unk* unknown, *AVM* arteriovenous malformation, *myect* surgical septal myectomy, *SA* alcohol septal ablation, *BB* beta-blocker

[a]Patient 3 had one exploratory laparotomy for bleeding. Patient 6 had two exploratory laparotomies for bleeding

[b]Had at least one recurrence of gastrointestinal hemorrhage after initiation of treatment

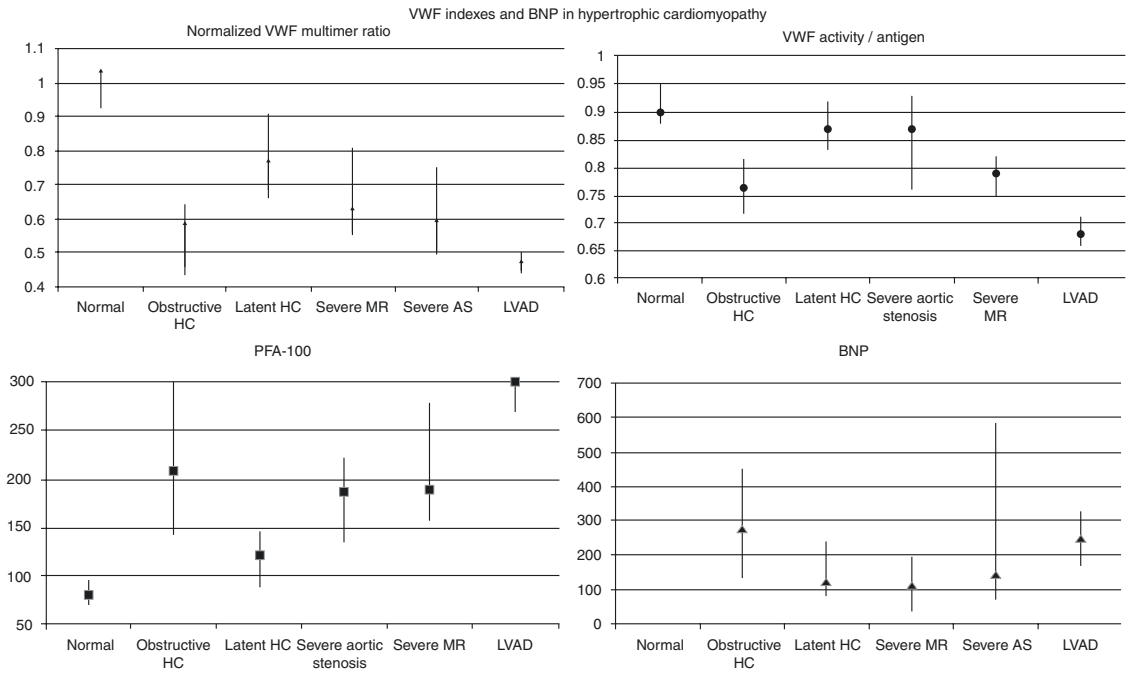
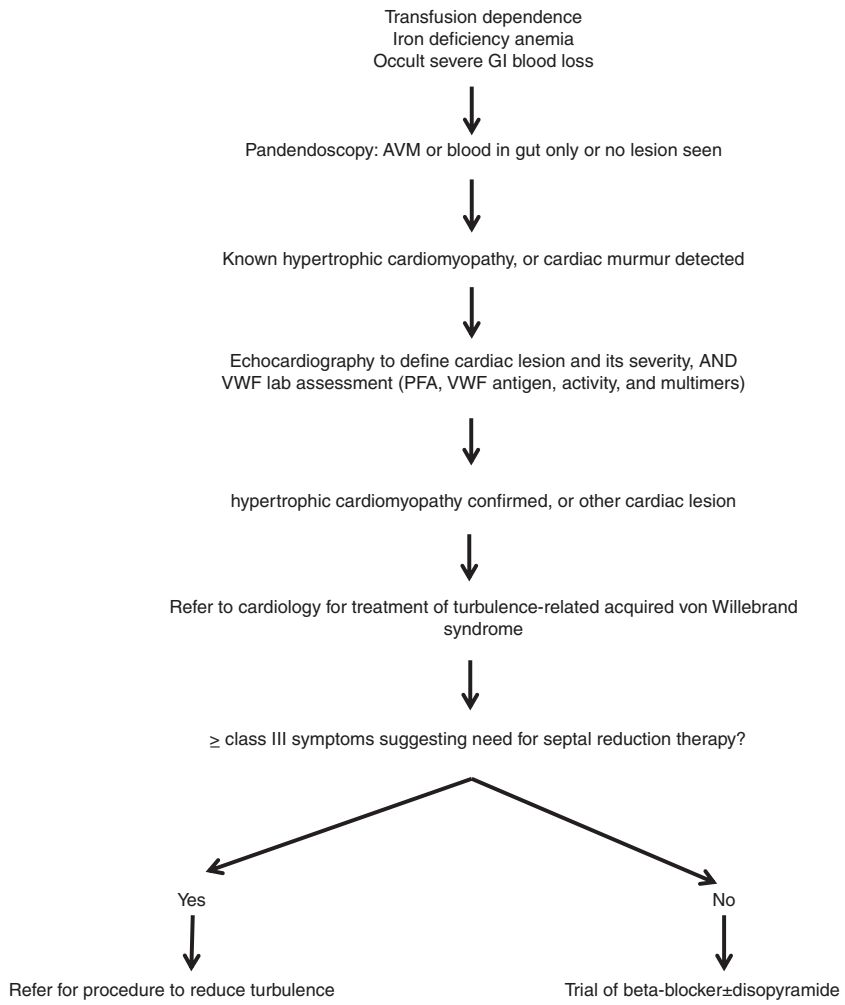


Fig. 18.7 VWF function tests in hypertrophic cardiomyopathy in comparison to other high shear entities. (Reproduced from reference [8] with permission)



Clinical Pearls

- The turbulent flow of left ventricular outflow tract obstruction plus associated mitral insufficiency is associated with almost universal abnormalities of von Willebrand factor function.
- As in severe aortic stenosis and left ventricular assist devices, the degree of abnormality in the obstructive phenotype is sufficient to cause acquired von Willebrand syndrome: gastrointestinal bleeding due to intestinal angiodysplasia, epistaxis, and other bleeding, and thus a bleeding history should be interrogated in hypertrophic cardiomyopathy patients.
- The most useful blood tests for evaluating acquired von Willebrand syndrome are VWF multimer analysis and platelet function analyzer 100 collagen adenosine diphosphate.
- VWF tests correlate with gradient, while BNP and NT-proBNP correlate with septal thickness and diastolic dysfunction. When applied in a screening context, the two biomarker approaches could be complementary.
- VWF tests not only reflect resting gradient; they accurately demonstrate the hemodynamic response to therapies designed to relieve left ventricular outflow tract obstruction.
- Severe bleeding in hypertrophic cardiomyopathy responds to septal reduction therapy with either surgical myectomy or alcohol septal ablation.

Questions

1. Acquired von Willebrand syndrome is limited to:
   A. Aortic stenosis
   B. Myeloproliferative disorders
   C. Obstructive hypertrophic cardiomyopathy
   D. Mitral regurgitation
   E. Not limited, occurs in all of the above

   Answer: E. In any situation in which a large fraction of the circulating plasma is exposed to elevated shear stress during each cardiac cycle, the possibility of AVWS exists. It also occurs via immune mechanisms in myeloproliferative disorders, for example, monoclonal gammopathy of undetermined significance (MGUS).

2. Which statement best characterizes the post-secretion normal physiology of von Willebrand factor?
   A. VWF multimers are degraded by proteolysis during microcirculatory passage.
   B. VWF multimers are shortened by passage through the normal heart.
   C. VWF monomers are secreted and form multimers in the circulation.
   D. VWF multimer shortening is nonenzymatic.
   E. VWF is generated in the liver.

   Answer: A. Unlike many proteins which are processed in organs, or after incoroporation into cells via specific receptors, the proteolytic enzyme which shortens VWF multimers, ADAMTS 13 circulates in plasma. The A2 domain binding site on VWF multimers is cryptic unless the globular protein is elongated, as during capillary transit, or in a high shear stress field.

3. Which of the following is not a characteristic of VWF
   A. Regulates angiogenesis
   B. Facilitates hemostasis in high shear environment
   C. Is a complex glycoprotein with several genetic variants causing von Willebrand disease
   D. Is secreted as a prohormone
   E. Carrier of coagulation factor VIII

   Answer: D. VWF has numerous functions, including regulation of angiogenesis, and acting as a "molecular bus" for factor VIII. It is secreted as a fully formed ultrahigh molecular weight multimeric protein which is then reduced in size during microcirculatory passage by ADAM TS 13.

4. Which of the following correlate with pressure gradient in hypertrophic cardiomyopathy?
   A. VWF antigen
   B. VWF activity to antigen ratio
   C. Loss of high molecular weight multimers of VWF
   D. Platelet function analyzer collagen ADP closure time
   E. B, C, and D

   Answer: E. Assays of VWF function which reflect the presence of high molecular weight multimers include PFA testing, VWF multimer analysis, and the VWF activity to antigen ratio (in some laboratories, a VWF collagen binding assay is substituted for VWF activity, and a VWF collagen binding activity / VWF antigen ratio is reported).

5. Which intervention most reliably normalized VWF multimers in a bleeding patient with obstructive hypertrophic cardiomyopathy?
   A. Beta blockers
   B. Disopyramide
   C. Pacing induced left bundle branch block
   D. Correction of atrial fibrillation
   E. Septal reduction therapy

Answer. E. Septal reduction therapy was associated with cessation of bleeding in patients with transfusion dependence, while medical therapy was associated with recurrence.

6. As screening biomarkers, BNP and PFA are:
   A. Redundant
   B. Complementarry
   C. Insensitive
   D. Non-specific
   E. Untested

   Answer. B. As suggested by the prior question, VWF measures correlate with the amount of turbulence present from a combination of high LVOT gradient and significant associated mitral regurgitation. BNP reflects the degree of structural abnormality as measured by degree of hypertrophy and also as reflected in elevation of filling pressures.

7. In patients with severe aortic stenosis, which of the following is incorrect?
   A. VWF multimers normalize almost immediately after valve replacement.
   B. If VWM multimers are abnormal prior to valve replacement, use of a mechanical prosthesis and anticoagulation increases bleeding risk.
   C. VWF multimers may fail to correct if either ≥moderate paraprosthetic regurgitation or patient prosthesis mismatch is present.
   D. PFA can be a useful test periprocedurally in transcatheter aortic valve replacement as a biomarker of ≥moderate paraprosthetic regurgitation.
   E. Balloon aortic valvuloplasty rarely causes VWF multimers to normalize.

   Answer: B. Once the turbulence associated with severe aortic stenosis is relieved, newly secreted multimers retain their high molecular weight status, and values rapidly return to normal. Despite a very high rate of abnormal VWF multimers before aortic valve replacement, bleeding in anticoagulated patients with mechanical valves after surgery is not increased.

8. What percent of severe aortic stenosis or obstructive hypertrophic cardiomyopathy patients have loss of high molecular weight multimers of VWF?
   A. 10%
   B. 25%
   C. 70-90%
   D. 100%
   E. 50%

   Answer: C. The percentage of abnormal VWF multimers reaches 100% only in the LVAD population. For other entities which physicians categorize as severe by usual echocardiographic and hemodynamic criteria, multimer abnormalities are present in 70–90%.

9. A patient with frequent epistaxis, some requiring emergency room visits, has class III angina and a left ventricular outflow tract resting instantaneous gradient of 55 mm Hg. VWF multimer testing is abnormal. She is to undergo septal myectomy for symptoms. Based on these data, you tell her:
   A. Nosebleeds are likely to stop after.
   B. Nosebleeds will not be affected by surgery
   C. Bleeding risk during surgery is high
   D. She must have an ENT consult before surgery
   E. She may not take aspirin or anticoagulation after surgery

   Answer: A. Mucosal bleeding, i.e., GI and nasal, are the two most common clinical manifestations of AVWS due to cardiac lesions. The high gradient, and abnormal lab tests of VWF function, and the high likelihood of a good hemodynamic response from myectomy suggest that epistaxis will be cured by myectomy.

10. Based on case reporting thus far, transfusion- dependent gastrointestinal bleeding from acquired von Willebrand syndrome in hypertrophic cardiomyopathy occurs in:
    A. Equal percentages of men and women
    B. Much higher frequency in women compared to men
    C. Much higher frequency in men compared to women
    D. Slightly more prevalent in women versus men
    E. Slightly more prevalent in men versus women

    Answer: B. Like takotsubo cardiomyopathy, this entity has shown a much higher occurrence in women versus men. This appears to be unique to hypertrophic cardiomyopathy, since such a gender imbalance of AVWS does not occur with other high shear states such as aortic stenosis or mitral regurgitation. Smaller chamber size in women compared to me could be a factor, but the precise reason why this should be is unknown.

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Epicardial and Microvascular Ischemia: Implications, Diagnosis, and Management

19

George S. Hanzel

Key Points

- Angina is present in a minority of HCM patients (20%), yet myocardial perfusion defects can be found in up to 75%. Therefore, like outflow tract obstruction, ischemia is a fundamental component of the pathophysiology of HCM in most individuals.
- Epicardial CAD contributes to heightened mortality in HCM patients, especially in older patients, and should be treated when found.
- Ischemia is at least partly to blame for the myocardial fibrosis found in patients with HCM; fibrosis can and does occur in the absence of ischemia.
- Myocardial bridging is seen in up to 15% of HCM patients, although its contribution to ischemia and angina remain controversial.

Introduction

Myocardial ischemia was first described in hypertrophic cardiomyopathy (HCM) patients without epicardial coronary artery disease (CAD) in the 1960s. Over time it has been recognized that angina is a common symptom in HCM and is seen in over 20% of patients. Evidence of silent myocardial ischemia is even more common and can be seen in 50–75% of patients. Furthermore, these patients with HCM and ischemia have been shown to have higher mortality rates (where ischemia has been proposed as a trigger for cardiac arrest), as well as greater degrees of myocardial fibrosis, adverse left ventricular remodeling, and left ventricular systolic dysfunction. Despite this, ischemia is an underappreciated facet of this complex disorder, most likely due to the dominance of other heart failure symptoms to the clinical picture [1].

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This chapter will review evidence regarding the presence and frequency of myocardial ischemia in HCM in the absence of concomitant epicardial CAD, the proposed mechanism of ischemia, and the clinical consequences of and prognosis associated with ischemia in HCM, including myocardial fibrosis, adverse left ventricular remodeling and systolic dysfunction, angina, congestive heart failure and mortality, and inclusive of sudden death. The diagnosis and management of both microvascular ischemia as well as epicardial CAD will be discussed.

Evidence for Ischemia and Injury in HCM

Multiple imaging modalities and various invasive techniques have suggested the presence of ischemia in HCM. However, autopsy studies have provided the most conclusive evidence for ischemia in HCM by documenting myonecrosis in HCM patients without epicardial coronary artery disease who had died suddenly (Fig. 19.1). Although only case series have been published the findings are compelling [2]. In one study of 48 patients without CAD, 15% had evidence of old transmural myocardial infarction [3]. In another study of 19 young patients with HCM who suffered sudden death, 58% had evidence of replacement fibrosis, and 74% had multifocal areas of acute or subacute myocardial necrosis [4]. Patients with replacement fibrosis were older and had greater septal thickness and small vessel medial hypertrophy. These findings suggest that supply-demand mismatch may lead to ischemia and even myocardial necrosis in a large number of HCM patients or at least those who suffer sudden cardiac death.

Cardiac troponin has also confirmed the presence of myocardial injury in HCM and has provided insight into the frequency and prognostic implications of myocardial injury in HCM. Interestingly, cardiac troponin elevation is very common and is detected in 50 to 75% of patients with HCM [5–7]. In a small study troponin remained elevated in 80% of patients, over nearly 2 years of follow-up suggesting that

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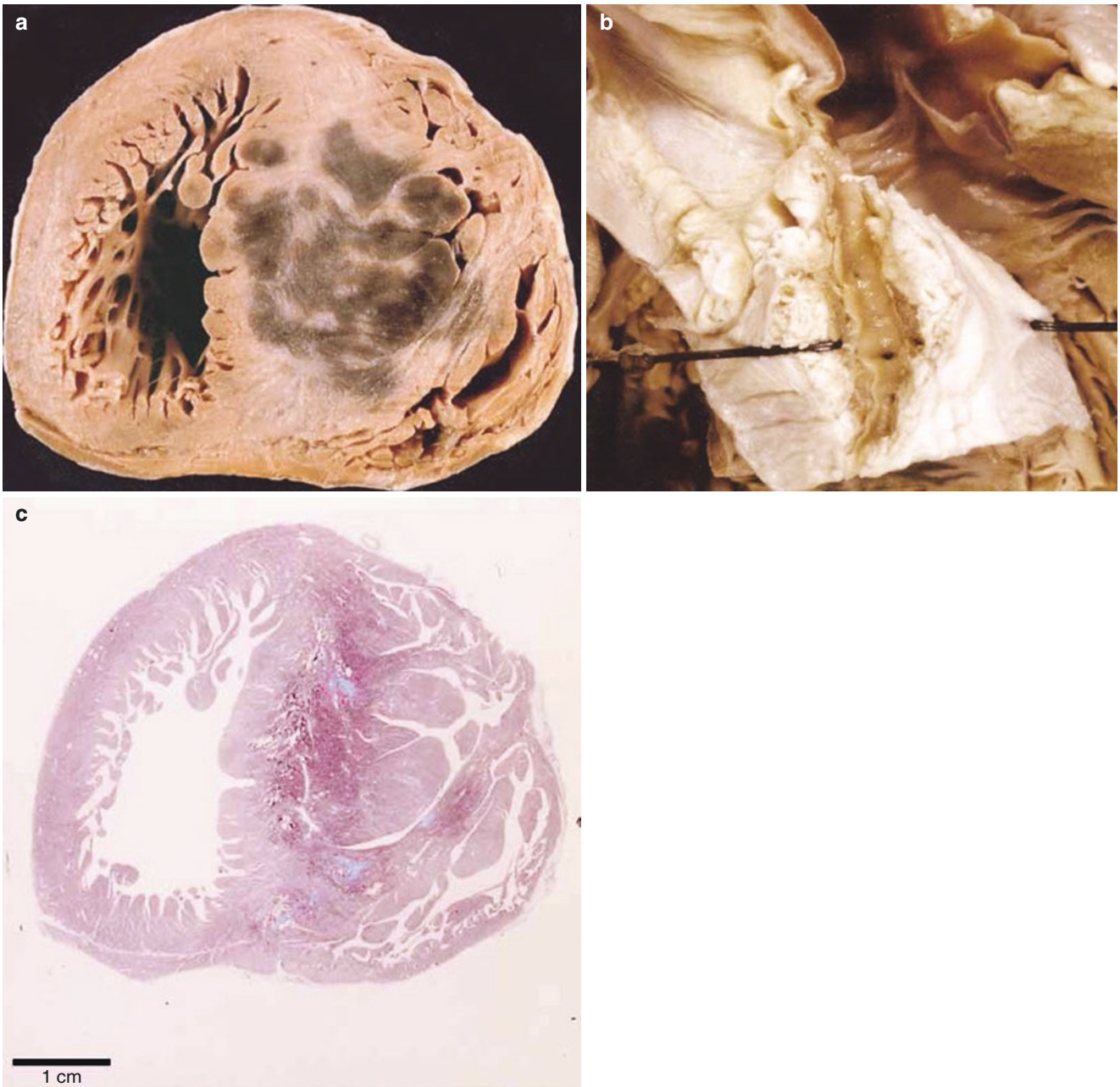

Fig. 19.1 Pathology specimen of an 8-year-old boy who died suddenly. Panel (**a**), severe septal hypertrophy with hemorrhagic septal infarct; panel (**b**), normal but intramyocardial left anterior descending coronary artery; panel (**c**), coagulation necrosis of the septum. (From Gori et al. [2]).

most patients are subject to repetitive ischemic insults [5]. Moreover, troponin elevation is associated with both left ventricular mass and extent of late gadolinium enhancement (LGE), a marker of fibrosis, on cardiac magnetic resonance (CMR) [6]. Similar to many other conditions, troponin elevation in HCM is associated with worse outcomes including higher rates of death, heart failure, progression to New York Heart Association class III or IV symptoms, or sustained ventricular tachycardia (32% vs 7% for the composite endpoint over 4 years of follow-up) [7]. Furthermore, higher levels of troponin are proportionally related to higher cardiovascular events (Fig. 19.2).

Myocardial perfusion abnormalities are commonly identified in both symptomatic and asymptomatic patients with HCM. Numerous studies, mainly using Thallium-201, have shown that 55–75% of HCM patients have perfusion abnormalities [8–10]. More recently, concordance between Thallium and Sestamibi studies has substantiated that these abnormalities are due to ischemia and not merely abnormalities with the Na-ATPase transporter, which has been proposed

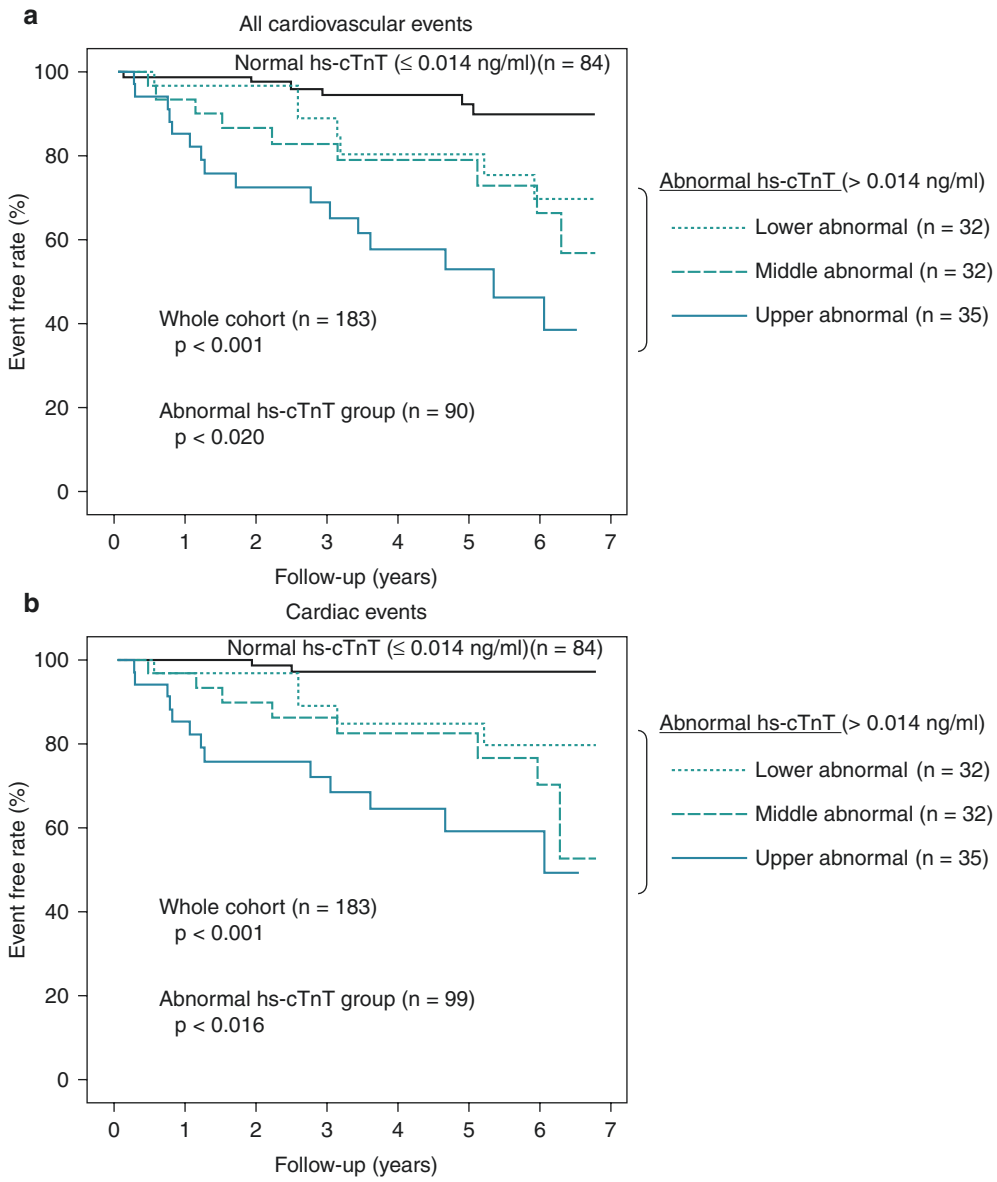

Fig. 19.2 Cardiovascular outcomes are associated with degree of troponin elevation. Panel (**a**), composite of heart failure related death, heart failure hospitalization, and New York Heart Association class III or IV symptoms; panel (**b**), composite heart failure and ventricular arrhythmias. (From Kubo et al. [7])

as a mechanism for possible false-positive Thallium studies in the past [11]. These patients may have fixed defects, reversible defects, or transient LV dilation [8]. Fixed defects are thought to reflect scar and are more frequently seen in HCM patients with LV systolic dysfunction. Reversible defects are thought to represent regional ischemia, whereas transient LV dilation is thought to represent global subendocardial ischemia. Those patients with reversible defects tend to have normal or supranormal left ventricular systolic function; however they have greater impairment in left ventricular diastolic function compared with those without perfusion abnormalities. Unfortunately, there is a poor correlation between angina and either the presence or extent perfusion abnormalities.

Cardiac MRI is a unique imaging modality that allows for the precise assessment of global and regional LV mass, myocardial fibrosis, and coronary physiology, including resting and hyperemic coronary blood flow. One MRI study found that 30% of patients have severe ischemia, while another study suggests 17% have severe ischemia (12.9–24% burden), 30% have moderate ischemia (4.8–12.8% burden), and 53% have minimal or no ischemia (0–4.7% burden). There was a correlation between degree of ischemia, hypertrophy, and fibrosis (Fig. 19.3) [12–13]. In another MRI study, resting myocardial blood flow was found to be similar between HCM patients and controls; however, the hyperemic myocardial blood flow was significantly lower in HCM patients compared with controls (1.84 ± 0.89 mL/min/g vs 3.42 ± 1.76 mL/min/g, $p < 0.001$) [14]. Additionally, hyperemic myocardial blood flow to the endocardium decreased in relation to LV wall thickness. Interestingly, the more impaired the hyperemic myocardial blood flow, the greater

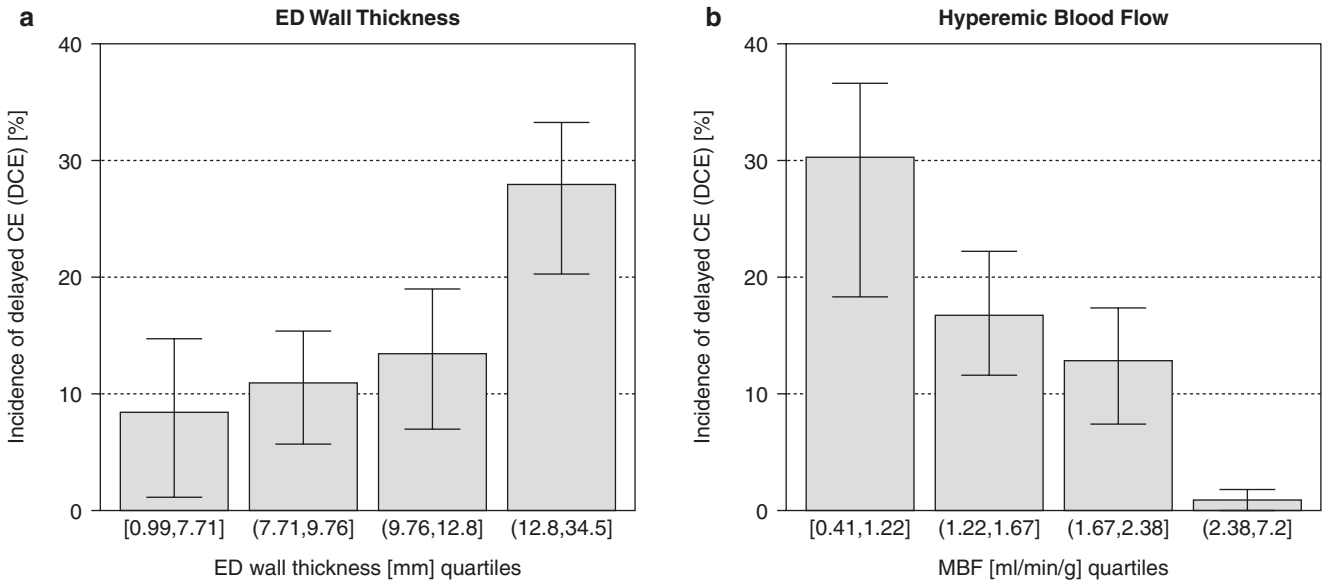

Fig. 19.3 Delayed enhancement on cardiac MRI is associated with left ventricular hypertrophy and hyperemic blood flow. Panel (**a**), fibrosis increases as hypertrophy increases; panel (**b**), fibrosis increases as hyperemic blood flow decreases. (From Peterson et al. [12])

the degree of myocardial fibrosis. Thus, not only does this provide evidence for impaired hyperemic coronary flow in HCM but, moreover, it also suggests an association between microvascular dysfunction, leading to ischemia, and myocardial fibrosis.

Several invasive techniques have also been utilized to assess the presence of ischemia in HCM. In one seminal paper, most patients were shown to have ischemia based on lower lactate extraction (on great cardiac vein sampling) during both rapid pacing (73%) and isoproterenol infusion (65%), and this metabolic proof of ischemia was associated with perfusion defects, left ventricular cavity dilation, and a greater increase in left ventricular end-diastolic pressure [9]. Another study reported a greater decline in coronary sinus pH following dipyridamole infusion in HCM patients compared with controls [15].

In yet another study of right ventricular pacing, 18 of 20 HCM patients with angina, but normal coronary arteries, not only developed chest discomfort but also were shown to have impaired myocardial blood flow, metabolic evidence of ischemia (decreased lactate consumption), and elevation in left ventricular end-diastolic pressure (increase from 16 mmHg to 30 mmHg), likely related to ischemia-induced diastolic dysfunction [16].

Several studies have specifically evaluated microvascular function in HCM by assessing myocardial blood flow (MBF) and coronary flow reserve (CFR) [17–20]. In general, MBF is higher, and coronary resistance is lower in HCM patients compared with controls. However HCM patients were found to have significantly lower CFR than controls [19–20]. This suggests that there is near maximal coronary vasodilation at rest, and the inability to significantly augment flow may contribute to the development of ischemia. Interestingly, phasic systolic flow and diastolic flow are significantly altered in HCM. Although diastolic flow is increased at end diastole, there is a more abrupt deceleration in diastolic flow. Systolic flow is greatly reduced, and in many patients even reversed, which adversely affects epicardial MBF which is typically preserved in systole [20].

An interesting observation is that among HCM patients those with confirmed sarcomere mutations have greater impairment in hyperemic blood flow [21].

Mechanisms of Ischemia in HCM

The etiology of myocardial ischemia in HCM is postulated to be a complex interplay between multiple pathophysiological mechanisms which together lead to supply/demand mismatch. Theses mechanisms include increased oxygen demand, microvascular disease and dysfunction, myocardial compressive forces, and in some patients epicardial coronary disease.

Myocardial oxygen demand is increased in HCM patients due to the increased metabolic demand of the hypertrophied myocardium. Furthermore, left ventricular outflow tract obstruction increases intracavitary pressures thereby intensifying metabolic demand. Impaired ventricular relaxation also increases oxygen demand. The diastolic derangements increase left ventricular diastolic pressures which also adversely affect the coronary perfusion gradient and thereby contribute to ischemia.

Autopsy studies have demonstrated several anatomical factors that could affect coronary flow including medial

hypertrophy and intimal hyperplasia of the arterioles causing diffuse luminal narrowing [22–23]. This has been associated with impaired coronary vasodilatory reserve. Additionally, it has been postulated that reduced capillary density may also contribute to reduced blood supply [23].

More recently wave intensity analysis has been employed to evaluate myocardial blood flow throughout the cardiac cycle. This has been studied more extensively in patients with aortic stenosis and heart failure with preserved ejection fraction but has recently also been explored in HCM [24–25]. The concept of cardiac-coronary coupling holds that the coronary arteries are not static conduits but undergo phasic compression and decompression during ventricular systole and diastole, respectively. Therefore, it is postulated that coronary flow is integrally dependent on the extent and duration of microvascular compression as well as driving pressures. The phasic compression and decompression of the small coronary arteries generate waves. Assessment of the proximal forward waves and distal backward waves, there are six in total, provides insight into factors affecting coronary flow. A detailed discussion of this complex arena is beyond the scope of this review.

One recent study has evaluated wave intensity analysis in HCM [26]. This study suggests that systolic myocardial compression of the microvasculature is the main culprit in reduced myocardial blood flow. The resultant backward compressive wave reflects decreased systolic flow with actual reversal of systolic flow in many patients. Both impaired ventricular relaxation, which blunts the suction wave which is responsible for diastolic blood flow (particularly to the endocardium), and decreased aortic driving pressure from left ventricular outflow tract obstruction contribute to a lesser degree to impaired MBF (Fig. 19.4).

Epicardial coronary artery disease exacerbates the supply/demand mismatch. Atherosclerotic coronary artery disease can certainly coexist with HCM and must be excluded in HCM patients with angina, especially the elderly with atherosclerotic risk factors. The diagnosis and management of epicardial coronary artery disease will be discussed in a later section [27]. Although myocardial bridging is seen in 1–3% of the general population, it is found in 10–15% of HCM patients [28–32]. Whether myocardial bridging induces ischemia has been a contentious issue since most MBF occurs during diastole. However, despite the fact that coronary blood flow is predominately diastolic the systolic contribution to MBF is not trivial (up to 20% in normal individuals). Also, it has been shown that coronary compression persists into diastole thus further reducing coronary flow. In over 50% of HCM patients with myocardial bridging compression persist for approximately 25% of the diastolic period [29]. These findings support the theory that myocardial bridging may contribute to ischemia in at least a subset of patients. The prognostic implications of myocardial bridging in HCM have been discordant. A small study of 36 children suggested that myocardial bridging was associated with an increased rate of angina (60% vs 19%) as well as cardiac arrest (50% vs 4%) [31]. However, this may be confounded by the extent of hypertrophy in these patients. The association between myocardial bridging and sudden cardiac death has not been confirmed in adults [32].

Prognostic Implications of Ischemia in HCM

Only small studies have evaluated the association between ischemia and prognosis in HCM. In one case series, inducible ischemia by Thallium-201 imaging was seen in all 15 patients with syncope or resuscitated sudden death but only 37% of an asymptomatic cohort [33]. In another study of 79 patients, 29 patients (37%) with ischemia had a worse event-free survival than those without ischemia (84.2% vs 36.2%; $p < 0.001$) [34]. A third scintigraphy study found an

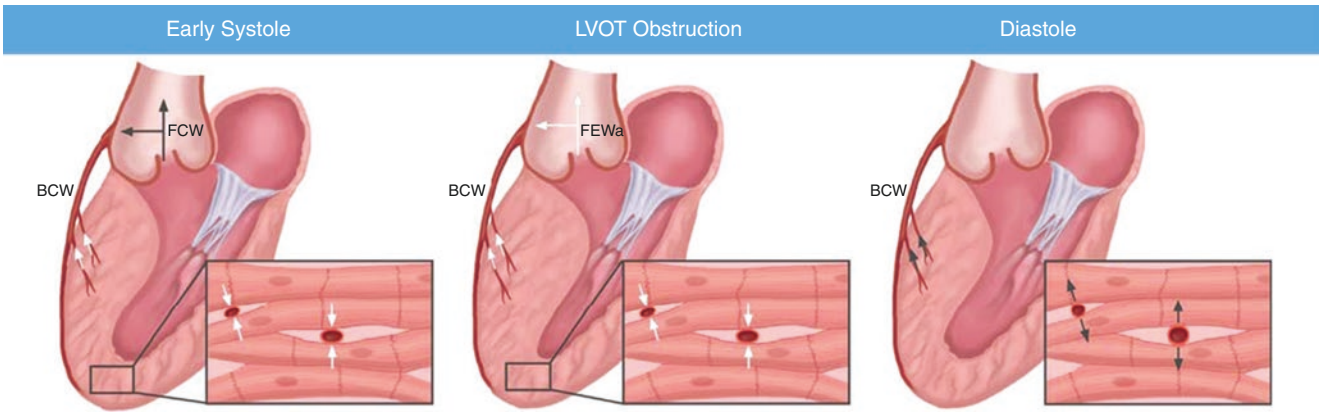

Fig. 19.4 Main mechanisms of decreased myocardial blood flow in HCM. In systole there is compression of the microvasculature resulting in reversal of flow. In patients with obstruction, there is decreased driving pressure and consequently reduced myocardial blood flow. In diastole, delayed relaxation blunts the suction wave and results in decreased myocardial blood flow. (Raphael et al. [26])

association between ischemia and LV dilatation and decreased exercise capacity [35].

Another small study with long-term follow-up was able to associate microvascular dysfunction with poorer prognosis in HCM patients. In a study of 51 HCM patients followed for a mean of 8.1 years, those in the lowest tertile of hyperemic myocardial blood flow had much higher risk of cardiovascular deaths (relative risk 9.6) and the combined endpoint of cardiovascular death, New York Heart Association Class III or IV symptoms, or ventricular arrhythmias necessitating implantation of a cardioverter-defibrillator (relative risk 20.1) (Fig. 19.5) [36].

Subsequent analysis of this data set suggests that microvascular dysfunction is also associated with long-term adverse LV remodeling and systolic dysfunction [37]. Of the 11 patients who developed systolic dysfunction (ejection fraction <50%), 9 were in the lowest tertile of hyperemic myocardial blood flow. The average hyperemic myocardial blood flow was 1.63 ml/min/g in those with preserved LV function, 1.04 mL/min/g in those with impaired LV function, and 0.89 ml/min/g in those who died or developed severe heart failure over 8 years of follow-up.

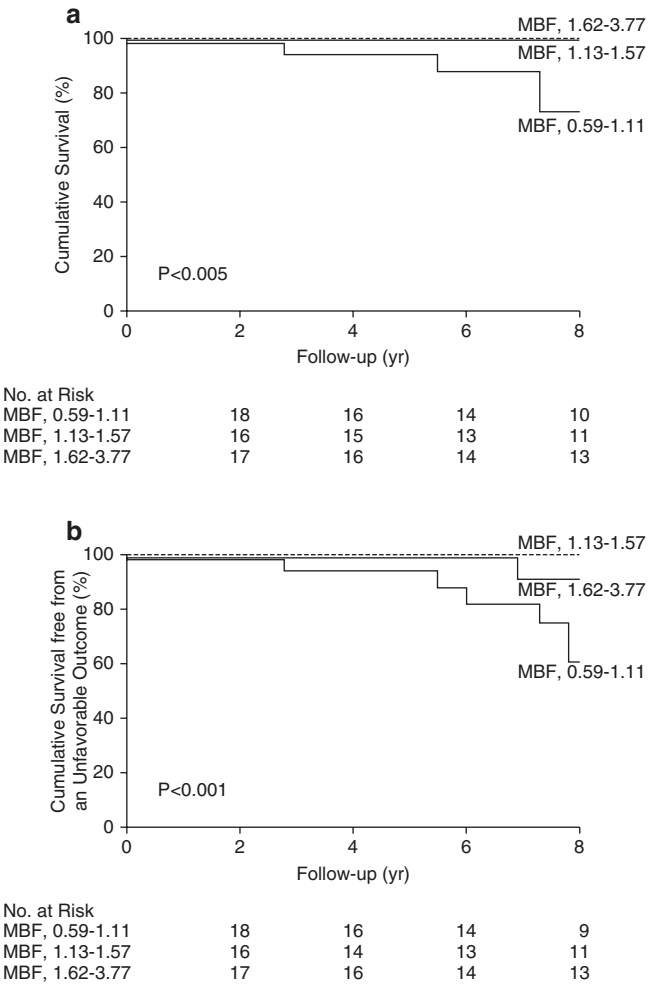

Fig. 19.5 Association between hyperemic myocardial blood flow and prognosis after 80 years. Panel (**a**), cardiovascular death; panel (**b**), cardiovascular death, New York Heart Association class III or IV symptoms, ventricular arrhythmia requiring implantable cardioverter-defibrillator. (Cecchi et al. [36])

As discussed earlier, troponin elevations are common in HCM. Troponin elevation is strongly associated with worse cardiovascular outcomes with a nearly fivefold increase in adverse events including death, ventricular tachycardia, and congestive heart failure [5–7].

As discussed in a previous section, the degree of myocardial fibrosis is increased in HCM patients with ischemia. Numerous studies have also shown that fibrosis is an important predictor of left ventricular dilation and systolic dysfunction [38–43]. In fact, patients who develop end-stage cardiomyopathy have fibrosis involving approximately 25% of the myocardium [39]. Thus ischemia could be an important factor in the transition from a hyperdynamic heart to end-stage cardiomyopathy in HCM. Lastly, emerging data suggests that myocardial fibrosis in HCM is associated with an increased risk of sudden death, with an apparent threshold of 15% of the myocardium. Therefore, repetitive ischemia may induce fibrosis, a substrate for sudden death, and may also serve as a trigger for sudden cardiac arrest in HCM [44–45].

Effects of Medical Therapy and Septal Reduction Therapy on Ischemia

If myocardial ischemia is common in HCM and is associated with adverse outcomes (including mortality, myocardial fibrosis, adverse left ventricular remodeling, and reduced ejection fraction), then the next logical question is whether medical therapy or septal reduction therapy can ameliorate ischemia in HCM and whether this may in turn improve survival as well as other cardiovascular outcomes. Several case series and small studies have demonstrated the ability of both medical and septal reduction therapies to decrease ischemia in HCM. Unfortunately, whether treating ischemia will ultimately translate into improved cardiovascular outcomes in HCM is unknown at this time.

There have been limited studies of medical therapy in HCM, and they have almost exclusively involved non-dihydropyridine calcium channel blockers [46–49]. The non-dihydropyridine calcium channel blockers have been shown to reduce ischemia in HCM patients with normal epicardial coronary arteries likely secondary to their negative inotropic and chronotropic effect and possibly due to improved diastolic and microvascular function. Verapamil has been shown to improve perfusion defects in 71% of asymptomatic HCM patients without epicardial coronary disease. In these patients 68% of ischemic segments improved with verapamil therapy

treatment [47]. Additionally, diltiazem has been shown to improve both perfusion defects and angina symptoms in over 60% of symptomatic HCM patients. Although beta-blockers and disopyramide significantly improve dyspnea and angina in HCM, their impact on ischemia has not been studied as thoroughly [46]. Theoretically, both medications should be efficacious in ischemia reduction; beta-blockers via their negative inotropic and chronotropic effects and disopyramide via its profound negative inotropic effect [50].

Surgical septal myectomy has been shown to improve myocardial perfusion abnormalities in the majority of patients [51–52]. Furthermore, coronary flow and myocardial oxygen consumption both improve after septal myectomy. The degree of coronary flow improvement correlates directly with the severity of outflow tract obstruction.

Several excellent studies of alcohol septal ablation have documented ischemia relief with the procedure and provide some insights into the mechanisms of ischemia in HCM. Myocardial blood flow velocity, as measured by myocardial contrast echocardiography, has been shown to improve, but not normalize, after alcohol septal ablation [53]. Doppler guidewires have also been employed to assess coronary flow patterns and coronary flow reserve before and after alcohol septal ablation [54, 55]. Pre-alcohol septal ablation systolic coronary flow is markedly reduced, and in many patients even reversed, and coronary flow reserve is significantly lower in HCM patients than in controls. Following alcohol septal ablation there is no change in diastole flow patterns, which remain unchanged, but there is normalization of systolic flow patterns. Additionally, there is normalization of coronary flow reserve. These findings suggest that the high intraventricular systolic pressure generated by left ventricular outflow tract obstruction causes coronary microvascular compression, reduces or reverses systolic coronary flow, and ultimately provokes ischemia. Septal reduction therapy should also reduce ischemia by decreasing myocardial work and therefore oxygen demand. This lends at least some support to the hypotheses generated by the wave intensity analysis studies (i.e., systolic coronary compression, impaired diastolic relaxation, and decreased aortic pressure head due to left ventricular outflow tract obstruction). Moreover, as systolic flow and coronary flow reserve improve immediately after alcohol septal ablation, it is likely that cardiac-coronary coupling is a greater contributor to ischemia than structural changes such as reduced capillary density or arteriolar medial hypertrophy.

Epicardial Coronary Artery Disease

It is typically thought that age is a protective factor in HCM patients in terms of sudden cardiac arrest risk. However, HCM does not provide immunity to the development of atherosclerotic coronary artery disease. In fact, it has been reported that 20–25% of HCM patients who undergo coronary angiography have significant coronary artery disease [40]. Furthermore, those patients with significant coronary artery disease have been shown to have a worse prognosis compared with those that do not. In a Mayo Clinic study of 433 patients with HCM who underwent coronary angiography, 26% of the patients had severe CAD, 27% had mild-to-moderate CAD, and 47% were free of CAD. Those with severe CAD have an annual incidence of mortality of 6.5% compared with 3.4% patients with mild-to-moderate CAD and 2.6% for those with no CAD (Fig. 19.6). The mortality rate exceeds that expected for general HCM population or the average CAD patient, and therefore the two conditions seem to synergize in a negative manner. It is likely that epicardial coronary disease compounds the underlying microvascular ischemia and thus increases the risk of sudden cardiac arrest in the HCM substrate.

A common clinical conundrum is the clinical assessment of the HCM patient who presents with angina. Approximately 25% of HCM patients have chest discomfort [56]. Although this is frequently due to microvascular dysfunction and increased oxygen demands, it is important to distinguish these causes from epicardial coronary disease [57–58]. Older patients and those at high or intermediate risk for atherosclerotic CAD should undergo invasive angiography or computed tomographic angiography. In low-risk patients, it is reasonable to proceed with either computed tomographic angiography, single-photon emission computed tomography, or positron-emission tomography (ACC/AHA Class IIa) although the European guidelines favor CTA [59–60]. The clear benefit of angiography, whether invasive or noninvasive, is its greater sensitivity and specificity in detecting atherosclerosis as well as its ability to detect myocardial bridging. In addition, proceeding with cardiac catheterization allows a full assessment of hemodynamics, including the presence, absence, and severity of obstruction, congestion, and pulmonary hypertension.

As discussed previously, over 50% of HCM patients have perfusion abnormalities on SPECT or PET imaging despite normal epicardial coronary arteries. Thus, the specificity of these imaging techniques is low for the detection of atherosclerotic CAD. Nevertheless, in low-risk patients scintigraphy could be considered because of their high negative predictive value. The resting electrocardiographic (ECG) abnormalities in HCM make exercise ECG of limited use. Likewise, stress echocardiography is not particularly useful in the assessment of CAD in HCM because the hyperdynamic myocardium regional variations in hypertrophy, and potential dramatic changes in loading conditions due to dynamic outflow obstruction, renders wall motion analysis challenging.

Although atherosclerotic CAD is associated with increased mortality in HCM, there is no available help to

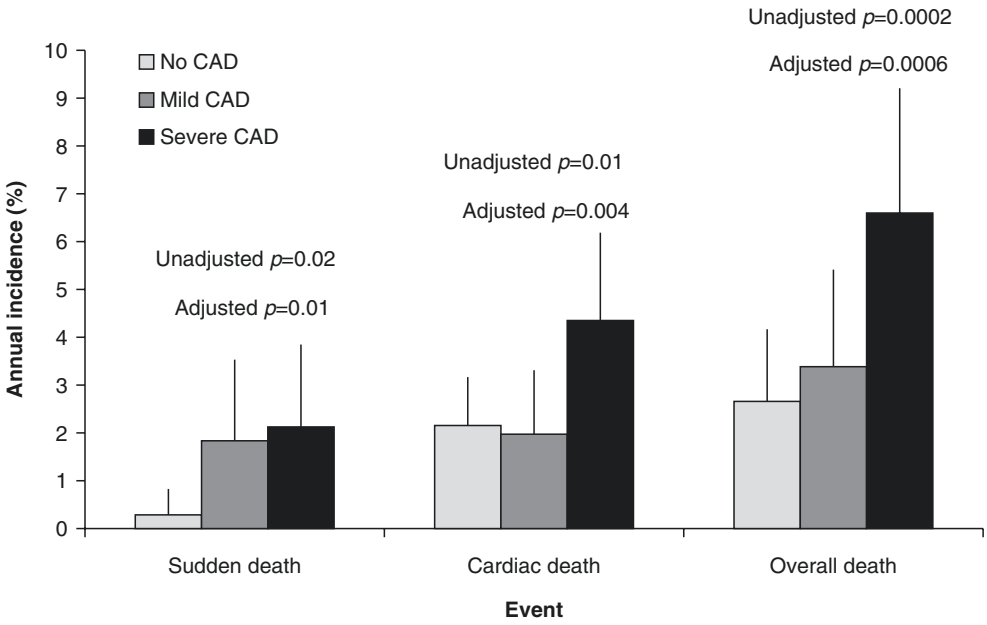

Fig. 19.6 Sudden death, cardiac death, and all cause death as a function of extent of CAD. (Sorajja et al. [27])

guide treatment. Aggressive risk factor modification and anti-ischemic therapy with beta-blockers and/or non-dihydropyridine calcium channel blockers is clearly indicated. Revascularization should be performed according to established guideline recommendations for stable ischemic heart disease. The choice of revascularization strategy and whether to perform concomitant septal reduction therapy can be complex and should be individualized based on the complexity of CAD, severity of outflow tract obstruction and severity of attributable symptoms, and the patient's clinical risk factors which may influence surgical risk.

Conclusions

Myocardial ischemia is a common pathological finding in HCM which can be caused by epicardial CAD (either atherosclerosis or possibly myocardial bridging) or, more commonly, supply-demand mismatch, abnormalities of cardiac-coronary coupling, or microvascular medial hypertrophy and dysfunction. In those patients with angina, it is paramount to evaluate for epicardial CAD (by invasive angiography or CTA) as its presence is associated with increased mortality. Although microvascular ischemia is associated with increased mortality, myocardial fibrosis, ventricular tachycardia, adverse ventricular remodeling, left ventricular systolic dysfunction, and CHF, there is currently no data that treating ischemia, with either medical or septal reduction therapy, will improve outcomes. Therefore the routine screening for microvascular ischemia is not recommended. Future research endeavors to discover whether treating microvascular ischemia improves outcomes would be very helpful to guide care in this large subset of HCM patients.

Clinical Pearls

1. Myocardial bridging is common in HCM patients, especially those with severe LVH of the septum, and is most commonly present in the mid-LAD; in virtually all patients these can be managed medically even though they likely contribute to ischemia.
2. Older patients with atherosclerotic risk factors for CAD and angina symptoms or a decline in LV function should undergo angiography; invasive angiography has the added benefit of comprehensive hemodynamic assessment and reduced contrast dose.
3. It is reasonable to be aggressive about treating epicardial CAD in patients with HCM, as the combination of HCM and epicardial CAD appears to increase mortality in this high-risk group of patients.

Questions

1. Which of the following is incorrect?
   A. 20% of HCM patients have angina.
   B. 90% of HCM patients have ischemia.
   C. 50–75% of HCM patients have chronic troponin elevations.
   D. Repetitive ischemia induces myocardial fibrosis.

   Answer: B. 50–75% of HCM patient have ischemia.

2. Which of the following are proposed mechanisms for microvascular ischemia in HCM?
   A. Supply-demand mismatch
   B. Microvascular hypertrophy and dysfunction

C. Perturbations of cardiac-coronary coupling
D. All of the above

Answer: D. All are proposed causes of myocardial ischemia in HCM.

3. According to wave intensity analysis (i.e., cardiac-coronary coupling) which of the following are important determinants of ischemia in HCM?
   A. Systolic reversal of flow due to microvascular compression.
   B. Decreased driving pressure due to LVOT obstruction.
   C. Blunted diastolic sucking wave due to impaired ventricular relaxation
   D. All of the above

   Answer: D. All of the above mechanisms are thought to impact myocardial blood flow in HCM.

4. Which of the following is false regarding myocardial blood flow (indexed per gram of myocardial tissue) in HCM?
   A. Resting myocardial blood flow is normal.
   B. Resting myocardial blood flow is decreased.
   C. Hyperemic myocardial blood flow is normal.
   D. Hyperemic myocardial blood flow is deceased.

   Answer: C. Coronary resistance is low in HCM with reduction in hyperemic coronary flow reserve. Coronary vasodilation at rest is necessary to meet metabolic demands of the hypertrophied ventricle.

5. Microvascular ischemia is associated with all the following but:
   A. Mortality
   B. Syncope
   C. Atrial fibrillation
   D. Congestive heart failure

   Answer: C. Microvascular ischemia has been associated with increased mortality, ventricular arrhythmias, syncope, adverse ventricular remodeling, and CHF but not atrial fibrillation at this time.

6. Which of the following is the best imaging modality to detect epicardial CAD in the HCM patient?
   A. Angiography (invasive or CTA)
   B. Myocardial perfusion imaging
   C. Positron-emission tomography
   D. Exercise echocardiogram

   Answer: A. Perfusion imaging studies and exercise echo suffer from poor specificity in detecting epicardial CAD in HCM patients. Therefore angiography is the preferred imaging modality. The choice of invasive angiography versus CTA is dictated by clinical suspicion for epicardial disease.

7. Which of the following is true regarding epicardial CAD?
   A. Epicardial CAD is seen in 25% of HCM patients.
   B. HCM contributes to premature atherosclerosis.
   C. Advanced age is protective in HCM patients with CAD.
   D. Epicardial CAD increases mortality to a greater extent in HCM vs non-HCM population.

   Answer: D. In HCM patients with epicardial CAD the annual mortality rate is 6.4%, far higher than the typical CAD population.

8. Which of the following is associated with increased mortality in the adult HCM population?
   A. Microvascular ischemia
   B. Epicardial CAD
   C. Myocardial bridging
   D. A and B
   E. A, B, and C

   Answer: D. Although myocardial bridging may cause angina is some patients with HCM, it has not been shown to influence mortality or other outcomes.

9. Which of the following if true:
   A. All HCM patients should undergo screening for microvascular ischemia.
   B. Medical therapy reduces myocardial ischemia in HCM.
   C. Medical therapy improves outcomes in HCM patients with microvascular ischemia.
   D. Septal reduction therapy should be considered the treatment of choice in patients with microvascular ischemia since it has been show to improve outcomes.

   Answer: B. Medical therapy has been shown to reduce perfusion abnormalities in HCM. It is unknown whether medical or septal reduction therapy influences outcomes in HCM patients with microvascular ischemia. Since it is unknown whether treatment of silent microvascular ischemia improves outcomes, routine testing to detect ischemia is not recommended.

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Indications and Outcome of PPM and ICD Placement

20

Joseph J. Germano, Joshua R. DeLeon, Daniel R. Zakhary, and Jason T. Jacobson

Key Points

- Devices for the management of conduction disease and arrhythmias play an important role in the treatment of hypertrophic cardiomyopathy (HCM).
- Beyond standard conduction disease indications, pacemakers may be used to treat heart failure or syncope symptoms associated with HCM. However, pacemaker placement to reduce outflow tract obstruction or increase ventricular filling through optimization of atrioventricular delay has been downgraded in recent guidelines.
- Implantable cardioverter-defibrillators (ICDs) have been used to prevent sudden cardiac death (SCD) in HCM and appear effective in defined high-risk HCM patients, but this has been based on limited data from observational outcome studies, with recommendations primarily derived from expert consensus.
- In patients with HCM, specific procedural and programming considerations should be taken into account.
- Complications of device placement, both procedural and long term, may be increased in patients with HCM. These include mechanical complications as well as electrophysiologic complications. Accordingly, the decision to place a device requires careful and individualized assessment of the risk-to-benefit ratio.

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Introduction and Overview

The use of synchronized atrioventricular (AV), or DDD pacing, has been an important component in the management of HCM. Dual-chamber pacing, utilizing right atrial and right ventricular (RV) leads, has been the method used. Indications for device placement in HCM patients follow the standard indications as in the non-HCM population, with distinct additional indications based on the potential to mitigate diastolic dysfunction and outflow tract gradients. More recently, reports of biventricular pacemaker placement to reduce outflow tract gradients have also been reported. ICDs have been proven to be a life-saving therapy in subsets of HCM patients, particularly those who meet defined high-risk criteria. However, the often times early placement of these devices within the lifetime of the average HCM patient means that they will be susceptible to a higher risk of complications over the ensuing decades.

In this chapter, we will examine the data supporting the indications for pacing and defibrillation in HCM patients and review the clinical and practical application of these therapies. Synchronized atrioventricular pacing in HCM is used primarily for conduction disease, heart rate support, and more controversially, symptom alleviation due to outflow tract obstruction and/or diastolic dysfunction. However, the recommendation for pacemaker placement to reduce outflow tract obstruction or increase ventricular filling through optimization

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of AV delay has been downgraded in recent guidelines. It is now clear that AV pacing is not very helpful in patients with nonobstructive HCM, no symptoms, or symptoms well controlled on medical therapy, nor is it helpful in patients who are candidates for septal reduction therapy. Also, pacing is not indicated for mortality benefit or to change the natural history of the underlying disease process. As already mentioned, ICDs have been used to prevent sudden cardiac death (SCD) in HCM and appear effective in defined high-risk HCM patients, but this has been based on limited outcome studies and recommendations derived primarily from expert consensus. Furthermore, in the past some have recommended that all patients with HCM receive an ICD; this, however, is controversial and not supported by either the recent AHA/ACC guidelines or the prior ACC/ESC guidelines.

Complications of device placement, both procedural and long term, may be increased in patients with HCM. These include mechanical as well as electrophysiologic complications. When deciding on the appropriateness of implantation, it is necessary to recognize the complex relationship between hemodynamic parameters, specifics of device programming, and the impact of lead position. Accordingly, the decision to place a device requires careful and individualized assessment of the risk-to-benefit ratio.

Once the decision to implant a device has been made, there are several procedural considerations that must be addressed. RV pacing leads should be placed in the distal RV apex rather than on the RV septum to effectively reduce the left ventricular outflow tract (LVOT) gradient without affecting cardiac output. ICD leads should also be placed apically for defibrillation threshold (DFT) optimization (which is usually higher in HCM) and may be challenging due to increased trabeculations and a bulging interventricular septum in these patients. Reported annual rates of appropriate ICD therapy are increased in HCM patients (ranging from 3.3% to 6.8%), which may be due to predisposing factors such as prior cardiac arrest or sustained ventricular arrhythmia, male gender, young age, and a history of atrial fibrillation. Lead complications are more common specifically in HCM patients given more vigorous muscular contractions of the hyperdynamic heart that could provoke lead fracture. Inappropriate ICD therapies are particularly problematic in HCM patients of young age due to faster heart rates and generally due to the increased incidence of atrial fibrillation, higher incidence of lead fracture, and T-wave over sensing. Both dual- and single-chamber ICD devices are safe and effective for detecting and treating life-threatening ventricular tachyarrhythmias; however, it is unclear whether dual-chamber devices offer any benefit over single-chamber devices in detection of supraventricular tachycardia (SVT) and the prevention of inappropriate therapies.

This chapter will therefore discuss the data supporting the indications for pacing and defibrillation in HCM patients, the clinical and practical application of these therapies, and the risks of procedural and long-term complications, both mechanical and electrophysiologic. Special populations, such as patients following alcohol septal ablation or surgical myectomy, will also be further discussed.

Device Indications Specific to HCM

Pacemakers

Synchronized atrioventricular pacing (AVP) in HCM has been used for three major indications: (1) conduction disease, (2) heart rate support, and (3) reduction in symptoms due to outflow tract obstruction and/or diastolic dysfunction. Table 20.1 summarizes the ACCF/AHA guidelines published in 2011 [1]. The European Society of Cardiology considers AVP a Class IIb (c) indication for reduction of LVOT gradient, or to facilitate treatment with β-blockers or verapamil in patients with LVOT gradient ≥50 mmHg, sinus rhythm and drug-refractory symptoms (1) have contraindications for septal reduction therapies or are at high risk of AV conduction block following such therapies or (2) have an indication for an ICD [2].

The first category includes traditional indications such as sinus node dysfunction as well as AV conduction disturbances unrelated to the diagnosis of HCM. In instances such as post septal myectomy or alcohol septal ablation, there is a higher incidence of complete heart block, especially in those of advanced age or with baseline conduction disease. Advanced conduction disease in this setting represents a clear indication for dual-chamber pacing.

Table 20.1 Pacing recommendations for patients with HCM

Class of recommendation	Recommendation	Level of evidence
Class I	*None*	
Class IIa	Relief of symptoms attributable to LVOT obstruction in patients with an existing dual-chamber device (implanted for non-HCM indications)	B
Class IIb	Medically refractory symptomatic patients with obstructive HCM who are suboptimal candidates for septal reduction therapy	B
Class III	Pacemaker implant should not be performed to reduce LVOT gradient in patients with HCM who are asymptomatic or whose symptoms are medically controlled	C
	Pacemaker implant should not be performed for symptom relief as a first-line therapy in patients who are candidates for septal reduction	B

Based on Gersh et al. [1]
Abbreviation: *HCM* hypertrophic cardiomyopathy

The second major indication has been to provide heart rate support for medical therapy (beta-adrenergic blockers, calcium channel blockers, or antiarrhythmic medications) used to treat the symptoms associated with HCM. As the number and/or doses of beta-blockers or calcium channel blockers typically required in the management of outflow tract obstruction may reach or exceed traditional maximal doses, heart rate support becomes an important indication, especially in elderly patients, prior to contemplation of invasive techniques such as alcohol septal ablation or surgical myectomy.

The third and most controversial indication for pacing in patients with HCM is symptom alleviation. Conceptually, it has been suggested that dual-chamber pacing reduces LVOT gradients and improves symptoms in obstructive forms of HCM by various proposed mechanisms, the most important of which include paradoxical septal motion [3, 4], asynchronous ventricular septal activation [4–6], influence on myocardial perfusion [7], increase left ventricular dimensions [8], negative inotropic effect [8], decrease in LV ventricular thickness [9], and decrease in mitral valve systolic anterior motion and the resultant mitral regurgitation [3, 4]. In addition, optimizing AV delay, which typically requires a shorter interval but is unique to each patient, may improve ventricular filling. This improves cardiac output both by increasing end-diastolic volume and by secondary reductions in outflow tract gradient.

Reduction in dynamic LVOT gradient with dual-chamber pacing has often been impressive but inconsistently observed and is extremely variable, with resting gradient reduction ranging from 25% to 72%. Symptomatic improvement has been reported in various trials, but many of these trials were observational, and placebo (i.e., no ventricular pacing) and "training" (initial symptomatic improvement of patients undergoing DDD pacing) effects could not be eliminated [3–6, 10, 11].

The M-PATHY trial [11] was a landmark randomized, double-blind, crossover study examining the role of pacing in reducing LVOT gradient, peak oxygen consumption, and symptoms in patients with obstructive HCM. Forty-eight symptomatic HCM patients with ≥50 mmHg resting gradient and who were refractory to drug therapy were randomized to 3 months each of DDD pacing and pacing backup (AAI-30) in a double-blind, crossover study design, followed by an uncontrolled and unblinded 6-month pacing trial. No significant differences were evident between pacing and no pacing for subjective or objective measures of symptoms or exercise capacity, including NYHA functional class, quality of life score, treadmill exercise time, or peak oxygen consumption. After 6 additional months of unblinded pacing, functional class and quality of life score were improved compared with baseline, but peak oxygen consumption was unchanged. The majority of patients showed up to a 40% reduction in LVOT gradient. At 12 months, six patients (12%) showed improved functional capacity; all were 65–75 years of age. Overall, left ventricular wall thicknesses in the study group showed no remodeling between baseline and 12 months. The authors concluded that despite the majority of patients showing a modest improvement in LVOT gradient, pacing cannot be regarded as a primary treatment for obstructive HCM. They also noted a perceived symptomatic improvement, which was most consistent with a substantial placebo effect with randomization. The authors advised caution in interpreting symptomatic improvements with longer, uncontrolled pacing periods given these subjective findings were unaccompanied by objective improvement in cardiovascular performance. A small, but potentially important, subset (12%) of patients ≥65 years of age showed a clinical response, suggesting that DDD pacing could be a therapeutic option for some elderly patients. This study represents the primary data supporting PPM utilization for symptom reduction in elderly patients, even though this was a post hoc analysis. As a result, most institutions (and the guidelines) suggest moving to invasive therapies (i.e., alcohol septal ablation or surgical myectomy) once symptoms are refractory to optimal medical therapy, rather than employing a trial of PPM. This is especially true for younger and middle-age patients, while elderly patients may have an option of a trial of pacing, based on their individualized risks of instead proceeding to septal reduction therapy.

Qintar et al. also analyzed the effects of LVOT gradient reduction in a recent analysis of randomized controlled trials of either parallel group (placebo-controlled) or crossover design, which examined the benefits and/or harmful effects of pacing in drug refractory or drug-intolerant HCM patients [12]. In the crossover studies, active pacing was achieved by DDD pacing. In nonactive pacing groups, backup AAI at 30 beats per minute was generally used. Both children and adults of either sex were included in this analysis. Primary outcomes were all-cause mortality, exercise capacity, symptomatic improvement as measured by New York Heart Association (NYHA) functional class and/or exercise capacity, and quality of life as measured by recognized scales. Secondary outcomes evaluated in this analysis were LVOT obstruction gradient, NYHA functional classification, LV wall thickness, peak oxygen consumption, complications related to device implantation, and cost-effectiveness. At the time of this publication, only five studies met the inclusion criteria, and all patients were adults. There was insufficient data to assess all-cause mortality, cost-effectiveness, quality of life, and peak oxygen consumption. Symptoms and NYHA class tended to improve in the studies that reported this data. However, given the small numbers of patients analyzed and the inconsistent reporting of these data, results were equivocal. Only one of these trials assessed exercise capacity time, which appeared to improve in the pacing arm,

albeit not impressively. The results of quality of life questionnaires were extremely variable and impossible to interpret. LV wall thickness was evaluated in only one study and was found to be unchanged with pacing. In that study, LVOT gradient, as in some prior studies, improved; however, as stated above, this is a physiologic measure and not a clinical outcome. Complications appeared to be in line with expected numbers. The authors summarized that review of the data showed no convincing evidence to support or refute the use of active pacing in patients with HCM [5, 10, 11, 13, 14].

Cheng et al. focused on the structural impact of pacing in 37 patients with obstructive HCM [9]. Patients were followed for up to 4 years after dual-chamber pacemaker implantation. They specifically followed programming parameters and echocardiographic findings in these patients, who were paced greater than 98% of the time. They found statistically significant declines in interventricular septal size, LVOT peak velocity, LVOT peak gradient, and an increase in LVOT diameter compared with pre-pacing measurements. Other parameters, including pulmonary artery systolic pressure and LV ejection fraction (LVEF), did not change. The authors concluded that beneficial cardiac structural changes can be derived from chronic dual-chamber pacing and assumed that their findings indicated an improvement in the pathophysiology of HCM. Unfortunately, there are significant limitations to this study, and no confident conclusions can be drawn from this report.

Silva et al. reported on 39 HCM patients with heterogeneous indications, including both patients with and without LVOT obstruction, as well as AV block [15]. These patients were followed for up to 17 years, representing the longest follow-up period for HCM patients receiving pacemaker therapy published. Of note, only 13 of the 39 patients received a device for gradient-related symptoms. Programming and stimulation mode were variable as well. The authors reported symptomatic and functional class improvement only in patients with obstruction. They concluded that pacing may be beneficial in drug treatment refractory obstructive HCM but could not exclude that clinical improvement may have been attributable to co-interventions, such as myectomy, frequently present in these patients. This study therefore, while reporting information on long-term outcomes of HCM patients receiving a pacemaker, provides little supportive or directive data with regard to device use.

Lucon and colleagues reported the very late effects of AVP (median 11.5 years) of 51 patients with dual-chamber PPM (47) and ICD (4) [16]. Forty-one percent underwent biatrial pacing via a coronary sinus lead, due to intra-atrial conduction delay. Of note, this study excluded patients that subsequently underwent septal reduction procedures (although one had undergone surgical myectomy many years prior to PPM), so it does focus on the effects of pacing. Twenty-two patients died (ten of cardiac causes), and two underwent cardiac transplantation. While no patients were NYHA functional Class I prior to AVP, 36% were at 3 months and 1–2 years at last follow-up. On the other hand, while 6% were NYHA functional Class IV at baseline, none were in follow-up. While the proportion of Class II patients increased (41% baseline, 57% at last follow-up), those with Class III symptoms decreased (53% baseline, 7% at last follow-up). Of interest, the changes in ejection fraction (64% baseline to 56% at last follow-up), LVOT gradient (79 mmHg baseline to 8 mmHg at last follow-up), and presence of mitral systolic anterior motion (96% of patients at baseline to 15% last follow-up) were progressive over the course of the study. However, septal thickness did not change. In an 18-year experience (median 8.5 years) of AVP in 82 patients, Jurado Román et al. reported similar but less impressive results [17]. Postimplantation, 96% of patients had ≥1 degree improvement NYHA functional class (83% ≥ 2), with a slight decrease to 89% (82%) at last follow-up. Four out of 17 deaths were cardiac in origin, and five required surgical myectomy for refractory symptoms. While the LVOT gradient did progressively decrease over the course of follow-up, the degree was less impressive than that reported in the Lucon study (94.5 mmHg baseline, 35.9 mmHg at last follow-up), and there was no difference in EF seen in this study. Regarding mitral regurgitation, a mean improvement in severity of 1.4 grade was seen. These progressive changes may help explain some of the conflicting data, as the M-PATHY trial was a 12-month study during which patients had only 6–9 months of continuous AVP.

Comparisons of AVP with other invasive therapies is scant; however, Kreci et al. have reported a retrospective analysis of AVP and alcohol septal ablation (ASA) [18]. All patients with AVP were included (mean follow-up time 101.2 months), while ASA patients with less than 5-year follow-up (mean 86.9 months) and those that required AVP due to complications of ASA were excluded. Despite similar mean decrease in LVOT gradient (AVP 60.9 mmHg, ASA 49.4 mmHg), patients that underwent ASA had a greater improvement in NYHA functional class (1.13 Vs 0.52 with AVP). While these data suggest similar hemodynamic effects, the nonrandomized nature of the study and subjectivity of symptom reporting certainly limit the strength of the conclusions that can be drawn.

Of note, Berruezo et al. reported beneficial structural changes as well as functional improvements in a small number of patients receiving biventricular pacemakers (BIV) [19]. In this pilot study, nine patients had successful implantation of a biventricular device. The optimal pacing mode was biventricular in six, LV only in two, and RV only in one. With biventricular pacing, functional capacity and quality of life progressively improved as demonstrated by a reduction in NYHA functional class, increase in 6-minute walk test distance, and quality of life improvement. The authors also

showed an incremental and progressive reduction in LV outflow gradient in the year after implant utilizing biventricular pacing over the other pacing configurations (LV only and RV only). Gradient reduction was associated with diminished peak longitudinal displacement of the LV septum and earlier displacement of the lateral wall. The authors theorized that these findings might be due to a reduction in systolic anterior motion of the mitral valve resulting in a progressive reduction in mitral regurgitation. Another novel finding in this study was LV reverse remodeling (i.e., progressive reduction of LV mass) seen predominantly in the interventricular septum with biventricular pacing. Although this study was a small pilot study, the findings are thought provoking and require further investigation. In a subsequent study, Berruezo et al. reported on the influence of native conduction (manifest as fusion between paced and conducted QRS) in a series of 21 patients [20]. A retrospective phase of this study reviewed the first 12 patients that underwent BIV and identified fusion in 7. Those with persistent LVOT gradient >50 mmHg and persistent Class II or greater symptoms were offered AV node ablation (3), one of which declined. These two patients were included in the prospective phase of this study, in which an additional nine patients (six with fusion that underwent AV node ablation) were assessed. Of note, LVOT gradient did not change significantly in the fusion group until after AV node ablation. Similar effects on LVOT gradient and decrease in functional class were seen in this cohort. Nonetheless, despite these findings, given the extensive interpretive limitations found in the literature on long-term use of pacing (especially BIV) in HCM, it is clear that conclusive recommendations cannot yet be made, and additional randomized studies of larger cohorts of patients are needed. It is worth mentioning that in patients with HCM that develop standard indications for CRT (LBBB, low EF, and NYHA Class II CHF), a small series suggests that the benefit is unclear in this population [21].

Knyshov et al. proposed a differentiated approach to the treatment of patients with obstructive HCM based on what they consider to be the three major pathogenic mechanisms underlying the development of HCM: hypertrophy of the myocardium, electromechanical disturbance of spatial activation and contraction, and pathology of the valvular and chordal apparatus of the mitral valve [22]. In a retrospective study of 194 patients, they divided patients into 3 treatment groups and addressed specifically the 91 patients that had obstructive HCM. This study demonstrated that in these patients with drug-refractory symptomatic disease, surgical myectomy, alcohol septal ablation, and dual-chamber DDD-mode pacing were equally effective at reducing left ventricular outflow tract obstruction, and each leads to similar subjective improvements in functional capacity. However, surgical myectomy was most effective in improving objective NYHA functional class.

They concluded from their research that the positive effects they observed in their patients from implantation of pacemakers were attributable to positive results from temporary DDD stimulation performed prior to device implant. They propose the following mechanism of benefit based on the assumption that LVOT peak gradient and mitral regurgitation are similarly dependent on the LV excitation sequence and the LV preexcitation efficacy of DDD-mode pacing and conforming to the pathogenic mechanisms noted above. Genetically determined abnormalities of myofibril and myocyte orientation lead to hypertrophy of the basal septum, resulting in narrowing of the LVOT and changes in the sequence of LV electrical excitation. These delays in excitation occur at the LV apex and the papillary muscle associated with the anterior mitral leaflet, and the authors assume that this leads to papillary muscle dysfunction and systolic anterior motion of the anterior mitral leaflet. This exacerbates the LVOT gradient and leads to mitral regurgitation. This in turn increases myocyte work and triggers secondary hypertrophy, creating a self-augmenting cycle. The authors report evidence that LV apex preexcitation leads to earlier papillary muscle activation, producing less mitral regurgitation and lower LVOT gradients. They propose that in selected patients, therefore, DDD pacing will be effective in the early phases of the disease. Consistent with this approach, they applied alcohol septal ablation therapy to those patients with LVOT gradients who did not demonstrate electromechanical disturbances of spatial activation and contraction or pathologic changes of the mitral valve. Surgical myectomy was selected for patients with LVOT gradient and significant mitral valve pathology.

Employing this therapeutic framework, they propose several indications for the use of dual-chamber pacing in HCM patients, based on results of temporary DDD-mode pacing evaluation. Most importantly, the indications include a reduction of the LVOT gradient of at least 30% and a residual gradient of less than 50 mmHg, as well as contraindications (either relative or absolute) to alcohol ablation or surgery. The authors note several important limitations to this study and the therapeutic approach that is derived from their findings, including small numbers in some subgroups, lack of randomization, and selection bias. Nonetheless, using a differentiated approach to patient selection based on assessing and understanding the pathogenesis of the hemodynamic derangements found for each individual patient may lead to clearer identification of those patients who will benefit from dual-chamber pacing.

As mentioned above, the M-PATHY trial [11] identified a subset of patients greater than 60–65 years of age that may derive specific benefit with respect to symptom improvement from pacing. Additionally, this group tends to include less than ideal candidates for septal reduction therapy [11, 23]. This was supported by a recent study that suggested that

older patients (average age of 62 years) with more advanced NYHA functional class (Classes III–IV) and with significant resting LVOT gradients (>50 mmHg) may have a sustainable decrease in LVOT gradient as well as a persistent reduction in NYHA symptoms at up to 10 years of follow-up after pacing. However, this study was limited to 50 patients treated at a single center; the study was not randomized, and it did not use crossover or placebo pacing protocols (all patients were fully paced in the ventricle) [23].

Overall, data supporting symptom improvement is generally lacking or limited and suggests that pacemaker implantation should be reserved for patients who have medically refractory symptoms and who are not candidates for septal reduction therapy. Specifically, DDD pacing is not helpful in patients with nonobstructive HCM, those with no symptoms or symptoms controlled with medical therapy, or for patients who are candidates for septal reduction therapy [5, 10, 11, 24]. It is, however, reasonable to try dual-chamber pacing in HCM patients who already have a pacemaker implanted for other indications [1].

Another factor tempering the utilization of DDD pacing (i.e., RV pacing) is that RV pacing has been shown to cause an increased incidence of congestive heart failure and atrial fibrillation. Whether or not this is applicable to patients with HCM is unknown [25]. Pacing should also not be used for mortality benefit or to change the natural history of the underlying disease process, as there is no data to propose these benefits [3, 11, 12]. Table 20.1 summarizes the ACCF/AHA guidelines published in 2011 [1]. Importantly, there are no Class I indications for pacing specific to HCM. In fact, the committee presented a total of five indications for pacing, two of which are Class III, identifying them as no benefit in HCM.

Lastly, in making a decision regarding the appropriateness of pacemaker implantation, it is necessary to recognize and recall the complex interrelationship between the hemodynamics of HCM, the specifics of pacemaker programming (discussed later in the chapter), and the impact of lead position. It is necessary to thoroughly understand the role of each of these factors in order to determine if any benefit from pacemaker implantation may be achieved. Given the variety of currently available options, therapy should be individualized to the patient.

Defibrillators

A subset of patients with HCM has an increased risk of SCD [26–29]. This risk may be dissociated from the degree of symptoms and exercise intolerance the patient may be suffering from, and indeed even asymptomatic patients may have a significant incidence of SCD. As such, screening for SCD is recommended for all patients with HCM [1], as it has been shown that ICDs are effective in aborting SCD in HCM patients [28]. In the past, some experts have recommended ICD implantation in all patients with a diagnosis of HCM. However, this universal recommendation is highly controversial and no longer supported by either the recent AHA/ACC guidelines or the prior ACC/ESC guidelines, especially considering that currently available SCD risk stratification strategies in this population do not always correctly identify all patients at risk, complication rates are high [30, 31], and the risk of SCD in the overall HCM population may be only minimally elevated [32]. In our HCM centers, where guidelines are strictly followed, ICD implantation is indicated in roughly one out of every three patients.

Results of recently reported clinical outcomes in a reasonably large cohort of patients continue to highlight important issues related to patient selection for an ICD [33], specifically those related to inappropriate shocks or implant complications. Thus, there is a continued need for focused patient selection algorithms for ICD implantation and accurate ICD programming methodologies to be developed to ensure the creation of appropriate implantation criteria. These issues are particularly difficult in the pediatric population with HCM, where there are additional technical difficulties associated with device implantation, high rates of inappropriate shocks and procedural complications, and particular psychiatric issues associated with the presence of a device, especially when aggregated over the lifetime of these young patients [34].

The subset of HCM patients with reduced LVEF and congestive heart failure are difficult to risk stratify. First, the etiology (or etiologies) responsible for developing the cardiomyopathy (CMP) is unclear and may be multiple. Diminished LVEF in HCM patients may result from standard pathologic processes seen in patients without HCM, such as CAD. Additionally, processes specific to HCM, such as chronic LVOT obstruction or myocyte abnormalities, may result in decreased contractile force, i.e., “end-stage” or “burnt-out” HCM. Second, HCM patients have not been included in the primary prevention trials of SCD in patients with coronary disease or other forms of CMP. Therefore, it is difficult to extrapolate data from those trials to the HCM population. Accordingly, we treat HCM patients with ICDs as we do in the non-HCM patient population, assuming their risk is similar, but have no definitive or comparable data. In summary, in reduced LVEF HCM patients, it is reasonable to utilize any and all therapies useful for primary (or secondary) prevention established for other reduced LVEF heart failure patients, including ICD therapy. Importantly, some experts recommend ICD implantation for EF < 50%, indicating any degree of systolic dysfunction, given that normal EF for HCM patients is usually hyperdynamic, while others utilize the more standard threshold of 30–35% seen in the general population. Further studies fine-tuning this approach will be necessary.

Table 20.2 ICD implantation recommendations for patients with HCM

Class of recommendation	Recommendation	Level of evidence
Class I	ICD implantation should follow a thorough discussion of the strength of evidence, benefits, and risks to allow the informed patient's active participation in decision-making, as well as the application of individual clinical judgment	C
	HCM patients with prior documented cardiac arrest, VF, or hemodynamically significant VT	B
Class IIa	First-degree relative with SCD presumably caused by HCM	C
	Maximum LV wall thickness ≥ 30 mm	C
	One or more recent, unexplained syncopal episodes	C
	NSVT (particularly those <30 years of age) in the presence of other SCD risk factors or modifiers	C
	Abnormal blood pressure response with exercise in the presence of other SCD risk factors[a] or modifiers[b]	C
	High-risk children with HCM, based on unexplained syncope, massive LV hypertrophy, or family history of SCD, after taking into account the relatively high complication rate of long-term ICD implantation	C
Class IIb	Isolated bursts of NSVT in the absence of any other SCD risk factors or modifiers	C
	Abnormal blood pressure response with exercise in the absence of any other SCD risk factors or modifiers, particularly in the presence of significant outflow obstruction	C
Class III	Routine strategy in patients with HCM without an indication of increased risk	C
	Strategy to permit patients with HCM to participate in competitive athletics	C
	Identified HCM genotype in the absence of clinical manifestations of HCM	C

Based on Gersh et al. [1]

Abbreviations: *HCM* hypertrophic cardiomyopathy, *Hg* mercury, *ICD* implantable cardioverter-defibrillator, *LV* left ventricular, *mm* millimeters, *NSVT* nonsustained ventricular tachycardia, *SCD* sudden cardiac death, *VF* ventricular fibrillation, *VT* ventricular tachycardia

[a]Established risk factors: personal history of sustained VT/VF; family history of SCD; syncope; NSVT; LV wall thickness ≥ 30 mm; abnormal blood pressure response to exercise

[b]Potential SCD risk modifiers: resting LVOT gradient of ≥30 mmHg; late gadolinium enhancement on cardiac magnetic resonance imaging; LV apical aneurysm; genetic mutations

Table 20.2 summarizes the ACCF/AHA guidelines published in 2011 [1]. Despite the creation of these formalized guidelines, most of the specific recommendations are based on expert consensus rather than clinical trials. Therefore, it is especially important to consider the risks associated with long-term ICD therapy prior to implantation.

The most recent ESC guidelines recommend employing a 5-year risk prediction tool (HCM Risk-SCD model) for primary prevention ICD consideration [2]. An ICD should be considered when a 5-year risk is ≥6%, may be considered when risk ≥4%–<6%, and generally not indicated when <4%.

With regard to outcomes in this population, there are no randomized trials demonstrating a mortality benefit attributable to ICDs. In the studies that do show "benefit," appropriate ICD therapies are used as a surrogate endpoint for SCD, which does not control for differences in programmed device parameters and other variables, limiting their clinical utility [27, 33, 35–37]. In addition, it is well known that roughly half of appropriate shocks would not have resulted in death, and thus this surrogate while helpful is not entirely accurate. Consistent with this, Germano et al. analyzed seven major ICD trials that randomized patients to ICD vs. medical therapy [35]. Appropriate ICD therapy rates equaled or exceeded control group all-cause mortality in six of seven of these trials. In studies that included death as an endpoint, appropriate ICD therapies outnumbered the incidence of sudden death in the control group by a factor of 2–3. The authors stated that appropriate ICD shocks cannot be equated with aborted sudden cardiac death, as has been done in the interpretation of various nonrandomized series of ICDs. In addition, they observed that the occurrence of appropriate therapies and effective shocks does not constitute proof that ICDs are superior to alternative management strategies, because not all VT and VF treated by ICDs would have resulted in sudden death.

Maron et al. conducted a retrospective analysis of HCM patients with ICDs [27] . The authors reported a 23% rate of appropriate ICD therapy and correlate that to a reduction in sudden cardiac death. As it was a retrospective study, there was no control for device detection and therapy parameters, which clearly affect the incidence of appropriate ICD therapies. This represents an example of the potentially exaggerated benefit of ICD therapy, as it is likely that not all ICD therapies would have resulted in sudden death. Despite the fact that the magnitude of ICD benefit may be exaggerated, the occurrence of VT and VF in high-risk HCM patients and the efficacy of ICD therapy in terminating them cannot be ignored.

Procedural Considerations and Device Complications

Once the decision to implant a pacemaker has been made, there are various procedural considerations that must be addressed. RV pacing leads should be placed in the distal RV

apex rather than on the RV septum. RV apical pacing has been shown to reduce the LVOT gradient without affecting cardiac output, which is not the case with RV septal pacing [38]. Preliminary data from at least one small study suggests that biventricular pacing may offer an even more substantial LVOT gradient reduction, implying that the mechanism of gradient reduction is complex and based on more than ventricular preexcitation, as discussed above [39] .

ICD leads are also placed in the RV apex both for pacing and defibrillation threshold (DFT) optimization. Apical placement is often more challenging in HCM due to increased trabeculations and the bulging interventricular septum, which frequently obstruct the RV as well as the LV. Apical placement is important as HCM patients have been shown to have higher DFTs, which generally increase with increasing LV wall thickness [40] . For this reason, DFT testing at implant should be strongly considered at the time of lead placement.

Device-related complications (not including ICD therapies) have been reported to be in the range of 15–40% in studies that followed patients for longer periods of time (up to 4 years). The most common complications included lead malfunction or displacement requiring revision as well as system infection. Lead problems are more common specifically in HCM patients given the more vigorous muscular contraction of the hyperdynamic heart provoking lead fracture in this group. HCM patients are also typically younger than other patients with ICDs, which may lead to issues of discomfort at the ICD site due to the muscularity of these patients and the fact that they are typically more physically active than older patients. These factors also contribute to lead fracture. Figure 20.1 shows various clinical manifestations of ICD lead fractures. Shown are examples of "noise" and impedance changes, both typical findings in ICD lead fractures. The serious procedural complications of pneumothorax or cardiac tamponade have also been reported but are relatively infrequent. Data on serious complications are inconsistent, due to variability in the clinical status of patients and disparities in reporting methods [41–43].

Inappropriate ICD therapies are a particular problem in HCM patients due to their young age (faster heart rates), increased incidence of atrial fibrillation, higher incidence of lead fracture, and T-wave over sensing (TWO). These issues are discussed in detail later in this chapter.

The decision as to whether to implant a single-chamber or dual-chamber ICD in HCM will vary based on clinical factors such as age, pacing indications, prior supraventricular arrhythmias, and physician choice. Intuition would suggest that young patients and those with no pacing indications would most likely benefit from a single-chamber device to minimize complications associated with an additional lead, and those with prior SVT or AF and pacing indications would benefit from a dual-chamber device to achieve AV synchrony, potentially reduce outflow tract gradient, and improve supraventricular tachycardia (SVT)/ventricular tachycardia (VT) discrimination. Dual chamber also allows better monitoring of subsequent events, including the frequency of AF. For patients without atrial pacing requirements, a single-lead atrial sensing (VDD) ICD system has been introduced recently [44].

As expected, however, in patients ≤30 years of age, dual-chamber devices have not demonstrated superior arrhythmia discrimination [45]. Further support for single-chamber devices is provided by analysis of the National Cardiovascular Data Registry (NCDR) in patients receiving ICDs for primary prevention without indications for pacing. These data demonstrate that the use of dual-chamber devices was associated with a higher risk of device-related complications [46, 47], increased in-hospital mortality [46], and similar 1-year mortality and hospitalization rates [47]. However, these data are not derived from randomized trials and are not unique to HCM, and selection bias for various clinical variables affecting mortality and morbidity cannot be eliminated. Arrhythmia discrimination was also not evaluated in this analysis from the NCDR. A small randomized trial showed that dual-chamber functionality resulted in less clinically significant adverse events than single-chamber functionality [48] .

Both dual- and single-chamber devices have been shown to be safe and effective for detecting and treating life-threatening ventricular tachyarrhythmias [49]; however, discrepancy exists as to whether dual-chamber devices offer benefit over single-chamber devices with regard to detection of SVT and subsequent prevention of inappropriate therapies [49–51]. In one study, dual-chamber ICDs allowed better rhythm classification, but the applied detection algorithms did not offer benefits in avoiding inappropriate therapies during SVT. This was due to inadequacy of the algorithms themselves and atrial sensing errors [49]. Nevertheless, retrospective physician adjudication of arrhythmic events is likely enhanced with dual-chamber detection and may aide in programming to prevent future inappropriate episodes.

An important consideration in device selection is that the typical ICD patient has either an ischemic or nonischemic CMP (diminished LVEF), but the typical HCM patient has preserved LVEF. This is important because dual-chamber devices are generally associated with increased RV pacing, which is a more ominous phenomenon in CMP associated with low LVEF than in HCM. This makes morbidity and mortality analysis and comparisons between these two groups extremely difficult.

Recently, a subcutaneous ICD has been developed that requires no intravascular hardware. It is important to note that this device cannot utilize antitachycardia pacing (ATP) or bradycardia pacing, although it can transiently provide post-shock ventricular pacing. Many regard the HCM population as ideal for this device due to the younger age and the

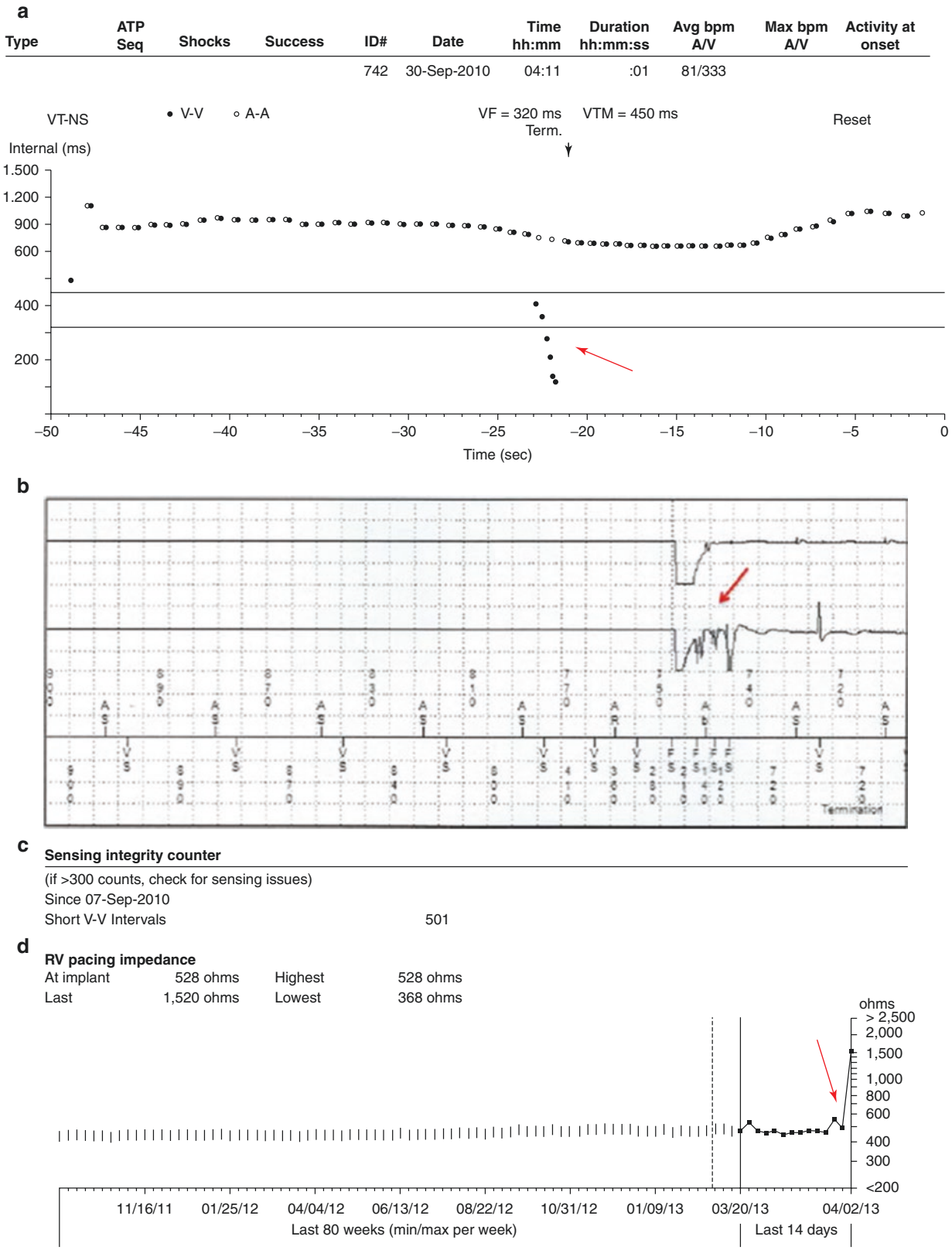

Fig. 20.1 Manifestations of ICD lead fracture. This figure shows the various manifestations of ICD lead fracture. Panel (**a**) depicts artifact representing "noise" on the ICD channel which is shown by the outlying short V-V intervals (*red arrow*) with no change in the A-A intervals. This is confirmed in Panel (**b**), where "noise" and not VF are apparent (*red arrow*). Panel (**c**) shows the sensing integrity counter, which tracks nonphysiologically short V-V intervals, indicating "noise." When >300 of these episodes are detected (assuming routine 3 month ICD interrogations), a lead fracture should be strongly considered. In this case, 501 episodes were noted. Panel (**d**) demonstrates another typical finding associated with lead fracture, a change in lead impedance. The *red arrow* demonstrates a rapid rise in lead impedance consistent with conductor fracture of the ICD lead

higher incidence of VF over that of VT, which does not respond to ATP. However, it should be considered that with current detection algorithms for the subcutaneous ICD, TWO can be an issue with HCM patients. A screening algorithm has been developed to identify candidates for this device, but recent data suggests screening should be done at rest and during exercise, as a large proportion of patients will fail screening with exertion [52].

Device Monitoring

Recommendations for pacemaker interrogation are every 3–12 months and every 3–6 months for ICDs. During these interrogations, information typically recorded includes battery longevity, system integrity and function, detected arrhythmia episodes, and device therapies. Interrogations in person or via remote monitoring are acceptable methods. The exact monitoring interval should be based on individual patient factors such as indication for implantation and clinical status. No distinct recommendations are made beyond these for HCM patients [53].

Reported annual rates of appropriate ICD therapy range from 3.3% to 6.8%. Factors identified as predictive of appropriate ICD therapies in HCM patients include NSVT, history of prior cardiac arrest or sustained ventricular arrhythmia, male gender, young age (usually defined as patient age < 30 years), and a history of AF [41–43, 54, 55].

Rates of inappropriate ICD therapy are reported to be 3.7–6.9% per year. The majority of inappropriate therapies are a result of rapid ventricular rates associated with AF and sinus tachycardia. Other common causes are lead noise due to lead failure/fracture and TWO. TWO is a phenomenon commonly seen in HCM patients, given the increased frequency of large T-waves in these patients. These T-waves are mistakenly interpreted as additional R-waves, artificially classifying sinus rhythm as ventricular rhythms [41–43, 54, 55]. Figure 20.2 shows a HCM patient with TWO noted on routine interrogation. This is traditionally managed by decreasing the maximum R-wave sensitivity. However, this adjustment has the potential risk of underdetection of future ventricular fibrillation (VF) given the variable sensitivity standard on ICDs to accommodate detection of R-waves for purposes of pacing and defibrillation. Some ICD manufacturers have proprietary algorithms to prevent this phenomenon. A full description of these algorithms is beyond the scope of this text. However, it is essential to perform defibrillation testing in patients after VF detection parameters are changed to ensure proper detection and effective treatment of VF.

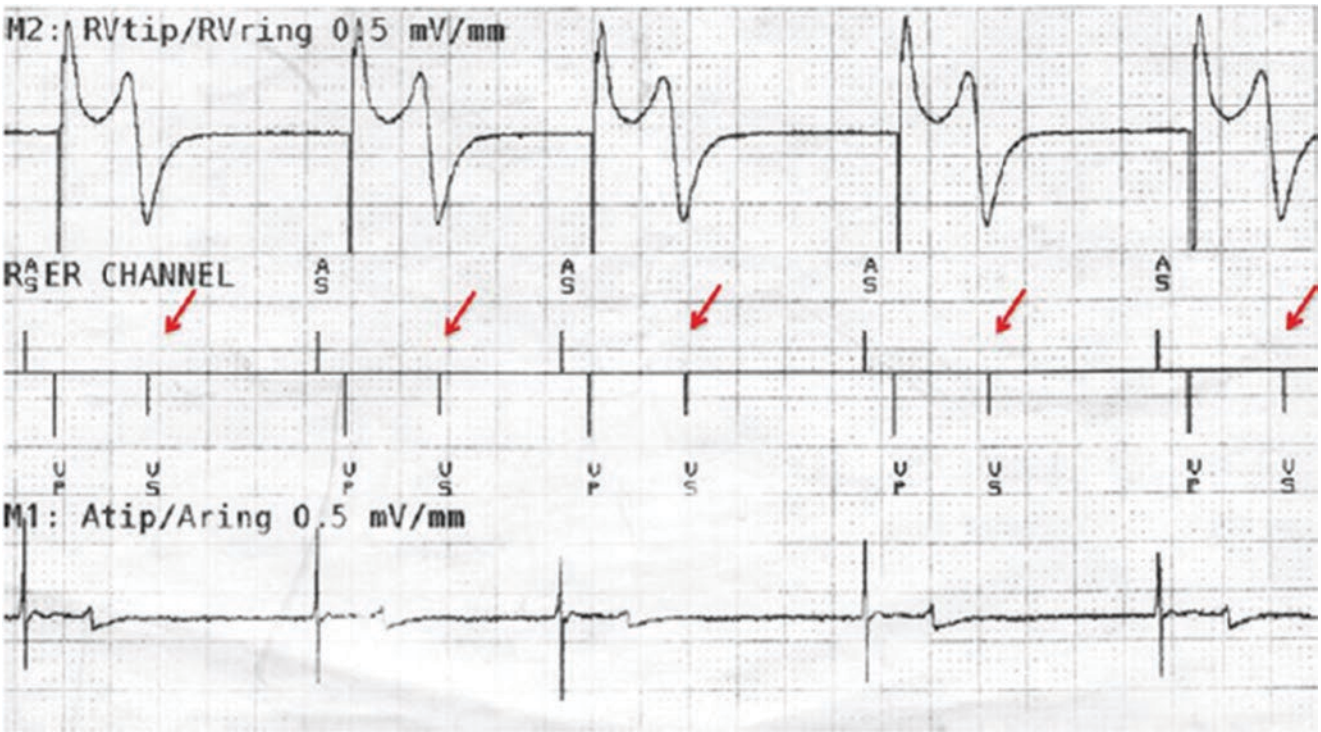

Fig. 20.2 T-wave oversensing. This figure depicts a phenomenon known as T-wave oversensing. The T-wave is inappropriately sensed as another R-wave (QRS complex) due to the large magnitude of the T-wave, common in patients with massive hypertrophy seen in HCM (depicted by *arrows*). This phenomenon can lead to double counting (counting both the R-wave and T-Wave) resulting in inappropriate ICD therapies due to falsely perceived high ventricular rates

Defibrillation threshold testing should also be performed when adding antiarrhythmic agents that can increase the defibrillation threshold (e.g., amiodarone). This should be done after an adequate loading dose of the antiarrhythmic drug has been administered. Defibrillation testing should also be considered when any cardiac structural changes have occurred, such as increased LV thickening, change in LV ejection fraction, myocardial infarction, and potentially after myectomy and alcohol septal ablation, depending on the extent of the septal injury.

Rates of ICD therapies (both appropriate and inappropriate) are influenced by numerous variables and include the subset of HCM patients being studied, the type of device used (single vs. dual-chamber), the use of SVT discriminators, and programmed ICD detection and therapy parameters. As such, careful attention to programming ICD parameters can help avoid unnecessary ICD therapies (see below).

Contemporary pacemakers and ICDs have expanded memory and diagnostic capabilities. These diagnostics have become a routine part of device interrogation, both at the bedside and via remote monitoring, and are important for subclinical arrhythmia detection and for alerting to device and lead malfunction or therapies. Remote monitoring has certainly benefitted patients, not only in convenience (less office visits), but has also been shown to decrease mortality, not only in patients with ICD but with PPM as well [53]. It is common to observe subclinical atrial fibrillation and atrial flutter. This detection capability is important as it may identify patients at increased risk of a future thromboembolic event and as such should prompt a discussion about rate/rhythm control and anticoagulation. Data from the TRENDS study [56] suggests that thromboembolic risk is a quantitative function of AF burden. AF burden ≥5.5 h on any of 30 prior days appeared to double the thromboembolic risk. Similarly, the ASSERT trial [57] showed that subclinical atrial tachyarrhythmias (atrial rate > 190 beats per minute for >6 min) detected on pacemakers and ICDs in patients over 65 years of age with hypertension and no history of atrial fibrillation were associated with a 2.5-fold increased risk of ischemic stroke or systemic embolism. Additional studies are needed to more precisely investigate the relationship between stroke risk and AF burden in patients with and without devices. An additional benefit of AF monitoring is the potential discontinuation of anticoagulation in patients who are AF-free for a period of time. This strategy is controversial and can lead to an increased risk of stroke but may be helpful in certain clinical scenarios [58].

The use of proprietary algorithms to determine intrathoracic impedance to assess fluid status (i.e., congestive heart failure) has been utilized in HCM patients although data is limited. In our centers, we use this measurement as an adjunctive tool to manage patients with HCM and CHF. Figure 20.3 demonstrates a patient with CHF and HCM, in which a rise in the fluid accumulation index preceded the development of clinical signs of CHF. Diuretic therapy improved the patient's symptoms and resulted in a decrease in the fluid accumulation index [59]. Note the variations in thoracic impedance over several months, which changed with clinical status and diuresis.

Device Programming

Pacemaker Programming

Pacemaker programming in HCM will depend on the indication for pacing. If the pacemaker was implanted for sinus node dysfunction, AV conduction disturbances, or to allow optimization of medical therapy for symptom control (traditional indications), the pacemaker is programmed accordingly. In patients in which the pacemaker was placed to treat symptomatic LVOT obstruction or in those where symptom alleviation is desired, short AV delays are generally used to ensure complete ventricular capture at both rest and with exertion and to optimize ventricular filling. In most cases, the optimal AV delay has been identified as the longest AV interval that results in complete ventricular preexcitation (i.e., ventricular pacing). This AV delay often results in deterioration in both systolic and diastolic function but to a lesser magnitude than pacing at the shortest AV intervals [60]. In addition, when dual-chamber pacing is desired, rate-adaptive AV delays should be used to ensure RV pacing with exertion.

As with non-HCM patients, rate response should be considered in patients with significant baseline bradycardia whether due to sinus node dysfunction and/or medical therapy. After device implantation, heart rate variability should be assessed by device histograms and rate response modes, and settings should be programmed accordingly.

ICD Programming

As noted earlier, inappropriate shocks are a particular problem in HCM. Efforts should be made to avoid these shocks using careful ICD programming. One method is to use higher detection intervals. Fortunately, this can usually be accomplished safely as slow monomorphic VT is rare in HCM, allowing higher programmed detection rates without the risk of neglecting slower VT [28]. Another method is to prolong detection intervals. Several recent studies have shown this to be a successful way to prevent inappropriate shocks without increasing the risk of mortality or syncope [61–63]. Utilization of antitachycardia pacing has been shown to be a safe and effective strategy in HCM [64]; however, this is generally not expected to be a major strategy utilized in HCM, as most ventricular arrhythmias are VF or

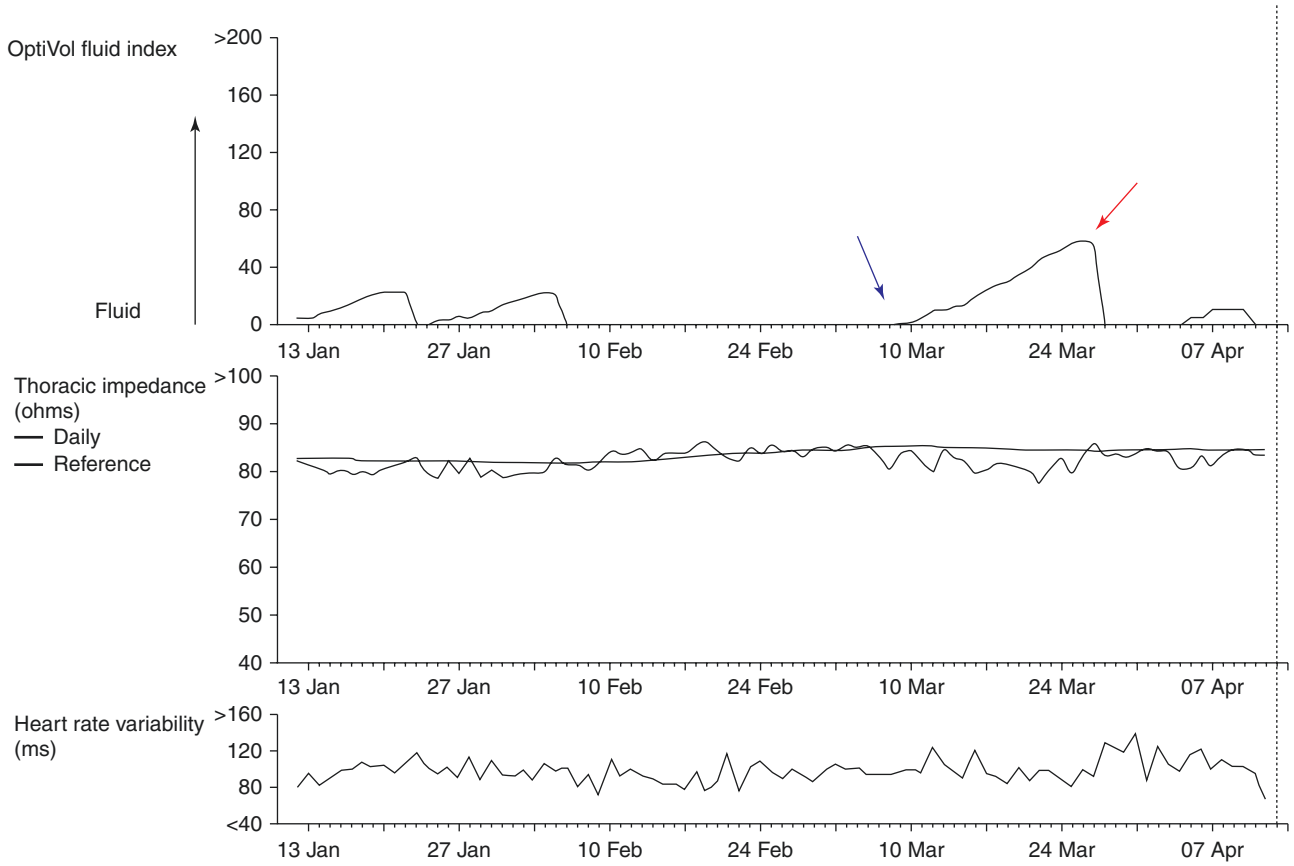

Fig. 20.3 Transthoracic impedance metrics in HCM and CHF. This figure demonstrates the variations in thoracic impedance in a patient with HCM and congestive heart failure seen over several months. The *blue arrow* shows the beginning of a period of fluid accumulation (increased fluid index), manifest as a drop in impedance. The *red arrow* shows the initiation of diuretic therapy and a return of fluid levels to baseline. Note that the fluid index is inversely related the thoracic impedance, i.e., a decrease in thoracic impedance corresponds to an increase in fluid accumulation

polymorphic VT [28]. Various other proprietary algorithms are available to assist in differentiating VT and SVT, as well as to prevent TWO, and should generally be employed. A discussion of each of these is beyond the scope of this text.

In most primary prevention trials, therapy zones often identify a ventricular rate of 188 beats per minute as the first VF (or VT) detection zone [65]. However, the recent Reduction in Inappropriate Therapy and Mortality through ICD programming trial (MADIT-RIT) showed a reduction in mortality utilizing more conservative programming, allowing for either longer VT duration prior to therapy delivery or programming therapies only for ventricular arrhythmia >200 BPM [66]. Programming will obviously vary with the specific clinical scenario and other factors, such as patient age.

Device Malfunction and Recall

Pacemaker pulse generator and lead performance have always been good and have improved since the 1990s. However, ICD system malfunction has become an area of growing concern. While ICD pulse generator function appears to be excellent and malfunction rates are very low, high-voltage-capability ICD lead failure rates have become an issue with the advent of recent recalls. Generally speaking, ICD leads fail at a rate of 0.5–1% per year. However, despite having been shown to be safe and effective in HCM patients, ICD leads fail at a higher rate (1.4%) in the younger more active population of HCM patients. These failures appear to be due more to faulty lead design than patient characteristics. Nevertheless, the contribution of a hyperdynamic heart and physical activity cannot be excluded as a precipitant in eliciting these defects [67–72].

Managing device system malfunction, advisories, and recalls are complex issues that are largely beyond the scope of this chapter; however, there are some important considerations specific to the HCM patient. First, as a group, this is a younger population of patients that may require device therapy for many decades. Given the increased length of time they are exposed to this therapy, their hyperdynamic LV systolic function, and increased physical activity, they will almost certainly have

system issues at some point. These issues should be discussed with patients before device implantation. Communication of all the issues associated with device implantation is particularly critical in these patients.

Clinical Pearls

- Pacemakers are commonly used in HCM, most often for traditional indications rather than because of the presence of HCM, but also to allow sufficient medical therapy for symptom control. The use of pacemakers for symptom control is not routinely beneficial but may have a role in elderly patients.
- Apical lead placement is essential in HCM patients for both pacing and defibrillation applications and also assures the lead is far away from any future alcohol septal ablation.
- Defibrillation threshold is often higher in the HCM population, and care must be taken to ensure proper programming.
- Attention must be paid to T-waves at implant, as TWO can be a significant issue in these patients.
- ICD patient selection is important. Most patients, even with clear indications, will never receive ICD therapies. Complications, which include inappropriate therapies, system malfunction, and other issues, are frequently higher in this population and may importantly affect the risk-to-benefit analysis. Therefore, patients should be counseled accordingly prior to device implantation.

Questions

1. A 35-year-old asymptomatic man with HCM, septal thickness of 20 mm, has a 5-beat run of NSVT detected on an outpatient monitor. He has no other risk factors for sudden death. What is the best course of action?
   A. Implant a dual-chamber ICD.
   B. Implant a single-chamber ICD.
   C. Electrophysiology study.
   D. Cardiac MRI.

   Answer: D. This patient does not meet indications for ICD, but risk modifiers might aid in borderline cases. Cardiac MRI can aid in quantifying LGE/scar burden and assessing maximal wall thickness more accurately. There is no firm indication for EPS in patients with HCM.

2. A 56-year-old woman with dyspnea on exertion presents for evaluation. Echocardiogram reveals HCM with septal thickness of 25 mm and an LVOT gradient of 100 mmHg. She has no known risk factors for sudden death. Resting ECG reveals a PR interval of 300 ms and a narrow QRS complex. You should:
   A. Start metoprolol succinate 25 mg daily
   B. Place an event monitor for 2 weeks
   C. Refer for septal reduction
   D. Implant a dual-chamber pacemaker

   Answer: B. Monitors in HCM are used for assessing conduction disease and palpitations and for routine monitoring for NSVT or AF. In this patient it may help determine if she can get metoprolol with her prolonged AV conduction as well. Septal reduction may be necessary but only after a trial of medications or for severe symptoms, which have not been elucidated in the presentation.

3. When a patient with HCM is to undergo ICD implantation, what is the optimal ventricular lead position?
   A. RV apex
   B. RV apex plus lateral coronary venous branch
   C. RV septum
   D. RV outflow tract

   Answer: A. Apical leads are best for relief of LVOT obstruction (when considered for this borderline indication) and also to avoid malfunction in the case of alcohol septal ablation.

4. When considering a subcutaneous ICD for an HCM patient, which of the following is a contraindication?
   A. Large T-waves on ECG
   B. Exercise-induced Mobitz II AV block
   C. History of atrial fibrillation
   D. Asymptomatic LVOTO

   Answer: B. Since backup pacing is an issue for these devices, the AV block would be a contraindication.

5. T-wave oversensing during exercise can be predicted by T-wave amplitude at UCD implantation.
   A. True
   B. False

   Answer: False. This is false and a deeper evaluation and management for TWO is required.

6. Of the following, which is a class I indication for ventricular pacing in HCM?
   A. Symptomatic type 1 second-degree AV block
   B. Medically refractory symptomatic LVOTO

C. RBBB after alcohol septal ablation
D. LBBB after surgical septal myectomy

Answer: A. AV block is a Class I indication, as HCM patients require AV conduction to maintain the atrial kick, given their significant diastolic dysfunction. Bundle branch blocks are not an indication, and relief of outflow tract obstruction is no longer considered a reasonable indication based on the M-PATHY trial.

7. HCM patients with apical aneurysm are ____ likely to benefit from antitachycardia pacing than those without.
   A. More
   B. Less

   Answer: A. Apical aneurysms are associated with scar and VT.

8. ICD implantation is a class III indication in which of the following patients?
   A. A 29-year-old woman with three 10–20 beat runs of NSVT on outpatient monitoring.
   B. A 40-year-old man with apical HCM and maximal wall thickness of 31 mm.
   C. A 16-year-old boy with family history of aborted sudden death and HCM in his father. He has the same mutation as his father on genetic testing but his MRI is negative for HCM.

   Answer: C. The young boy has the gene that is running in his family for HCM but negative phenotype. Currently, ICD is not indicated for gene +, phenotype – patients. MWT > 30 is an indication for ICD, as is recurrent, rapid NSVT, although isolated short bursts of NSVT are considered Class IIb.

9. Randomized trials have proven the benefit of ICD in HCM patients with high-risk features.
   A. False
   B. True

   Answer: A. There have been no randomized trials of ICD in HCM. All data are based on observational experience.

10. A 30-year-old woman with HCM, septal thickness of 15 mm, reports an episode of syncope at the age of 19 after donating blood. In the absence of other risk factors for sudden death, is an ICD indicated?
    A. Yes
    B. No

    Answer: No. This is likely vasovagal, and in the absence of other risk factors for SCD, an ICD is not indicated. The patient would benefit from longer event monitoring and ETT testing.

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Management of Arrhythmia: Medications, Electrophysiology Studies, and Ablation

21

Daniel R. Zakhary and Joseph J. Germano

Key Points

- Ambulatory electrocardiogram (ECG) monitoring should be used annually and when new symptoms potentially referable to arrhythmias arise, both to screen and diagnose arrhythmic disease in HCM patients, as arrhythmias are more frequent and significant in this population.
- Electrophysiology studies (EPS) are typically not helpful as a risk stratification tool in HCM and are thus not routinely recommended.
- Atrial fibrillation (AF) is usually poorly tolerated in HCM patients, and sinus rhythm should be maintained when possible.
- Stroke risk in HCM patients with AF is high, and most data suggest they should be anticoagulated, irrespective of the presence or absence of other risk factors for thromboembolism.
- Radiofrequency ablation for AF can be beneficial in patients with HCM who have refractory symptoms or who cannot tolerate or are poor candidates for antiarrhythmic drugs.
- In HCM patients with two or more major risk factors for sudden cardiac death (SCD), the annual incidence of SCD approaches 4–5%, warranting prophylactic implantable cardioverter defibrillator (ICD) therapy; in those with one major risk factor and depending on the actual risk factor, ICD should be considered. Patients with minor risk factors may also warrant ICD consideration on a case-by-case basis.
- The amount of late gadolinium enhancement by MRI may be related to a higher risk of sudden cardiac death and may prove to be an important predictor of high-risk HCM patients; further studies are necessary.
- VT ablation in HCM is associated with good long-term outcome but may be challenging.

Introduction

In patients with hypertrophic cardiomyopathy (HCM), all arrhythmias including atrial fibrillation (AF), supraventricular tachycardia (SVT), and ventricular tachycardia (VT)/ventricular fibrillation are common, and the general prevalence increases with age. The diagnosis of arrhythmias in HCM may be suggested clinically based on symptoms such as palpitations or syncope, but it generally requires further testing. Ambulatory ECG monitoring is important for screening, as arrhythmias are usually of greater significance in the HCM population. All patients should also be screened with echocardiography mainly to assess the degree of LVH, as it is directly related to an increased risk for sudden cardiac death (SCD). Implantable loop recorders or ambulatory event monitors may be particularly helpful in patients with recurrent unexplained symptoms, especially prior to contemplation of ICD implantation.

There is an important association in HCM with several preexcitation syndromes, but limited data exists regarding the significance and treatment of these SVTs. For patients with AV nodal reentry tachycardia (AVNRT), high-dose AVN blockers are usually sufficient, but it may be reasonable

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to pursue electrophysiology studies (EPS) and ablation in poorly tolerated or difficult to control cases. For patients with Wolff-Parkinson-White (WPW) syndrome, there is a risk of maintaining patients on AVN monotherapy without the use of concurrent antiarrhythmic medications, due to the underlying potential to develop atrial or ventricular tachyarrhythmias. Overall, evidence suggests WPW should be identified and treated with RF ablation when found.

Atrial fibrillation is poorly tolerated in hypertrophic cardiomyopathy, and as with all patients with AF, HCM patients can be managed with either a rate control (controlling the ventricular rate while allowing the patient to remain in AF) or a rhythm control strategy (using cardioversion, antiarrhythmic drugs, and/or procedures to maintain sinus rhythm). Stroke risk is high in this population, and consequently anticoagulation is the cornerstone of AF treatment. All patients with HCM should be anticoagulated, even after a first or short-lived episode, because the likelihood of further (oftentimes subclinical) episodes is high. AF is frequently eliminated by pulmonary vein isolation (ablation), which disrupts the electrical activity between tissues containing these arrhythmogenic triggers and substrate and the left atria. Ablation can be successful in restoring long-term sinus rhythm and improving symptomatic status in most HCM patients with refractory AF but may require multiple lesion delivery and repeat procedures, with the risk of increased complications. There is a role for novel convergent (combined surgical and percutaneous) procedures to achieve successful ablation, especially in refractory cases or when non-PV triggers are found in the hypertrophied and disorganized atrial myocardium.

The recommendations for management of ventricular arrhythmias in HCM patients are less clear than for atrial arrhythmias. Although nonsustained VT (NSVT) is a common finding and is associated with an increased risk of SCD, suppression does not necessarily lead to a reduction in SCD or increased survival. Accordingly, NSVT is given a Class IIb recommendation in the current guidelines, meaning that ICD implantation may be considered. In patients with sustained monomorphic VT in the setting of structural heart disease such as HCM, ICD therapy is generally the standard of care. Patients with recurrent sustained episodes of ventricular arrhythmias or firing of their ICD should be treated with adjunctive antiarrhythmics. VT mapping and catheter ablation are important especially in cases of medically refractory VT and VT storm and can be a safe and successful method for eliminating VT in these patients.

The guidelines for ICD implantation for SCD prevention in HCM are continuously evolving based on incomplete data and thus rely heavily on expert consensus. High-risk HCM patients should have ICD placement for primary prevention. Clinical factors and noninvasive testing continue to be the cornerstone of risk assessment; however, there is an obvious need for further risk stratification, especially in intermediate-risk patients. The role of EPS is heavily debated as a risk-stratifying tool based on the rationale that ventricular arrhythmias are a common cause of syncope and/or SCD in HCM, but routine EPS is not recommended in the current guidelines. EPS may however be useful in identifying electrophysiological abnormalities and selecting prophylactic antiarrhythmic therapy.

Incidence of Arrhythmias

In patients with hypertrophic cardiomyopathy, the general prevalence of all arrhythmias, especially atrial fibrillation (AF), increases with age. In one series, overt AF was present in approximately 5% of patients at the time of diagnosis of HCM and developed in an additional 10% during a 5-year follow-up period [1]. In another series of HCM patients followed for 9 years, AF occurred in 22% of patients, giving an annual incidence of approximately 2% per year [2]. In these series, AF was paroxysmal about two-thirds of the time. Clinically silent AF may be present in up to an additional 24% of patients, when a group of HCM patients with dual-chamber ICDs were followed [3]. Other studies in patients with cardiac implantable electronic devices showed an incidence of up to 7% per year [4]. Clinical variables such as female sex, advanced age, left atrial diameter, New York Heart Association class, hypertension, vascular disease, and extent of septal hypertrophy have been reported to predict AF in HCM patients [5]. Overall, the reported incidence of AF in HCM is approximately fivefold higher than that of the general population. Furthermore, the presence of AF in HCM patients confers an approximate two- to fourfold increase in mortality relative to HCM patients without AF [4, 6].

In the apical variant of HCM, a study of 306 consecutive patients demonstrated AF to occur with an incidence of 25.2% (4.6%/year). In this group, AF was independently predicted by advanced age and a left atrial diameter of >45 mm. After adjusting for age and gender, AF incurred a 6.6-fold increased risk of all-cause death and a 5.1-fold increase in risk of stroke [7].

Ambulatory ECG monitoring demonstrates that SVT is common in HCM patients (between 25% and 37%) and occurs more commonly in patients with left ventricular outflow tract obstruction [8, 9]. The majority of these events are asymptomatic and self-limited, rarely requiring therapy. Accessory atrioventricular pathways, which are responsible for preexcitation syndromes such as AVNRT and WPW, are thought to result from developmental failure to eradicate remnants of the atrioventricular connections during

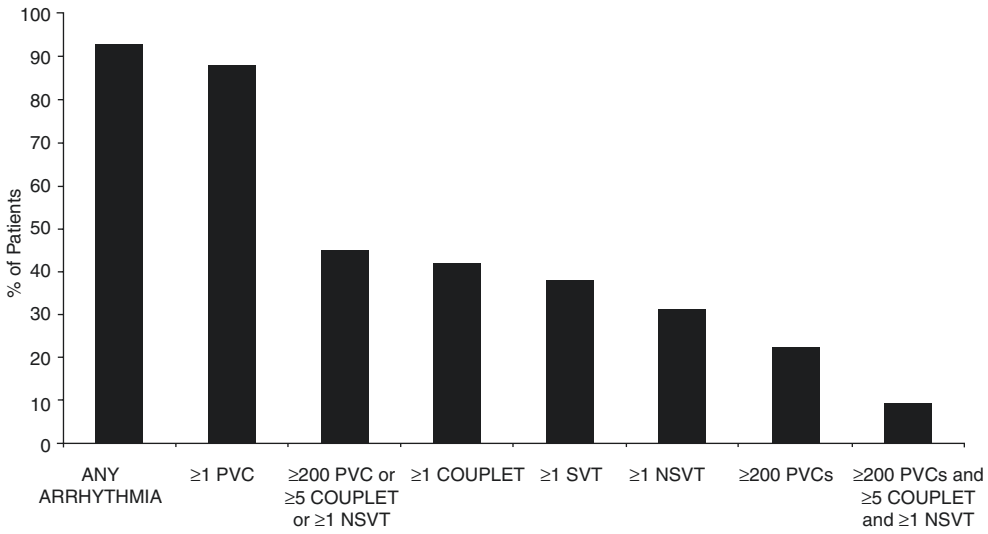

Fig. 21.1 Prevalence of ventricular and supraventricular arrhythmias on ambulatory electrocardiogram monitoring in patients with hypertrophic cardiomyopathy. NSVT nonsustained ventricular tachycardia, PVC premature ventricular complex, SVT supraventricular tachycardia. (Figure from Adabag et al. [8])

cardiogenesis, resulting in abnormal anatomical and electrical continuity [10]. Wolff-Parkinson-White syndrome (WPW) is one of the most common congenital cardiac abnormalities with a general prevalence of 0.15–3 per 1000 adults [11, 12]. However, the prevalence of accessory pathways in hypertrophic cardiomyopathy is markedly increased, with approximately 5% of HCM patients having ventricular preexcitation [13].

While HCM is commonly associated with SVT, the presence of ventricular arrhythmias is more concerning. Premature ventricular contractions (PVCs) and nonsustained VT are relatively common in patients with HCM (Fig. 21.1). Evidence from ambulatory ECG monitoring has shown that PVCs are present in 88% of patients with HCM [8]. However, data does not exist to show that frequent PVCs lead to an increased incidence of sustained VT. In another study, the incidence of nonsustained ventricular tachycardia (NSVT) (defined as ≥3 beats of VT at 120 beats per minute) was approximately 15–30% on ECG monitoring [14]. NSVT is more likely in patients with greater degrees of left ventricular hypertrophy (LVH) and New York Heart Association (NYHA) Class III or IV symptoms. It is well established that NSVT is associated with an increased risk for SCD in patients with HCM [9, 14–17]. This increased risk is greatest in younger patients and those with symptoms; however, there is no clear relation to prognosis in terms of the duration, frequency, or rate of the NSVT episodes.

Data from HCM patients who received appropriate ICD firing indicate that the underlying rhythm is polymorphic VT, VT leading to VF, and less commonly sustained monomorphic VT [18]. Overall, the annual incidence of these malignant events is approximately 6–11% [18, 19]. Caution must be taken in equating appropriate ICD therapies to SCD, as appropriate device therapy has been shown to roughly double true SCD in most studies [20]. The development of these ventricular arrhythmias is likely from a combination of physiological events in addition to the proarrhythmic substrate of the hypertrophied myocardium and intramyocardial scar. This is evidenced by the abnormal hemodynamic and autonomic responses during or soon after mild to moderate exercise in these patients, which may also provoke the underlying arrhythmogenic substrate [21, 22].

SCD is the most feared complication of HCM, and the annual incidence of SCD is approximately 1% [23]. Although this overall rate is not too dissimilar from the general population of non-HCM patients, a subset of HCM patients have significantly higher rates of SCD, whereas others are at much lower risk; hence, in the population as a whole, a normal average life expectancy can be expected, and efforts to evaluate the risk of SCD in HCM patients focus on mechanisms to identify those at high risk.

Sustained VT, either resuscitated or aborted, without any known inciting factors is a major risk factor for SCD and requires an ICD for secondary prevention [18]. A family history of SCD in HCM patients, especially if a first-degree relation at a young age (<50), is associated with an increased risk of sudden death in other affected family members, and this risk is particularly high for multiple SCD events or those occurring in younger members [9]. Other major risk factors include massive myocardial thickening >3 cm, recurrent unexplained syncope despite optimal medical therapy, and abnormal blood pressure or arrhythmia response to exercise treadmill testing. In general, the risk of sudden death in HCM parallels the number of patient risk factors, approaching approximately 60% for patients with three or more risk factors (Fig. 21.2). More information on risk stratification for SCD may be found elsewhere in this textbook.

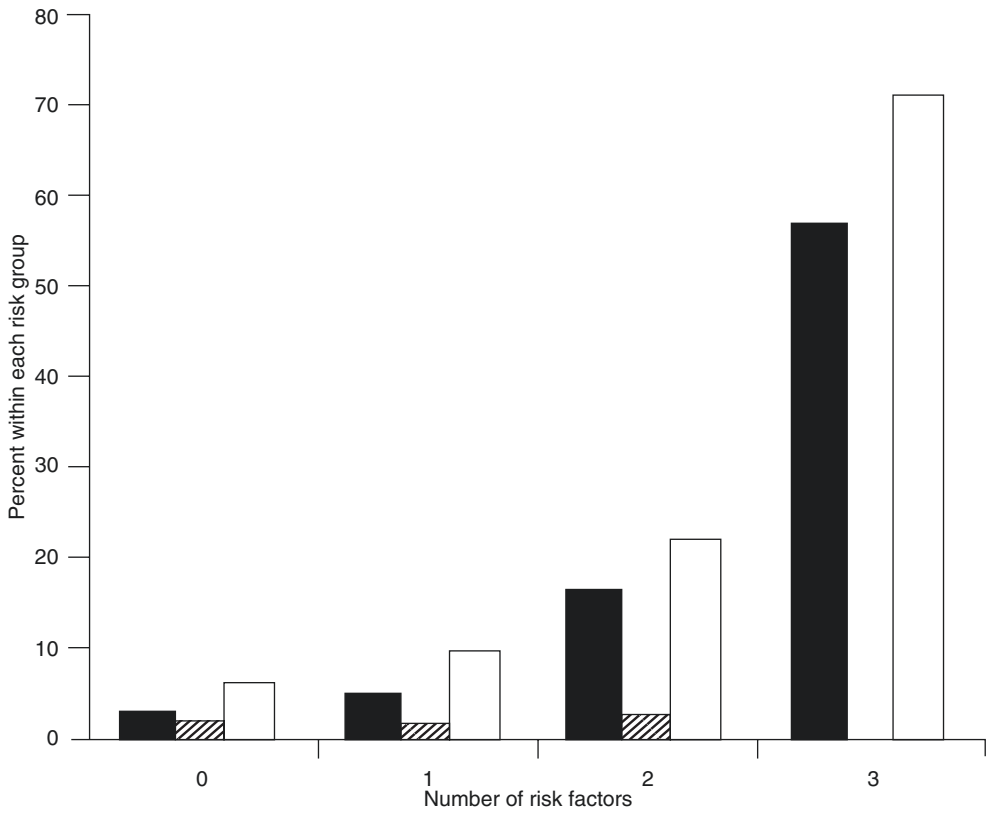

Fig. 21.2 Sudden cardiac death in hypertrophic cardiomyopathy. Bar graph showing the percentage of each risk factor group (zero, one, two, and three risk factors) in which patients died during follow-up (sudden deaths = black bars, overall deaths = white bars). (Figure from Elliott et al. [24])

Diagnosis

The diagnosis of arrhythmias in HCM may be suggested clinically based on symptoms such as palpitations or syncope, but it generally requires further testing. Separate from hemodynamic syncope caused by LVOT obstruction, SVT and VT may be involved in the etiology of syncope in HCM patients and are important predictors of sudden cardiac death [24, 25]. Atrial tachyarrhythmias may be more common in middle-aged patients, and programmed atrial stimulation can be a useful means to identify this etiology of syncope [26]. The development of ventricular tachyarrhythmias is related to several predisposing factors, including myocardial fibrosis and ischemia [27, 28], myocyte disarray, and autonomic disturbances. The degree of myocardial fibrosis as it relates to the arrhythmic substrate can be assessed by late gadolinium enhancement (LGE) on cardiac MRI [29] to predict events in HCM [30]. Myocyte disarray is histologically characterized by an irregular arrangement of abnormal shaped myocytes that contain bizarre nuclei and surrounding areas of increased connective tissue. Interstitial fibrosis can cause dispersion of activation and results in myocardial fibers having differential conduction velocities and refractory periods, thereby leading to reentry.

Noninvasive Testing

All patients with HCM should be screened with ECGs and echocardiography. An ECG should be performed at every patient visit, as subclinical arrhythmias may be captured in this manner (Fig. 21.3). The majority of patients with SVT have sporadic brief episodes of tachycardia that may be difficult to capture on a standard 12-lead electrocardiogram. Although ambulatory monitoring may be useful in patients with frequent runs of SVT to ascertain the frequency and duration of events, it is perhaps less useful in establishing a diagnosis, since only several channels are typically used making it difficult to discriminate between SVT mechanisms. In one study using Holter monitoring of such events, the result was an incorrect SVT diagnosis in 55% of cases [31]. In patients with WPW, ambulatory monitoring may be useful in risk assessment. In one case series, patients with intermittent preexcitation had EPS consistent with lower risk of ventricular fibrillation (VF) compared with those with persistent preexcitation [32].

Hypertrophic cardiomyopathy is associated with arrhythmia-related consequences, particularly sudden cardiac death. Ventricular tachyarrhythmias have been reported as markers for sudden death in highly selected HCM populations. Studies examining the prevalence and prognostic

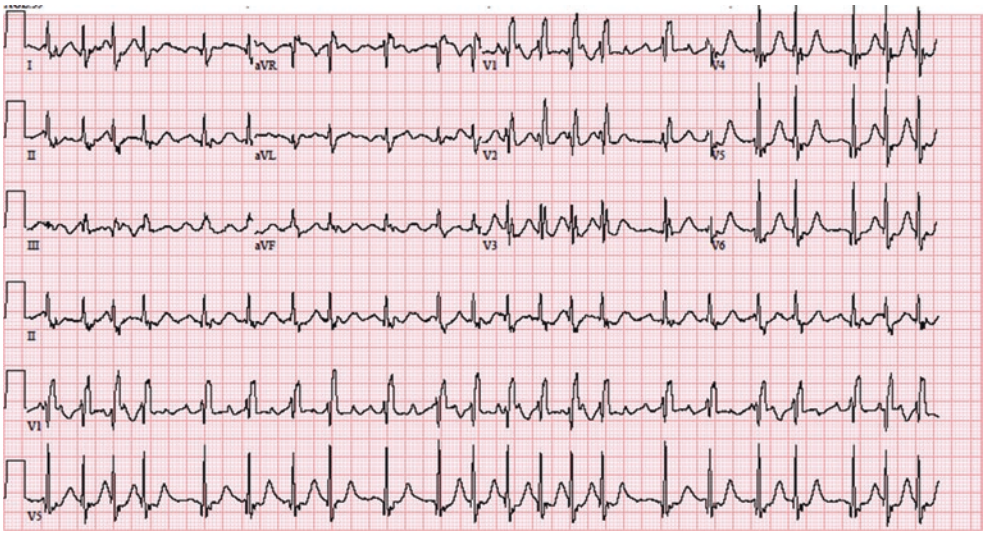

Fig. 21.3 ECG from an asymptomatic young patient with advanced HCM prior to AF ablation. Atrial activity is seen as irregular fibrillary waves suggesting atrial fibrillation. Right bundle branch block is present potentially obscuring left ventricular hypertrophy

significance of ventricular and supraventricular arrhythmias showed they were frequent and demonstrated a broad spectrum on ambulatory ECG monitoring. Ventricular tachyarrhythmias were shown to have a low positive and relatively high negative predictive value for sudden death in this HCM population [8]. Nevertheless, according to the ACC/AHA practice guidelines for ambulatory ECG monitoring, for patients with idiopathic hypertrophic cardiomyopathy, there is only a IIb indication for routine ambulatory ECG monitoring to detect arrhythmias and to assess the risk of cardiac events in patients without symptoms [33].

Several studies indicate that the degree of LVH by echocardiography is directly related to an increased risk for SCD. The incidence of SCD almost doubles for each 5 mm increase in wall thickness [34]. However, not all studies have confirmed the association between massive LVH (greater than 3 cm) and SCD, and overall it has a low positive predictive value [35]. Thus, as with the other major risk factors, massive LVH is most useful when considered within the full context of the clinical history, although many experts consider this risk factor as sufficient to warrant ICD placement in amenable patients. If present, patients should undergo full evaluation for markers of hemodynamic and electrical instability such as symptom-limited upright exercise testing. Approximately 30% of HCM patients cannot appropriately increase their baseline blood pressure during exercise, and in some patients the blood pressure actually falls below baseline values. This abnormal blood pressure response during maximal exercise is associated with an increased risk for SCD, especially in patients younger than 40 years of age and those with a family history of premature SCD [36, 37]. It is not clear whether this abnormal response is due to the development of outflow tract obstruction, abnormal autonomic vascular response, or changes in diastolic dysfunction with exertion. See chapter on risk stratification of sudden cardiac death for more discussion.

Invasive Testing

Clinical factors and noninvasive testing (as discussed above) have and continue to be the cornerstone of risk assessment, but there is an obvious need for further risk stratification, especially in intermediate-risk patients. The role of EPS has been heavily debated as a risk-stratifying tool based on the rationale that ventricular arrhythmias are a common cause of syncope and/or SCD in HCM. EPS may be useful in identifying an electrophysiologic abnormality and selecting prophylactic antiarrhythmic therapy [38]. However, EPS that demonstrate inducible ventricular arrhythmias have not been shown to be a reliable predictor of SCD, even though properties of the septum that are consistent with arrhythmogenic scarring (such as reduced voltage and conduction delay) can be found [16]. This may be due in part to varying substrate, unrelated factors such as vascular and hemodynamic responses (as previously discussed), and/or other poorly understood mechanisms. In summary, there is limited (if any) value of invasive electrophysiology testing for clinical decision-making in patients with HCM to justify the risk of complications associated with these procedures. Accordingly, the role of invasive EPS has been removed from the guidelines to be used as a tool for risk stratification.

Affected individuals with both preexcitation and hypertrophy often exhibit high-grade AV block, which is usually regarded as an uncommon phenomenon in HCM [39–41]. The syndrome of WPW is typically recognized by the characteristic changes on the surface electrocardiogram;

however, definitive diagnosis of preexcitation may require electrophysiologic testing. EPS can be used in patients with WPW syndrome to determine several important electrophysiologic properties including conduction capability and refractory periods of the accessory pathway and the normal AV nodal and His-Purkinje conduction system [42, 43]. In addition, EPS can evaluate the number and locations of accessory pathways (necessary for catheter ablation) and/or the response to pharmacologic or ablation therapy.

Management

SVT

There is limited data regarding the significance of SVT in HCM. There is however an association with certain preexcitation syndromes; HCM has been described in patients with mutations in the PRKAG2 or LAMP2 genes [44, 45]. The proteins encoded by these genes are involved in carbohydrate metabolism rather than sarcomere structure like the other HCM mutations, emphasizing the genetic heterogeneity of the disease. Progressive conduction system disease requiring pacemaker implantation is common with PRKAG2 mutations, while progression to end-stage HF in early adulthood is common with LAMP2 mutations. AVNRT can be managed using beta-blockers or calcium channel blockers as first-line therapy for these patients with HCM since these agents are advantageous for their diastolic dysfunction and LVOT obstruction. In addition, high-dose AVN blockers will probably be sufficient, but it may be reasonable to pursue EPS with catheter ablation in poorly tolerated or difficult to control cases.

The association of WPW syndrome with autosomal dominant familial hypertrophic cardiomyopathy is well established in the literature. Recently, the genetic substrate linking hypertrophic cardiomyopathy to WPW syndrome has been identified; ventricular preexcitation and hypertrophic cardiomyopathies were shown to segregate as a single autosomal dominant disorder by genetic linkage analyses to chromosome7q3 [46, 47]. Treatment of WPW is based on AV nodal blocking medications to slow AV nodal conduction and antiarrhythmic drugs to slow accessory pathway conduction, in addition to radiofrequency ablation of the accessory pathway. Radiofrequency catheter ablation has practically eliminated surgical ablation in the vast majority of WPW patients, except in patients with failure of repeated RFA attempts and possibly also patients undergoing concomitant cardiac surgery for other indications.

For patients with WPW (in contrast to AVNRT), there may be an earlier indication for ablation since they are often difficult to manage medically. It is important to recognize the risks of maintaining patients with HCM plus WPW on monotherapy with beta-blockers or calcium channel blockers without the use of other antiarrhythmics. This may be due to an increased risk of subsequent AF and/or VF in the absence of other background agents. At our center, patients with HCM and WPW would likely undergo ablation in order to be able to maximize AVN blockers, as the incidence of AF in their lifetime is high.

AF and Atrial Flutter

As with all patients with AF, HCM patients can be managed with either a rate control (controlling the ventricular rate while allowing the patient to remain in AF) or a rhythm control strategy (using cardioversion, antiarrhythmic drugs, and/or procedures to maintain sinus rhythm). Selecting the proper strategy must take into account individual characteristics and must weigh symptoms and hemodynamic tolerance of AF against risks associated with antiarrhythmic medications and procedural complications (Fig. 21.4). Given the specific hemodynamic derangements associated with HCM and these arrhythmias (namely, the loss of atrial contraction and rapid irregular ventricular rates discussed above) as well as the more common association with symptoms, a rhythm control strategy is more frequently utilized in patients with AF than similar patients with AF but without HCM. In most respects, rhythm control in HCM patients is similar to patients without HCM, with a few important differences.

Chemical or electrical cardioversion is often needed to restore sinus rhythm, frequently with adjuvant antiarrhythmic therapy. As for patients with unknown duration of AF in the non-HCM population, a transesophageal echocardiogram is often required to exclude left atrial appendage thrombus. Importantly, patients with HCM oftentimes have abundant trabeculae, which may also be present in the left atrial appendage. Careful attention to these, which may be mistaken for thrombus, must be undertaken. Flow velocities in the appendage may assist in differentiating the two. In difficult cases, cardiac MRI or CT may be useful if a rhythm control strategy is needed. The treatment of atrial flutter in HCM is similar to AF in terms of medical management, as well as transesophageal evaluation, with select patients being good candidates for ablation.

The choice of antiarrhythmic agents is limited by significant LVH but also the lack of clinical experience (refer to the 2011 HCM guidelines) [48, 49]. Of the antiarrhythmic drugs available, amiodarone has been found to be the most effective. Disopyramide may also be used, but because of the concern for accelerated AV conduction, it should only be given in combination with an AV nodal blocking agent, such as a beta-blocker or a non-dihydropyridine calcium channel blocker [48, 50]. Patients with significant concomitant outflow tract obstruction may be best served by an initial trial of disopyramide, as opposed to amiodarone, given the former

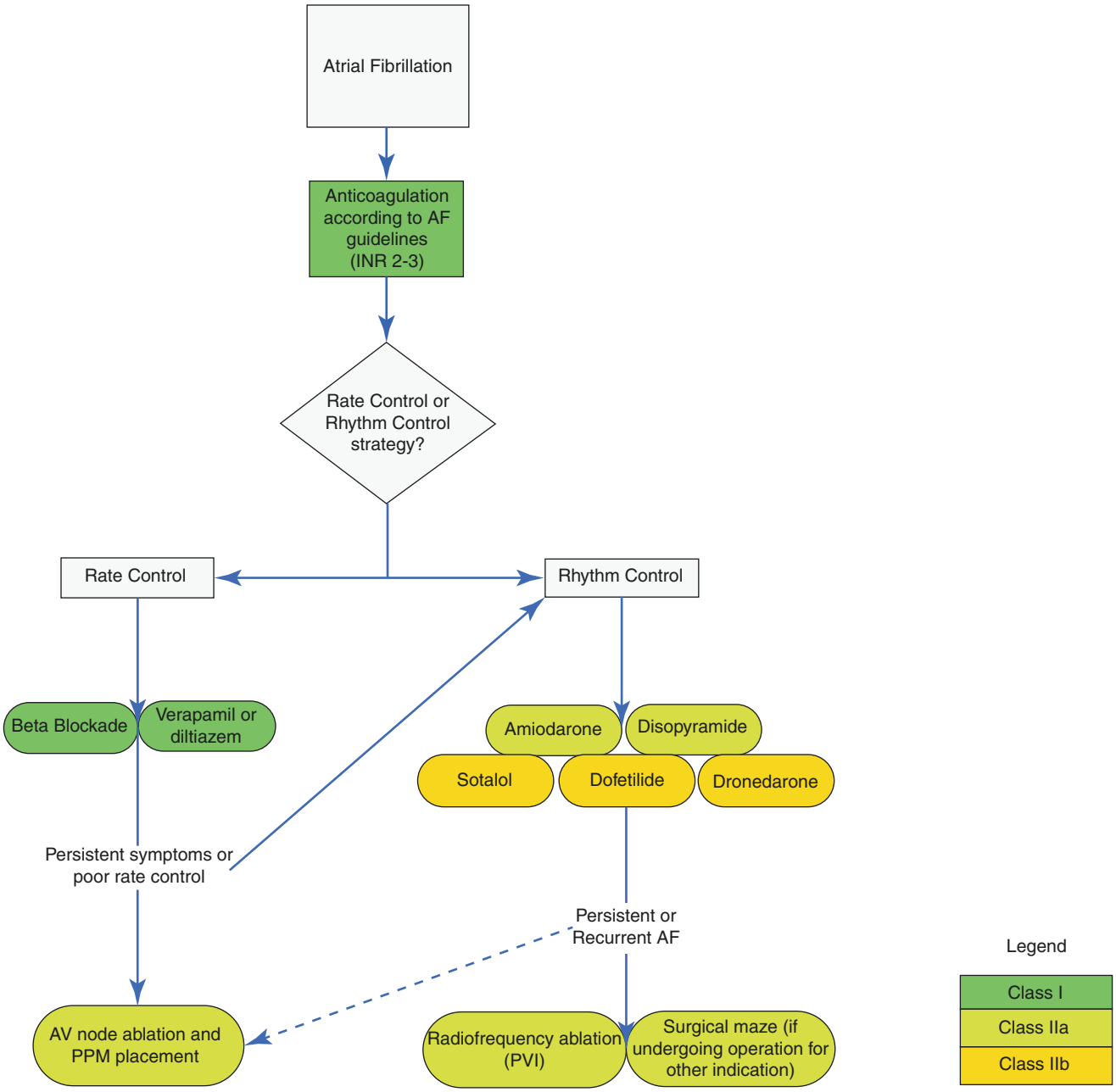

Fig. 21.4 Flowchart for general management strategies of AF in the setting of HCM. AF indicates atrial fibrillation, AV atrioventricular, INR international normalized ratio, PPM permanent pacemaker, PVI pulmonary vein isolation. (From Writing Committee Members et al. [77])

drugs effect on inotropy and reduced resting and provocable gradients. In addition, although amiodarone is effective in reducing the incidence of recurrent AF or heart rate in AF, its use is limited by long-term toxicity, which can be significant in this younger patient population who might require therapy for decades. Efficacy data in HCM patients with AF is limited (see discussion below) for both agents, however.

In the instances when rate control is chosen (i.e., failure to maintain sinus rhythm, lack of symptoms associated with AF, and/or hemodynamic stability), beta-blockers and calcium channel blockers are the preferred agents. Digoxin should be avoided, as it may worsen LV outflow obstruction due to its positive inotropic effects. If rate control is not possible, AV nodal ablation with placement of a permanent pacemaker is an effective treatment option. In such cases dual-chamber pacemakers are required to reconnect the atria with the ventricles, given the heavy reliance on atrial contraction in this patient population.

Anticoagulation

Anticoagulation is the cornerstone of AF treatment and is especially important in patients with HCM [51]. All patients

with HCM should be anticoagulated as described in the 2011 HCM guidelines, even after a first or short-lived episode, because the likelihood of future subclinical episodes and the association with stroke are high. In the largest cohort of HCM patients with AF studied, 22% of 480 outpatients with HCM developed AF during a 9-year follow-up period (incidence of approximately 2% per year). The occurrence of nonfatal ischemic stroke overall was 14%, and stroke-related death was 7%, which was independent of whether AF was exclusively paroxysmal or chronic [2]. In addition, in these HCM patients, ischemic strokes were eight times more frequent among AF patients than among those in sinus rhythm, and the annual HCM-related mortality was 3% in AF patients compared to 1% in sinus rhythm.

Anticoagulation can be achieved with warfarin for a goal INR of 2.0–3.0. Newer agents such as direct thrombin inhibitors (DTI), or factor Xa inhibitors, can also be used, although these agents have not been studied specifically in the population of HCM patients. In large randomized trials of patients who are at intermediate or high risk for clinical thromboembolism, compared to warfarin, anticoagulation with each of the novel oral anticoagulant agents (NOACs) leads to similar or lower rates both of ischemic stroke and major bleeding. Three meta-analyses regarding pooled results from the RELY (dabigatran), ROCKET-AF (rivaroxaban), and ARISTOTLE (apixaban) trials have confirmed these results [52–54].

Patients with AF often have an AF burden that improves after surgical myectomy or alcohol ablation. Although there is no consensus as to the optimal duration of anticoagulation post AF ablation, it is likely reasonable to continue full anticoagulation for a short time (e.g., 1 year) provided there has been no documented recurrence. Based on our center experience overall, select patients may come off anticoagulation, as long as vigorous monitoring for recurrence of AF continues. However, many experts would disagree and maintain anticoagulation due to the risks associated with even relatively brief AF.

AF Ablation

The data are limited for ablation of atrial fibrillation specifically in the HCM population. Several obstacles to treating AF with antiarrhythmic drugs include limited choices (due to insufficient data, contraindications, or the extended duration of therapy), variable efficacy in maintaining sinus rhythm, and frequent medication side effects. Catheter ablation can therefore be used as an effective alternative, especially for refractory cases. AF is usually eliminated by pulmonary vein isolation, which disrupts the electrical activity between tissues containing these arrhythmogenic triggers and substrate (the antral and ostial portions of the pulmonary veins) and the left atria. Atrial tissue can also be directly ablated using the maze procedure concomitantly in HCM patients undergoing septal myectomy. Although pulmonary vein isolation is effective in eliminating AF in other patient populations, results in patients with HCM are less well established. One study confirmed successful PVI ablation using 3D electroanatomical mapping in a population of HCM patients [55]. Recurrence rates after the first pulmonary vein isolation were shown to be higher in patients with HCM. It is possible that atrial tissue itself may be more arrhythmogenic in this patient population, leading to a high incidence of non-PV triggers and hence a higher failure rate after PV isolation. Additionally, the thick myocardium may make the creation of transmural lesions more difficult. In terms of substrate, the degree of heart failure, left atrial size, and patient age were shown to be important predictors of success or failure [56, 57] (Fig. 21.5).

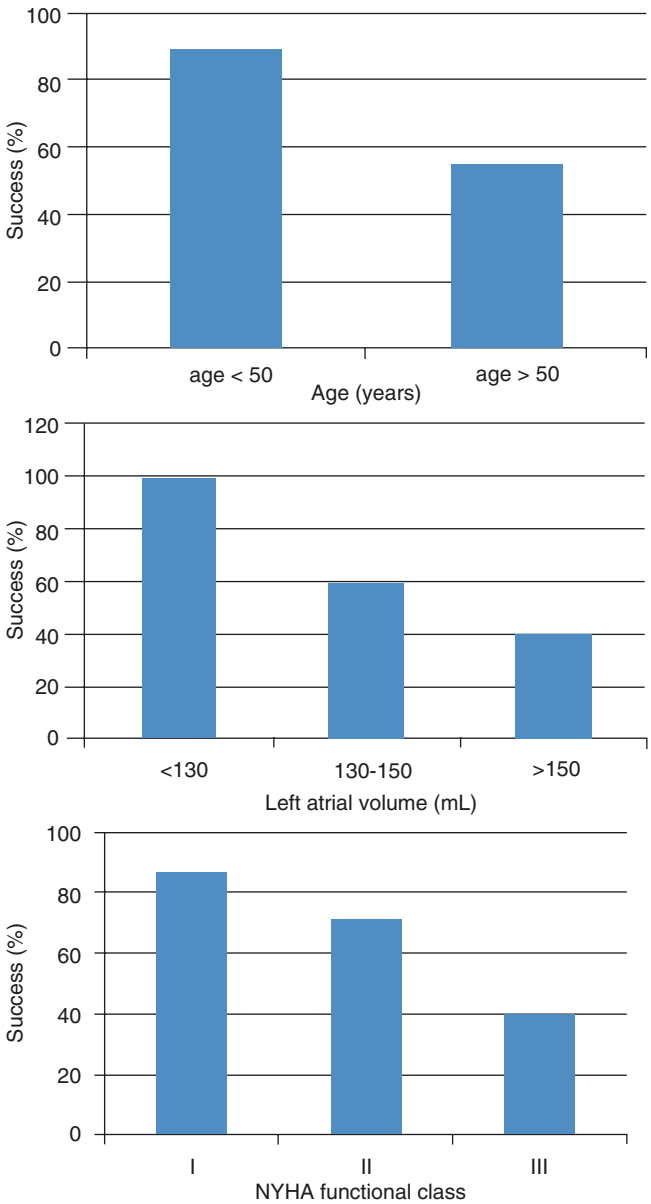

Fig. 21.5 RFA success in HCM patients based on age, left atrial volume, and NYHA functional class. Vertical bars represent the proportion of HCM patients in sinus rhythm (success rate) after the ablation. (Adapted from Di Donna et al. [57])

The best candidates were younger HCM patients with a small atrial size (indicative of less atrial remodeling) and those with mild symptoms. Those patients with sarcomere gene mutations often required repeat procedures. However, after repeated ablation procedures, long-term cure was achieved in a significant percentage of patients [58]. Overall, results show that ablation can be successful in restoring long-term sinus rhythm and improving symptomatic status in most HCM patients with refractory AF but require multiple lesion delivery and repeat procedures, with the risk of significant complications.

The newer methodologies for eliminating atrial fibrillation (AF) have been shown to have fewer potential complications than standard radiofrequency ablation [59]. The STOP AF trial recently demonstrated that cryoballoon ablation is a safe and effective alternative with risks within accepted standards for ablation therapy [60]. However, balloon-based ablation therapies have not been studied specifically in HCM patients. There is also a role for novel convergent (combined surgical and percutaneous) procedures to achieve successful ablation, especially in refractory cases, or when nonpulmonary vein triggers in the hypertrophied, and disorganized myocardium are found. These combined electrophysiologic and cardiothoracic surgical procedures can offer a viable treatment alternative for atrial fibrillation patients who have failed other ablations or who have enlarged atria (>4.5 cm) secondary to structural heart disease such as HCM. In this procedure, a comprehensive biatrial lesion pattern on the outside of the heart is created surgically using a transdiaphragmatic approach, while in the same setting, catheter ablation is used to complete the lesion pattern endocardially and diagnostically and check that all reentrant circuits have been interrupted (electrical isolation of the pulmonary veins). In summary, the overall outcome of AF ablation for HCM patients is relatively favorable but takes a sustained and comprehensive approach.

Ablation of AF in patients with the apical variant of HCM has shown similar success rates to the more common asymmetrical septal type of HCM but lower than AF ablation in non-HCM patients. Both HCM types had overall larger and "stiffer" left atriums. High LA diameter index >25 mm/m was an independent predictor of AF recurrence [61].

Ventricular Arrhythmias

The recommendations for management of ventricular arrhythmias in HCM patients are less clear than for atrial arrhythmias, and much of the evidence comes from previous trials in post-MI patients. Asymptomatic PVCs do not require therapy, but beta-blockers may be effective in symptomatic patients. NSVT is a common finding and is associated with an increased risk of SCD [24]; however, the decision to treat HCM patients for NSVT and the antiarrhythmics of choice remain controversial. The CAST trial demonstrated that treating NSVT with antiarrhythmic agents actually leads to an increase in sudden death and total cardiovascular mortality [62], but these data were based on ischemic patients using Vaughan-Williams Class Ic antiarrhythmic agents such as flecainide and encainide, and did not involve patients with HCM. Furthermore although NSVT, among other risk factors, is associated with increased SCD in HCM patients, suppression with chronic amiodarone therapy did not necessarily lead to a reduction in SCD or increased survival [63]. In summary, it is unclear whether suppression of NSVT is related to improved outcomes in HCM patients. Accordingly, NSVT was given a Class IIb recommendation in the recent guidelines, meaning that ICD implantation may be considered.

Guidelines for ICD implantation for SCD prevention in HCM are constantly evolving due to incomplete data and therefore rely heavily on expert consensus. Commonly, patients with NSVT as their sole risk factor for SCD are monitored more frequently for additional risk factors, such as extent of LV thickening, extent of outflow tract obstruction, response to exercise testing, or presence of significant late gadolinium enhancement, the presence and % scar burden of which might elevate the recommendation for ICD implantation. In patients with sustained monomorphic VT in the setting of structural heart disease such as HCM, ICD therapy is generally the standard of care. Patients with recurrent sustained episodes of ventricular arrhythmias or firing of their ICD should be treated with adjunctive antiarrhythmics, preferably amiodarone [64]. Antiarrhythmics are indicated as an alternative to ICD implantation in patients who are not candidates or refuse the procedure [65].

Adjunctive therapy with catheter ablation is sometimes offered to patients with ICD to improve symptoms and quality of life but is usually not performed without prior ICD placement. Also, a significant percentage of patients ultimately require concomitant therapy with antiarrhythmic drugs to decrease the recurrence of clinical arrhythmia and the frequency of ICD shocks [66]. Catheter ablation of VT in patients with hypertrophic cardiomyopathy is important in cases of medication refractory VT and VT storm. In patients without an ICD, VT storm has been defined as the presence of two or more ventricular tachyarrhythmias within 24 h, VT occurring immediately after termination, or sustained and nonsustained VT resulting in a total number of ventricular ectopic beats greater than sinus beats in a 24-h period [67]. Recent evidence suggests that VT mapping and ablation can be a safe and successful method for eliminating VT in these patients [68–70].

It is well established that endocardial ablation almost always fails if the VT originates from a deep intramural or epicardial source. The data is limited, but studies using a combination of voltage-based substrate mapping and activation, entrainment, and late/fractionated potential mapping

suggest that standard endocardial mapping and ablation alone cannot fully target the involved VT circuits in HCM patients [71, 72]. Combined with MRI data regarding fibrosis and scarring [73], this suggests that the VT circuits in HCM involve the epicardium, a thick myocardium, as well as the endocardium [74]. Additionally, the arrhythmogenic substrate may be atypical and extremely variable in this specific patient population. An epicardial approach may be needed to overcome the thick ventricular wall and characteristic midcavitary obliteration [75]. Fortunately, long-term outcomes of combined epicardial and endocardial ablation have been shown to be successful in patients with HCM-related monomorphic VT, although all have been anecdotal experience. In one study, 78% of patients who underwent ablation alone had freedom from recurrent ICD shocks at a median of 3-year follow-up [71].

Most studies using catheter ablation therapy for VT are based on RF ablation, but the success depends on whether or not there is concomitant structural heart disease [76]. Few studies have been performed on the specific population of HCM patients [68] demonstrating safety and effectiveness. All patients should receive an aggressive trial of antiarrhythmic medication therapy and an adequate trial of ATP pacing beforehand. Overall, catheter ablation of VT is an effective option to consider for HCM patients who fail aggressive trials of antiarrhythmic medications and antitachycardia pacing.

Clinical Pearls

- Ambulatory ECG monitoring is important for screening in HCM, as arrhythmias are usually of greater significance in this population. Implantable loops or event monitors may be especially helpful in patients with recurrent unexplained symptoms, especially prior to contemplation of ICD implantation.
- AF is a significant problem in HCM. Rhythm control is often needed in this population with diastolic dysfunction and outflow tract obstruction.
- TEE may not adequately differentiate left atrial appendage trabeculae in HCM from thrombus; given the need for maintenance of sinus rhythm in these patients, further testing with cardiac MRI or CT may be needed to exclude thrombus.
- If rate control is not achieved with medications and rhythm control is not a viable option, patients should undergo AV nodal ablation with placement of a permanent dual-chamber pacemaker for definitive rate control and assurance of atrial kick.
- Stroke risk is high in this population. Patients with HCM and AF/AFL should be anticoagulated irrespective of the CHADS2/CHADS-VASC score. If there is reason to believe that AF burden or incidence has decreased (e.g., after septal reduction therapy or antiarrhythmic therapy) and is supported by documentation on implantable devices, select patients may come off anticoagulation, as long as vigorous monitoring for recurrence continues.
- NSVT is common in HCM and associated with increased risk of SCD, but benefits of treating NSVT are uncertain. ICD implantation for NSVT alone is a Class IIb recommendation; most experts require additional risk factors to warrant ICD implantation and its concomitant acute and long-term risks.
- High-risk HCM patients should have ICD placement for primary prevention. The number of major risk factors to warrant ICD placement is still debatable; all experts consider the presence of two major risk factors an indication, while some experts will consider one risk factor as sufficient, especially when it is a first-degree relative with SCD, spontaneous VT/SCD in the index patient, or massive LVH > 3 cm. Newer risk models are now available from the ESC guidelines.
- VT catheter ablation may be a useful emerging therapy in the HCM population.
- AF ablation may be useful but might require more aggressive approach and repeat procedures, due to non-PV triggers in a subset of patients.
- WPW should be identified and treated with RF ablation when found.

Questions

1. All of the following are true regarding AF except:
   A. Roughly 25% of HCM will evidence AF over the course of their disease.
   B. It is associated with stroke.
   C. Stroke risk tracks with standard scoring systems and some patients may reasonably avoid anticoagulation.
   D. It may be associated with clinical deterioration.
   E. Patients may receive convergent therapy as second-line ablation therapy.

   Answer: C. All patients with AF, either PAF or chronic AF, must be anticoagulated because the estimated risk of stroke is > 4%, and therefore there does not appear to be a low-risk cohort for which anticoagulation can be safely withheld. Further studies are necessary to validate standard scoring systems in this population of patients.

2. The following are true about SVTs in HCM except:
   A. WPW is more common in HCM than in the general population.
   B. WPW should be treated by ablation whenever possible.
   C. SVTs are generally well tolerated.
   D. AV nodal blockers are first-line therapy for SVTs.
   E. Patients with fast SVT should be anticoagulated.

   Answer: E. There is no evidence that fast SVTs should be anticoagulated. However, all of the other responses are true. WPW is seen frequently and responds well to catheter ablation. This also allows safe institution of AV nodal blocking agents in these patients who require these medications for control of obstructive physiology and/or diastolic dysfunction.

3. Major risk factors in the US 2011 AHA guidelines that prompt ICD consideration include the following except:
   A. Maximal wall thickness > 2.5 cm
   B. Recent unexplained syncope
   C. FH of SCD in a first-degree relative < 50 years of age
   D. Sustained VT
   E. Resuscitated cardiac arrest

   Answer: A. Maximal wall thickness > 3.0 cm is a major risk factor and should prompt consideration of ICD. When thickness is > 2.5 cm, then other risk modifiers should be evaluated, including blood pressure response to exercise by treadmill test, the presence of obstruction, LGE scar burden on MRI, and others.

4. The best anti-arrhythmic medication in HCM or AF or VT is:
   A. Disopyramide
   B. Amiodarone
   C. Propafenone
   D. Flecainide

   Answer: B. Amiodarone is considered the best anti-arrhythmic medication to be used in HCM, although disopyramide may be used in patients with AF and LVOT obstruction to help control both aspects of the disease. When used for this purpose, an AV nodal blocker must also be used, in order to avoid rapid conduction while in AF. The other medications are not used in the management of HCM.

5. The following is true about EPS in HCM:
   A. EPS is recommended to risk stratify patients into intermediate or high risk for SCD and to guide ICD placement in borderline cases.
   B. EPS may be helpful in the evaluation of conduction disease and whether PPM may be indicated in patients with HCM.
   C. EPS is a Class 2b in the US 2011 AHA guidelines for risk stratification.
   D. All of the above.
   E. None of the above.

   Answer: B. EPS may be helpful for the evaluation of conduction disease, as in other patients without HCM. In patients with surgical myectomy or alcohol ablation, conduction studies and the appropriate timing of conduction studies have not been confirmed, however.

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Indications for and Individualization of Septal Reduction Therapy

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Key Points

- Septal reduction therapy is recommended for patients with severe LV outflow tract obstruction and drug-refractory symptoms, such as severe dyspnea or chest pain (usually NYHA or CCS functional class III/IV), or other important exertional symptoms (syncope or near syncope).
- Selected patients who do not meet NYHA or CCS class III/IV criteria can be considered for septal reduction therapy, most typically when obstruction-related recurrent syncope is present despite optimal medical or device therapy.
- A detailed and comprehensive morphologic and physiologic evaluation of the HCM patient as a whole is of paramount importance to delineate the precise causation of symptomatology and implicate outflow tract obstructive physiology in particular.
- Patients must qualify from symptomatic, hemodynamic, and anatomic standpoints to be considered for septal reduction therapy.
- Transaortic septal myectomy is an effective treatment strategy for the majority of patients with LVOT gradient and severe drug-resistant symptoms given documented long-term results and safety data at experienced centers.
- ASA is a minimally invasive catheter-based approach that results in a lesser degree of patient discomfort and more rapid recovery when compared with an open-heart surgical procedure; however, only patients with certain anatomic criteria, including coronary anatomy, are good candidates for ASA.
- For many patients, both ASA and myectomy procedures could provide reasonable treatment options; alternatively, some patients are better suited for myectomy, while others are better suited for ASA.
- Evidence from nonrandomized trials suggests that ASA and surgical myectomy result in similar short- and long-term outcomes with respect to hemodynamic and functional improvements, with greater propensity for pacemaker placement with ASA.

Introduction: The Importance of Outflow Tract Obstruction

It has been over 50 years since the first hemodynamic observations of hypertrophic cardiomyopathy (HCM) based on cardiac catheterization and surgical descriptions in 1957 by Brock [1]. Early reports of HCM focused on descriptions of intraventricular systolic pressure gradient, making dynamic obstruction within the left ventricular outflow tract (LVOT) the most recognized and integral feature of HCM [2]. The dynamic nature of LV outflow tract obstruction could be provoked by exercise, infusion of isoproterenol, premature ventricular beats, and vasodilation with amyl nitrite inhalation

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or nitroglycerin, as well as by altering preload via the commonly performed Valsalva maneuver [2, 3]. Although dynamic obstruction of LV outflow has been widely reported, its prevalence and clinical implication in this disease state have been the subject of controversy for many years [4, 5].

The important role of obstruction in HCM, and therefore the potential value of surgical myectomy or alcohol septal ablation, has now been confirmed in the last several years by a substantial body of literature from both clinical and echocardiographic studies. Echocardiographic studies confirmed systolic anterior motion (SAM) of the mitral valve as the mechanism of LV outflow obstruction. Anterior mitral valve leaflet to septal contact (during systole) has been shown to cause LV outflow obstruction in the majority (~95%) of obstructive cases [6]. Left ventricular outflow tract obstruction at rest is observed in approximately 25% of patients with HCM [7]. However, a large proportion of HCM patients without a resting gradient have a provocable outflow gradient. Indeed, a multicenter study utilizing stress echocardiography to evaluate physiologically provocable outflow gradients demonstrated that ~70% of HCM patients have an LV outflow gradient either at rest or with Valsalva maneuver or exercise challenge [8]. Identification of LV outflow obstruction with exercise echocardiography or provoking it during cardiac catheterization may help to identify symptomatic HCM patients who may benefit from therapies to relieve the obstruction, including medications and invasive septal reduction.

A relationship between LV outflow tract gradient, symptoms of heart failure, and long-term prognosis has been demonstrated in several multicenter cohort studies [7, 9–12]. For instance, Maron, MS et al. showed in a large HCM cohort of >1100 patients a strong relationship between having a (resting) peak instantaneous gradient of >30 mmHg and probability of death due to HCM (relative risk 2.0, $p = 0.001$) or probability of progression to NYHA class III/IV heart failure or death from heart failure or stroke (relative risk 4.4, $p < 0.001$) [7]. Elliott et al. demonstrated in a cohort of >900 HCM patients a strong relationship between LV outflow tract gradient and sudden death or ICD discharge [10]. The severity of LV outflow gradient was also found to be related to a higher occurrence of sudden death or ICD discharges. In addition, the risk of progression to NYHA class III/IV or death was particularly pronounced in patients older than 40 years of age, suggesting that the presence of prolonged LVOT obstruction or an interaction with comorbidities more frequent in the elderly, such as coronary artery disease or atrial fibrillation, might be related to more adverse events in patients with HCM.

Autore, C et al. in a cohort of >500 HCM patients have also shown that those with obstruction were at a greater risk for cardiovascular death compared with those without an obstruction (relative risk 2.1, $p = 0.02$) [9]. However, LV obstruction was only a significant predictor of cardiovascular mortality in NYHA class I or II patients, whereas in those with severe heart failure symptoms (NYHA III or IV patients), the NYHA functional class became the main prognostic indicator independent of the presence of LV outflow gradient. These epidemiological data raise the possibility that septal reduction early in the natural history of the disease, contrary to the manner in which it is oftentimes performed today, may be of benefit to modify its course. Notably, many patients with class III or IV symptoms presenting for septal reduction already have marked left atrial enlargement and have experienced or are at risk for the development of atrial fibrillation. Accordingly, it may also be possible that early and aggressive medical therapy to reduce outflow obstruction may impact the natural history of the disease.

Role of Surgical Myectomy

Surgical septal myectomy (known as the Morrow procedure) emerged as the primary strategy for relieving mechanical obstruction to LV outflow, even before it was widely accepted that SAM of the mitral valve was the primary mechanism of the obstruction [13]. The surgery is indicated in HCM patients with pronounced LV outflow obstruction and severe heart failure symptoms (New York Heart Association classes III and IV). Traditionally, the myectomy consisted of transaortic resection of a small amount of basal septal muscle with consequent enlargement of the LV outflow tract that resulted in permanent elimination of mechanical impedance to LV outflow, SAM-related mitral regurgitation, and eventual normalization of LV pressures and improvement in diastolic function [14]. Contemporary surgeries for HCM include extended septal resections and if necessary partial resection or mobilization of the papillary muscles. Suturing of the medial and lateral segments of the anterior leaflet of the mitral valve to the posterior annulus is a more recent and novel addition that may be associated with improvement in mitral regurgitation and prevention of residual and recurrent LVOT obstruction [15].

As a result, a majority of patients undergoing myectomy experience low post-procedural outflow gradients that lead to relief of heart failure symptoms and ability to return to normal exercise capacity and quality of life [16–20]. Long-term studies after myectomy report sustained clinical improvement with 85–90% of patients becoming asymptomatic (or only mildly symptomatic) for up to 25 years after myectomy. In addition to improvements in quality of life, there is also observational evidence that myectomy may favorably alter the natural course and progression of HCM and may improve long-term survival, with a normal or near-normal life expectancy in HCM patients after myectomy [11]. Importantly, however, these outcomes have been limited to a relatively small number of high-volume HCM centers, mostly in the United States, and relatively young patients with few comorbidities.

Advent of Alcohol Septal Ablation

In 1994, Sigwart introduced an unconventional percutaneous catheter approach that used absolute alcohol to induce a small, targeted myocardial infarction in the septum as an alternative to surgical myectomy [21]. When performed by skilled operators at high-volume centers, alcohol septal ablation (ASA) results in an increase in LV outflow diameter, a reduction in LVOT gradient in >80–90% of patients, a regression of LVH, and an improved diastolic function [22, 23]. Long-term benefits result from the creation of a localized septal infarction and scarring, which lead to progressive increase in LVOT diameter as a result of septal thinning and LV remodeling [24–26]. After ASA, the severity of mitral regurgitation is reduced, the LV end-diastolic pressure falls, and the size of the left atrium decreases, likely contributing to secondary effects including beneficial reduction in atrial fibrillation burden and severity of pulmonary hypertension [27–29]. Improvement in diastolic function may be explained by an improvement in LV load-dependent relaxation and a reduction in LV stiffness due to regression of LV hypertrophy and decrease in interstitial collagen content [26, 29–31].

Similar to surgery, ASA results in a significant improvement in functional class (NYHA and CCS class), peak oxygen consumption, and exercise capacity for up to 8–10 years. In addition, recent studies have indicated that ASA results in improvements in LV synchrony, microvascular function of the subendocardium, and myocardial energetics parameters [24, 25]. Importantly, HCM patients after a successful ASA procedure also appear to have long-term survival rates that are comparable to the non-HCM population [32]. These data suggest that ASA, similar to surgical septal reduction, may positively alter the natural history of this disease.

Evaluation of the Patient for Septal Reduction Therapy

For invasive therapies to be indicated, the patient must qualify from symptomatic, hemodynamic, and anatomic standpoints. Furthermore, symptoms and hemodynamic criteria must be present despite optimal medical therapy. Accordingly, oftentimes several weeks to months of uptitration and sequential addition of medications are necessary in order to determine response to therapy and document persistent severe symptoms and obstructive physiology. When done correctly, many patients will respond to aggressive medical therapy, obviating the need for invasive management. However, even in the subset of patients controlled with medications, the disease may progress or side effects may develop, and invasive therapy may become warranted at a later time.

Assessment of Symptom Parameters

A detailed and comprehensive evaluation of the HCM patient as a whole, even in the presence of significant LVOT gradient, is of paramount importance to delineate the precise causation of symptomatology. In particular, symptoms of dyspnea or angina must be clearly related to HCM physiology, and not due to other comorbid conditions. For example, concomitant presence of severe coronary artery disease or intrinsic lung disease can be the explanation for either incremental or sudden change in effort tolerance by the HCM patient. Patient selection for either form of septal reduction therapy, myectomy or ASA, is thus based on very careful individual assessment of symptoms to determine the extent to which they may be caused by HOCM physiology. Prior to embarking on invasive therapies, the physician must be convinced that relief of obstruction, and the cascade of LV unloading, reduction in LVH, and improvement in diastolic dysfunction, will result in significant improvement in symptoms.

In patients with HCM, chest pain/discomfort, and risk factors for coronary artery disease, invasive coronary angiography is essential in addition to stress testing to exclude obstructive coronary artery disease, particularly if the patient is undergoing evaluation for septal reduction therapy. In HCM patients with chest pain/discomfort and low likelihood of CAD, particularly if not a candidate for septal reduction, assessment of ischemia or perfusion abnormalities suggestive of CAD with single photon emission computed tomography, positron emission tomography myocardial perfusion imaging, or computed tomographic imaging could be reasonable.

For patients with dyspnea, objective evaluation of functional capacity, NYHA class, or response to medical therapy may be needed. Treadmill exercise testing can be utilized, particularly if symptoms are vague and inconsistent with the results of noninvasive imaging. In patients with declining functional status, treadmill exercise testing in combination with exercise echocardiography may be helpful in correlating the degree of symptomatic progression of disease with the nature and severity of obstruction. In patients without LV outflow resting gradient, exercise echocardiography can be helpful to detect and quantify exercise-induced dynamic LVOT obstruction and exercise-induced blood pressure response [8, 33–35]. Cardiopulmonary testing parameters, such as peak oxygen consumption (VO_2) and anaerobic threshold, have been found to be reduced in the HCM population [36]. Cardiopulmonary testing may help to elucidate the mechanism of exercise limitation on an individual basis. Although clinical utility of such testing has not been well demonstrated in this population, it may be beneficial in those with mixed diseases, such as concomitant pulmonary disease or anemia [37]. The combination of LVOT obstruction, mitral regurgitation, and COPD can result in severe

dyspnea with remarkable improvements following septal reduction.

It is important to note that the majority of symptomatic patients with HCM will respond to medical therapy with negative inotropic drugs (β-blockers, verapamil, and disopyramide); however, ~10% of patients will remain with severe symptoms refractory to medications or intolerable side effects that limit medication use or dose escalation [38]. Septal reduction therapy is generally recommended for those patients with an LV outflow obstruction and severe drug-refractory symptoms, such as severe dyspnea or chest pain (usually NYHA functional class III/IV or CCS class III/IV), or other exertional symptoms (syncope or near syncope) that interfere with daily activities or quality of life despite optimal medical therapy [39, 40]. There is no established consensus regarding the definition of optimal medical therapy; however, most experts would agree that β-blockers and/or verapamil titrated to a resting heart rate of <60–65 beats per minute, and perhaps addition of disopyramide to β-blocking drugs or verapamil for those who do not respond to monotherapy, would constitute optimal medical therapy [41]. Septal reduction therapy may also be indicated in patients who are intolerant of optimal medical therapy, due to comorbid conditions, such as bradycardia or asthma.

Selected patients who do not meet NYHA or CCS class III or IV criteria can be considered for septal reduction therapy as well. Those with symptoms refractory to optimal conservative therapy that interfere substantially enough with their quality of life (NYHA or CCS class II) can be considered for invasive therapy, as long as they understand and accept the potential morbidity and mortality of an invasive management strategy. This may be more common in younger patients (e.g., <40 years of age) in whom marked limitations to cardiac output and reserve may occur, while the patient can still maintain NYHA class II activities. Furthermore, selected patients with advanced NYHA or CCS class II symptoms, such as postprandial dyspnea, those with NYHA class II and acute exacerbation of CHF due to paroxysmal atrial fibrillation, and those with obstruction-related syncope or severe near syncope with chronic NYHA or CCS class II symptoms may also be considered for these procedures. In patients with syncope or near syncope, the symptoms should be caused by LV outflow tract obstruction or combination of LVOT obstruction and autonomic dysfunction, rather than being arrhythmogenic in origin. Currently, there are no data to suggest that the indication for performing septal reduction should be extended to patients with HOCM and no or very mild symptoms, regardless of the severity or chronicity of obstruction.

Right heart catheterization should be considered in addition to left heart catheterization in HCM patients being evaluated for septal reduction therapy, particularly in those with complaints of dyspnea, symptoms of heart failure, or angina. It is imperative to differentiate other pulmonary or noncardiac causes of dyspnea, including COPD, as well as alternate cardiac etiologies, such as aortic stenosis, in the symptomatic patient with HCM. This assessment can also elucidate treatable congestion, as well as document the severity of cardiac output impairment at rest or upon exertion. When present, the degree of pulmonary hypertension should be quantified, including calculation of the pulmonary vascular resistance. Pulmonary hypertension may be common in obstructive HCM patients with advanced heart failure [42]. For patients with symptoms of heart failure and low/normal filling pressures, either fluid or exercise challenge can be performed to further investigate the etiology of symptoms. For those patients who have high pulmonary arterial pressures and low/normal filling pressures, nitric oxide inhalation or other vasodilators can help to establish pulmonary hypertension as a primary determinant of symptoms and assess for reversibility and need for treatment.

Assessment of Hemodynamic Parameters

Candidates for septal reduction therapy must have an LV outflow tract gradient of ≥50 mmHg at rest, with physiologic provocation, or with exertion. While echocardiography is the gold standard, permitting evaluation of obstruction provoked by Valsalva maneuver or treadmill exercise, cardiac catheterization is frequently complementary and often necessary in patients with poor echocardiographic "windows" to evaluate or confirm the severity of LVOT gradient at rest and with provocative maneuvers. This can be particularly important in patients with labile LVOT gradients [43]. Cardiac catheterization in HCM patients requires meticulous attention to detail, due to a number of potential errors that can occur as a result of measurements inside a small, hypertrophied, hyperdynamic ventricle, including catheter entrapment. Peripheral augmentation or discrepancies due to peripheral arterial disease must be taken into account. The dynamic outflow obstruction leads to a characteristic arterial pressure waveform, frequently described as a "spike-and-dome" configuration, most apparent in the proximal aorta. It is important to measure the LV pressure at the apex, so as to include the entirety of the ventricle and all potential areas of obstruction. The characteristic arterial morphology becomes even more evident during maneuvers that increase the dynamic gradient, such as the Valsalva or presence of extrasystoles. The narrowing in pulse pressure of the spike-and-dome arterial waveform as a result of obstruction and reduced stroke volume is commonly known as the Brockenbrough-Braunwald sign and confirms the dynamic, subvalvular nature of the obstruction. Care must be taken to rule out concomitant supra- or subvalvular membranes as well as

valvular stenosis. These assessments should be performed in the awake patient, as sedation may result in abolition of resting or provocable gradients in some patients.

Diagnostic catheters can get entrapped in a small ventricle, inducing ventricular ectopy that can make precise gradient measurements difficult during single-catheter pullback. Dual-pressure transducers, with simultaneous measurements of left ventricular pressure and aortic/arterial pressures, are therefore required. Although some operators have used transseptal catheterization for the measurement of left ventricular pressures, thereby avoiding catheter entrapment and confirming subvalvular obstruction (as opposed to mid-cavitary obstruction), this is rarely required today [44]. When a retrograde catheter approach is utilized to measure LVOT gradient, pigtail catheters with multiple sideholes should be utilized first in order to determine the maximal gradient across the entirety of the outflow tract; however, they should then be exchanged for an end-hole catheter (i.e., multipurpose catheter). Slow pullback across the outflow tract and into the aorta then facilitates precise localization of the level of obstruction. If the location of obstruction is evident on echocardiography, then the exchange and slow pullback may not be necessary.

Given the dynamic nature of the gradient, resting gradient will not always be present during the catheterization procedure. Some experts elect to hold all HCM medications prior to the procedure in order to more easily assess gradients, while others want to continue them to assess response to therapy. Sedatives and intravenous fluids should generally be avoided during catheterization so as not to mask the presence of LVOT gradient. If a significant resting gradient (gradient of ≥50 mmHg) is not found during catheterization, provocative maneuvers such as the Valsalva or an induction of an extrasystolic beat to measure the Brockenbrough-Braunwald sign (or a combination of both maneuvers) should then be performed. If a significant gradient is still not provoked, either exercise (e.g., supine bicycle exercise) or pharmacologic challenge (amyl nitrite, nitroglycerine, or isoproterenol) is helpful when the clinical picture strongly suggests obstructive physiology. Isoproterenol hydrochloride provides direct stimulation of the β1- and β2-receptors that simulates exercise and, therefore, may uncover a labile outflow tract gradient [45]. From a practical standpoint, if significant obstruction cannot be elicited with physiologic maneuvers, LVOT obstruction as the primary etiology of the symptoms is unlikely.

Diastolic dysfunction can be evident by elevated left ventricular diastolic pressure and abnormal contour of the diastolic pressure tracing. Left ventriculography will frequently demonstrate a hyperdynamic, hypertrophied ventricle, with a relatively small cavity. Dynamic outflow obstruction can sometimes be seen during ventriculography as a "swan-neck" deformity in a "banana-shaped" ventricle [46]. Significant mitral regurgitation from systolic anterior motion of the mitral valve leaflet can frequently be expected and seen during ventriculography, especially when PVCs are elicited.

Assessment of Anatomic Parameters

Noninvasive testing, particularly echocardiography, is generally the initial step in the diagnosis and, importantly, patient selection for septal reduction therapy from both the anatomic and hemodynamic standpoints. Septal wall thickness < 15–16 mm is considered a contraindication to either myectomy or ASA due to the potential risk of septal perforation with creation of a ventricular septal defect. Although this complication has been reported more often with surgical myectomy than with ASA, septal thickness in this range remains a contraindication for both.

Left ventricular outflow tract anatomy with regard to basal septal thickness and distribution/extent of thickness can be quite variable from patient to patient. It is important to identify patients with severe septal hypertrophy (≥30 mm) as well as those with focal basal septal hypertrophy ("septal bulge") as those patients may preferentially benefit from surgical myectomy or ASA, respectively. Significant intrinsic mitral valve as well as aortic valve disease needs to be carefully evaluated as it will have an important impact on selection of septal reduction therapy. The echocardiographic characteristics, severity, and direction of mitral regurgitation will provide important data regarding etiology of obstruction and mitral regurgitation and potential benefit of septal reduction therapy. Mitral regurgitation caused by SAM is invariably associated with a late systolic, posterolaterally directed jet. If mitral regurgitation is not posterolaterally directed on color flow Doppler imaging and especially when it is anteriorly displaced, the mitral apparatus should be examined very carefully with either transthoracic or transesophageal echocardiography (TEE) to determine an alternate cause.

Transesophageal echocardiography becomes of particular importance when mitral regurgitation is suspected to be due to structural abnormalities of the mitral and submitral valve apparatus, including direct insertion of the anterolateral papillary muscle into the anterior mitral leaflet, accessory papillary muscles producing mid-cavity muscular obstruction, mitral valve prolapse, severe calcification, or presence of elongated mitral valve leaflets or chords [47–49]. TEE can also be of importance if discrete or tubular fixed subaortic stenosis or supra- or subvalvular membranes are suspected [50].

Cardiac magnetic resonance can supplement echocardiographic data by providing high-resolution images with excellent and uniform contrast at the endocardial borders and permitting virtually complete reconstruction of the left ventricular cavity. When critical morphological data regarding

magnitude or distribution of hypertrophy and anatomy of the mitral valve apparatus or papillary muscles cannot be obtained from conventional echocardiographic studies, magnetic resonance imaging can become essential [51, 52]. CT angiography may also improve anatomical localization of infarct and procedural success after ASA [53].

Selective coronary angiography should be performed to exclude concomitant coronary disease. Furthermore, in those undergoing workup for septal reduction treatment, the size and distribution of the septal perforator arteries need to be carefully evaluated. Not infrequently coronary angiography will demonstrate marked systolic compression of septal branches of the left anterior descending artery and a "sawfish" systolic narrowing of the LAD artery [54]. In addition, septal arteries may arise from the left main, ramus, diagonal branches and even from the right coronary artery, and thus, meticulous angiography in multiple views is imperative.

In summary, patients ultimately will be deemed to be candidates for isolated septal reduction therapy when (a) symptoms are clearly and primarily attributed to obstructive HCM physiology despite optimal medical therapy; (b) symptoms are severe heart failure or angina (as measured by NYHA or CCS class, respectively), recurrent obstruction-related syncope, or recurrent clinical decompensation due to refractory paroxysmal atrial fibrillation; (c) a gradient ≥50 mmHg can be documented on optimal medical therapy, either at rest or with provocation; and (d) obstruction is clearly subvalvular and dynamic, from septum-to-anterior mitral leaflet contact, and not due to fixed obstructive valvular disease or membranes (Table 22.1).

Table 22.1 Primary indications for septal reduction therapy

Symptoms are clearly and primarily attributed to obstructive HCM physiology (including secondary phenomena such as diastolic dysfunction, mitral regurgitation, reduced cardiac output, and pulmonary hypertension)
Symptoms interfere substantially with life despite optimal medical therapy
NYHA functional class III/IV or CCS class III/IV or other exertional symptoms (syncope or near syncope) that interfere with daily activities or quality of life despite optimal medical therapy
Patients who are intolerant of optimal medical therapy due to comorbid conditions, such as bradycardia or asthma
Selected patients with advanced NYHA or CCS class II symptoms may also be considered, such as acute exacerbation of CHF due to paroxysmal atrial fibrillation, or those with obstruction-related syncope or severe near syncope
Septal thickness ≥ 15–16 mm at point of septal-mitral valve contact
Left ventricular outflow tract gradient ≥50 mmHg at rest or with provocation/exercise
Basal asymmetric septal hypertrophy and systolic anterior mitral valve leaflet to septal contact causing dynamic LV outflow obstruction, with associated mitral regurgitation and posterolaterally directed jet

Individualization of Septal Reduction Therapy

Transaortic septal myectomy has traditionally been considered the most effective and appropriate treatment strategy for the majority of patients with significant LVOT gradient and severe drug-resistant symptoms, given documented long-term results and safety data [39]. In the early years of septal myectomy, perioperative mortality was relatively high ≥5% [55]. Over the last 20 years, however, surgical results have dramatically improved, with operative mortality <1%. Such results remain limited to relatively few centers with extensive experience with this operation in dedicated HCM centers [47, 56].

Besides septal thickness < 15–16 mm, there are no other anatomical contraindications for surgical myectomy; indeed, most other abnormalities may be addressed during the same operation. The traditional myectomy (Morrow procedure) with ~3 cm septal resection or "extended myectomy" with ~7 cm resection is currently being used [47, 56, 57]. Intrinsic disease of the mitral valve apparatus or papillary muscles may significantly contribute to the generation of LVOT gradient. Such patients are better served by surgical myectomy with additional surgical intervention as needed. In particular, surgical myectomy can be supplemented with mitral valve repair or leaflet plication, sometimes with the "extended myectomy" to mid-ventricular level, and with reconstruction of subvalvular apparatus [58, 59]. Enlarged or malpositioned papillary muscles contributing to obstruction can be "shaved," incised off the ventricular wall, and repositioned to the adjacent papillary muscle. When mitral valve surgical interventions are required, repair is preferred because of improved survival compared with replacement [60].

Surgery is often preferred in younger patients; those with massive septal hypertrophy (e.g., ≥30 mm) (Fig. 22.1);

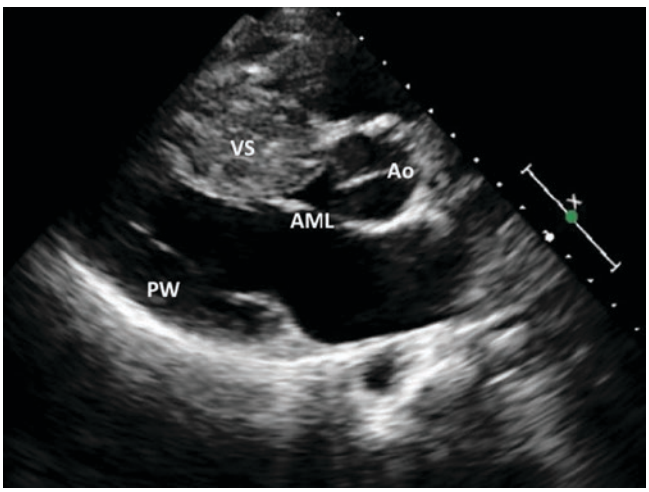


Fig. 22.1 Massive asymmetric hypertrophy of the ventricular septum, favoring septal myectomy. Ao aorta, AML anterior mitral leaflet, VS ventricular septum, PW posterior free wall

those with diffuse rather than focal left ventricular hypertrophy that extends to the mid-ventricle or even apex (Fig. 22.2); those with preexisting left bundle branch block (since ASA usually causes right bundle branch block, resulting in a high incidence of complete heart block); those with concomitant cardiac disease requiring surgical intervention: intrinsic severe mitral valve disease, presence of membranes (Fig. 22.3), moderate/severe aortic stenosis (Fig. 22.4), coronary artery disease favoring coronary artery bypass grafting; and those with atrial fibrillation that might require a maze procedure or left atrium appendage ligation. It is important to have a high index of suspicion for concomitant cardiac conditions such as subaortic membranes [61]. These patients may be at increased risk for developing progressive heart failure symptoms, and surgical intervention with a relief of obstruction is associated with excellent outcomes.

The major advantage of ASA is its minimally invasive catheter-based approach that results in lesser degree of patient discomfort and morbidity when compared with an open-heart surgical procedure, mainly by avoiding sternotomy, cardiopulmonary bypass, and ~4–6 weeks of postoperative recovery. On the other hand, only patients with certain anatomic criteria are good candidates for ASA as it requires favorable septal perforator anatomy (size, distribution, and accessibility) for delivery of alcohol to the target basal portion of the septum [62] (Fig. 22.5). Factors that favor ASA over myectomy include advanced age (>65 years), comorbid conditions that would increase

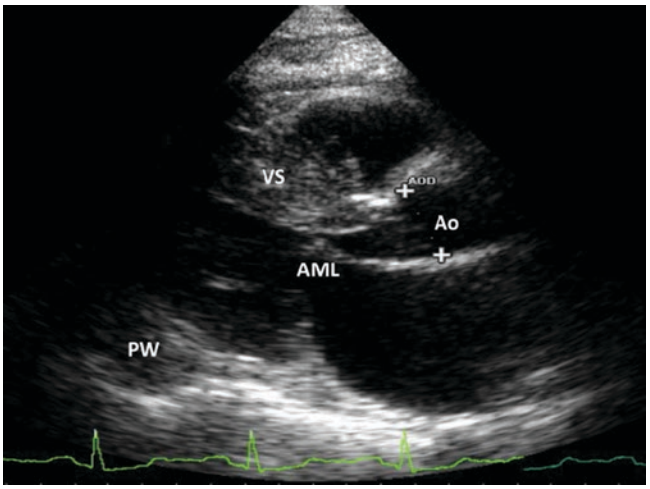


Fig. 22.2 Diffuse, concentric left ventricular hypertrophy that extends to the mid-ventricle, favoring septal myectomy. Ao aorta, AML anterior mitral leaflet, PW posterior free wall, VS ventricular septum

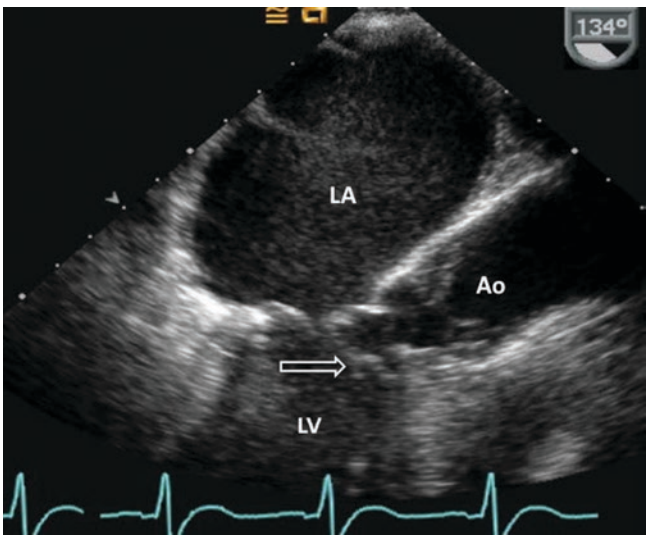
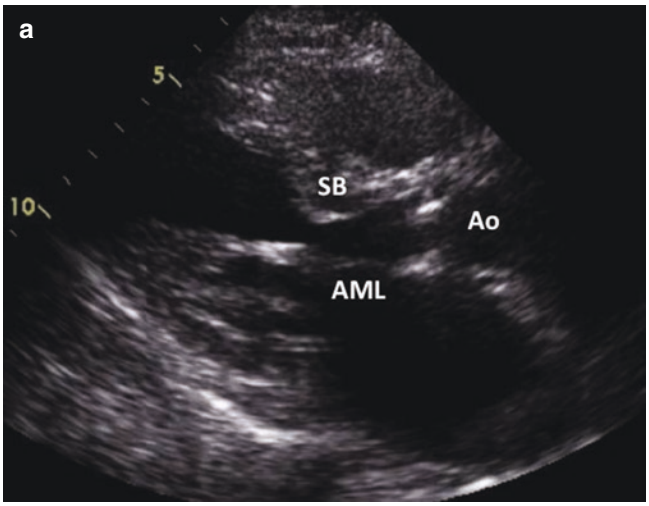


Fig. 22.3 Transesophageal echocardiographic (TEE) image of subvalvular membrane (arrow), favoring septal myectomy. Ao aorta, LA left atrium, LV left ventricle



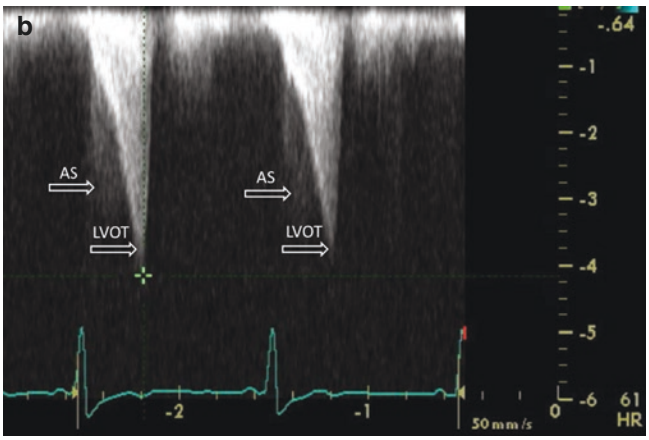


Fig. 22.4 Concomitant hypertrophy of the basal septum just below the aortic valve (dynamic obstruction) and valvular aortic stenosis (fixed obstruction) favoring combined septal myectomy and aortic valve replacement (**a**) (Ao aorta, AML anterior mitral leaflet, SB septal bulge). Continuous wave Doppler spectra obtained from the apex demonstrating both aortic stenosis (faint spectrum) and left ventricular outflow tract obstruction with typical late-peaking configuration resembling a dagger or ski slope (**b**) (AS aortic stenosis, LVOT left ventricular outflow tract)

surgical risk (e.g., pulmonary hypertension or severe COPD causing significant concerns about lung or airway management), preexisting right bundle branch block (because myectomy usually causes left bundle branch block and a high incidence of complete heart block), presence of pacemaker/ICD that would substantially lower the procedural risk of ASA, prior cardiac or thoracic surgery (given the risks inherent to reoperation), and focal CAD that can be treated with stenting. In patients who are candidates for pacemaker/ICD, implanting the device first can simplify the ASA procedure and shorten the observation period to 24–48 h. ASA should generally be avoided in children.

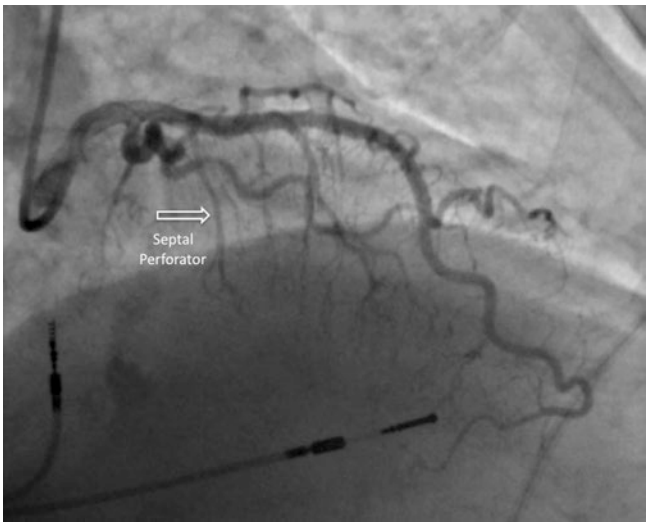


Fig. 22.5 Favorable septal perforator anatomy (adequately sized and accessible septal perforator) for delivery of alcohol to the target basal portion of the septum

Recent studies have suggested that ASA may be safe in younger patients, associated with a lower rate of pacemaker implantation compared with older patients, and effective for relief of symptoms [63, 64]. Further studies are needed to investigate whether the indication for ASA can be broadened to younger patients.

Certain anatomical criteria make ASA more favorable, such as focal "septal bulge" (Fig. 22.6), wide angle of papillary muscles and chords to the ventricular septum, absence or minimal intrinsic disease of mitral valve apparatus and papillary muscles, and favorable coronary anatomy with a single septal perforator of appropriate size supplying the targeted asymmetric hypertrophied basal septum territory (Table 22.2).

For many patients, both procedures could provide reasonable treatment options. In such cases, the principle of patient autonomy suggests that patients can choose between myectomy and ASA after a thorough discussion of the risks and benefits related to each procedure. A heart team approach in dedicated HCM centers may offer patients an easier access to experienced interventional cardiologists and surgeons, skilled in patient selection for septal reduction therapy. ACCF/AHA 2011 Hypertrophic Cardiomyopathy Guidelines recommend that in those patients who are acceptable surgical candidates, surgical myectomy should generally be preferred (class IIa) over ASA (class IIb), whereas in those patients who are not acceptable candidates for surgical intervention, ASA would be the favored treatment option (class IIa) [39]. Patient preference for alcohol septal ablation over surgical myectomy was also reasonable after a balanced and thorough discussion (class IIb). However, as previously described, an individualized

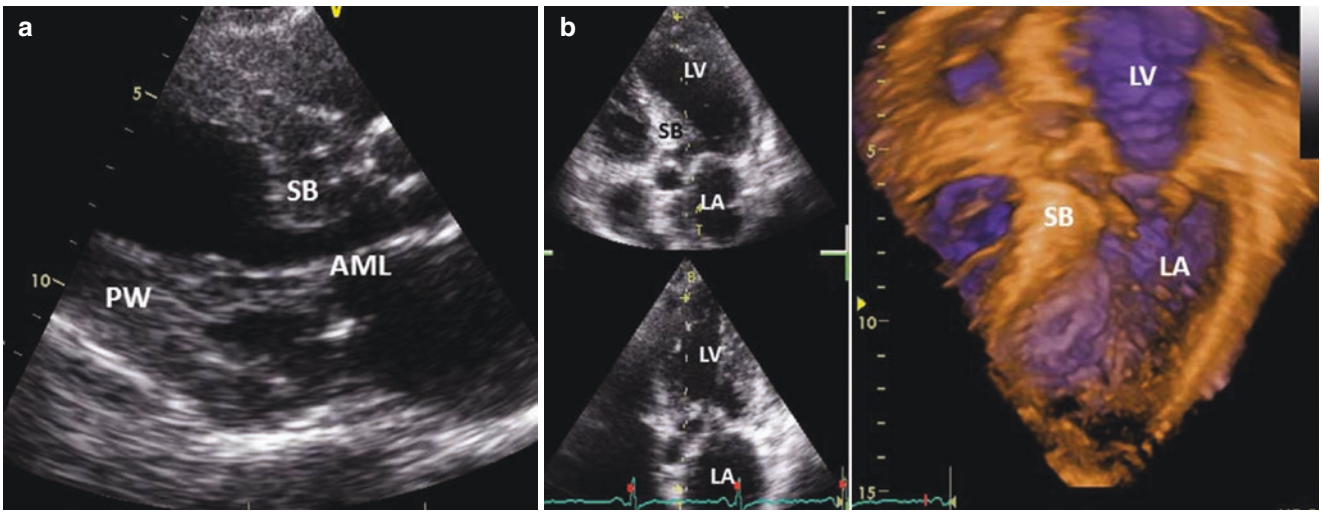


Fig. 22.6 Hypertrophy confined to the basal (proximal) septum just below the aortic valve ("septal bulge"), favoring ASA (**a**) (AML anterior mitral leaflet, PW posterior free wall, SB septal bulge). Two- and three-dimensional echocardiographic images of HCM with focal septal hypertrophy (**b**) (LA left atrium, LV left ventricle, SB septal bulge)

Table 22.2 Features favoring septal myectomy versus alcohol septal ablation

Favor septal myectomy	Favor alcohol septal ablation
Symptoms that interfere substantially with lifestyle despite optimal medical therapy[a] Septal thickness ≥ 15–16 mm[a] Left ventricular outflow tract gradient ≥50 mmHg at rest or with provocation/exercise[a]	
Younger patients Massive septal hypertrophy (e.g., ≥30 mm) Diffuse left ventricular hypertrophy that extends to the mid-ventricle or even apex Preexisting left bundle branch block Concomitant cardiac disease requiring surgical intervention (e.g., intrinsic mitral valve disease, presence of membranes, moderate/severe aortic stenosis, coronary artery disease favoring coronary artery bypass grafting) Atrial fibrillation that requires a maze procedure or left atrium appendage ligation	Advanced age Comorbid conditions that would increase surgical risk (e.g., pulmonary hypertension or severe COPD) Preexisting right bundle branch block Presence of pacemaker/ICD Prior cardiac or thoracic surgery Concomitant focal CAD that can be treated with stenting Focal septal hypertrophy ("septal bulge") Wide angle of papillary muscles to the septum Absence or minimal intrinsic disease of mitral valve apparatus and papillary muscles and of other conditions for which cardiac surgery is indicated Favorable coronary anatomy with an adequately sized, single septal perforator supplying the targeted myocardial segment Patient preference for septal ablation when both options are reasonable and patient has been fully informed regarding benefits and risk of both procedures

[a]Presence of features when both procedures could be performed

approach to selection of septal reduction therapy is commonly required, with comprehensive assessment of clinical symptoms, associated comorbidities, and echocardiographic and angiographic features that might favor one approach over another.

Comparison of ASA and Septal Myectomy

No randomized controlled trials comparing ASA to surgical myectomy have been performed, and it is unlikely that a randomized trial comparing these two therapies in patients with anatomy favorable for both procedures will ever be performed [65]. In the absence of a randomized trial, we must rely on nonrandomized, retrospective studies from relatively few centers with extensive experience in the treatment of HCM. This evidence suggests that ASA and surgical myectomy result in similar outcomes with respect to hemodynamic and functional improvements [66–69]. One report from the Thoraxcenter (Erasmus Medical Center) suggested higher mortality rates for ASA, although in that study investigators used higher doses of ethanol (mean ~3.5 ml) than is currently being used in clinical practice [70]. In contrast, Sorajja, P et al. have reported the Mayo Clinic experience and demonstrated similar mortality rates after ASA and myectomy in age- and gender-matched cohorts [71]. In a large multicenter North American registry of 874 patients undergoing ASA, Nagueh, SF et al. reported that ~95% of patients were free from NYHA class III and IV symptoms [72].

The overall 1-, 5-, and 10-year survival after surgical myectomy at the Mayo Clinic was 98%, 96%, and 83%, respectively, and did not differ from that of the general age- and gender-matched US population nor from patients with nonobstructive HCM [11]. Similarly, investigators from the Czech Republic reported that after ASA in 178 highly symptomatic patients, overall survival free of all-cause mortality at 1, 5, and 10 years was 97%, 92%, and 82%, respectively [73]. This observed mortality was comparable to the expected survival for age- and gender-comparable general population. Furthermore, the Mayo Clinic investigators have reported that the presence of ≥3 key patient and anatomic characteristics (age ≥ 65 years, gradient <100 mmHg, septal hypertrophy ≤18 mm, LAD diameter < 4.0 mm) was associated with superior 4-year survival free of death and severe symptoms (90%) in comparison to those with one or two such characteristics [74]. Their analysis also suggested that greater ASA case volume (>50 patients) was associated with superior outcomes [74].

Several meta-analyses of comparative studies of myectomy versus ASA have now been performed, demonstrating no difference in mortality and post-procedural NYHA class with these two approaches [75–77]. Agarwal, S et al. have analyzed 12 studies and demonstrated, in addition to no differences in short-term mortality (Fig. 22.7) and long-term mortality between ASA and myectomy, no differences in NYHA functional class, ventricular arrhythmia occurrence, re-interventions performed, and post-procedural mitral regurgitation between the two procedures [75]. Similar to prior analyses, there were a small yet significantly higher residual LVOT gradient among ASA as compared with myectomy and a higher incidence of permanent pacemaker implantation after ASA. In another meta-analysis of 19 ASA studies and 8 surgical myectomy studies, Leonardi, RA et al. have demonstrated similar unadjusted rates of all-cause mortality and sudden cardiac death [78]. However, ASA patients were older and had less septal hypertrophy when compared with myectomy patients. When adjusted for baseline characteristics, ASA was associated with lower all-cause mortality and sudden cardiac death rates, with no difference in NYHA class [78]. This may speak to inherent selection bias between two approaches, with older patients and those with more comorbidities being preferentially referred and treated with ASA.

In addition to long-lasting reduction in symptoms of heart failure after ASA and surgical myectomy, septal reduction

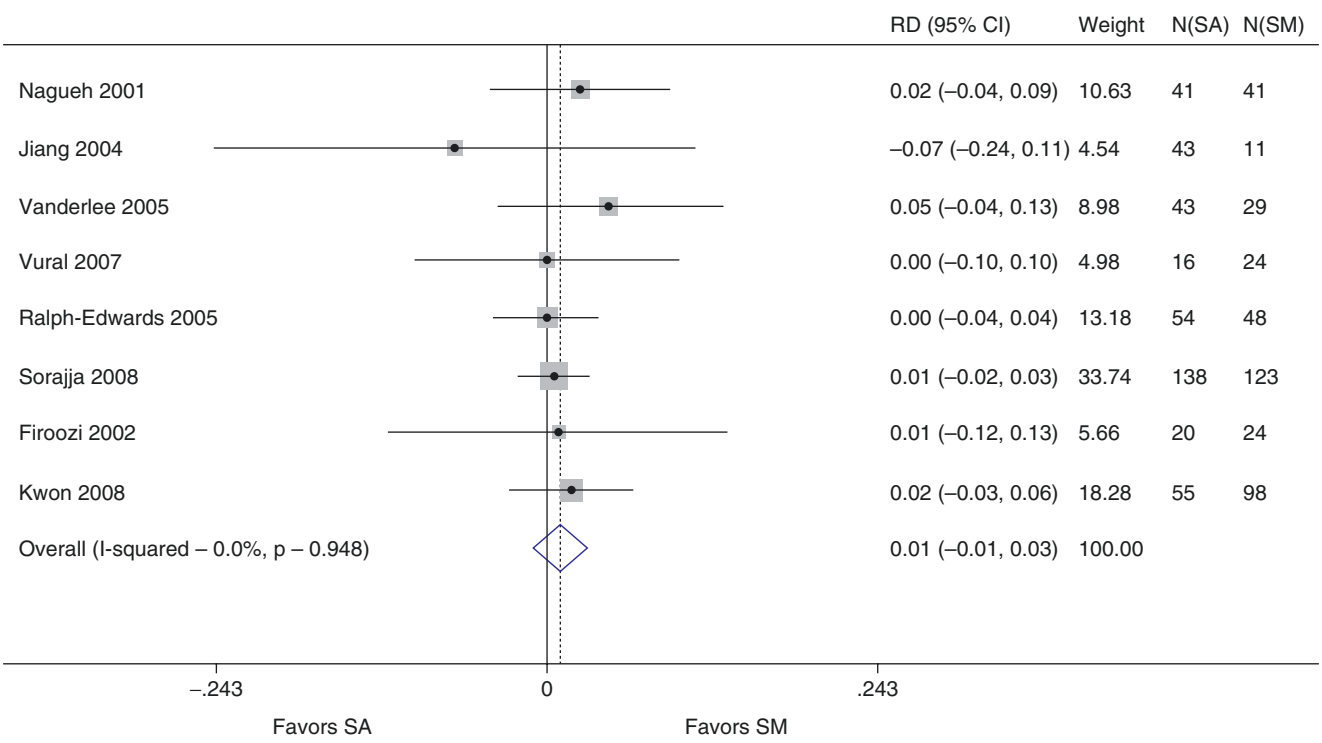


Fig. 22.7 A pooled meta-analysis comparison of short-term mortality between ASA and septal myectomy. The risk difference in short-term mortality between ASA and septal myectomy was insignificant (risk difference 0.01; 95%CI 0.01–0.03, $p = 0.35$). (Adapted from Agarwal et al. [75]. Copyright 2010 by Elsevier Inc. Adapted with permission). RD risk difference, SA septal ablation, SM septal myectomy, CI confidence interval

therapy may result in a long-term survival benefit as has been demonstrated in a number of retrospective studies [79, 80]. In the large Mayo Clinic series of >1300 HCM patients, 1-, 5-, and 10-year overall survival after surgical myectomy was 98%, 96%, and 83%, respectively, and did not differ from that of the age- and gender-matched general US population and was similar to patients with nonobstructive HCM [11]. Furthermore, when compared to nonoperated obstructive HCM patients, myectomy patients experienced superior survival free from all-cause mortality (98%, 96%, and 83% vs. 90%, 79%, and 61%, respectively; $p < 0.001$) and sudden cardiac death (100%, 99%, and 99% vs. 97%, 93%, and 89%, respectively; $p = 0.003$). Similarly, in a small cohort of ASA patients, overall survival at 1, 5, and 10 years (97%, 92%, and 82%) was comparable to the expected survival for age- and gender-comparable general population [73]. These data suggest that invasive normalization of LVOT gradient and LV pressure, prevention of further LV remodeling, and possibly reduced arrhythmogenicity of the myocardial tissue may alter the course of this disease and improve long-term survival [13].

Given similar survival rates when comparing ASA and surgical myectomy in multiple retrospective cohort studies and meta-analyses, with follow-up out to 8 years, one would expect similar longer-term (>10 years) survival rates as well. And indeed, a similar analysis by Mayo Clinic reported that age- and gender-adjusted survival rates for surgical myectomy and alcohol septal ablation were tracking together out to 8 years, suggesting that both septal reduction therapies may positively and similarly impact the natural history of disease [32].

The debate of whether myectomy and ASA are truly equivalent options in terms of efficacy and outcomes has persisted since the introduction of the ASA technique over 20 years ago [81]. Given the above studies, it is clear that the debate regarding early symptomatic improvements in NYHA heart failure class, syncope, angina, and LV outflow tract gradient has been largely settled. There are sufficient data from retrospective cohort studies regarding rates of acute complications, LVOT gradient reduction, and short-term symptomatic improvement; both procedures are similarly efficacious in the modern era. In most reports, more complete gradient reduction is still achieved with surgery, but the magnitude does not translate into clinically meaningful differences in outcomes [75–78].

The second debate revolved around the early, periprocedural risks including the incidence of complete heart block and need for permanent pacemaker placement. Indeed, early experience with ASA encompassed the operator learning curve, which was associated with relatively good clinical efficacy, but more complications, including complete heart block, early ventricular arrhythmias, and even death or distant myocardial infarction from coronary dissection or inadvertent spillage of ethanol [82]. The next era of ASA, between years 2001 and 2010, was characteristic of improvements in technical aspects of the procedure, leading to less

periprocedural complications. Myocardial contrast echocardiography was used more commonly to select the target septal perforator, ethanol volume and rate of injection were reduced, and more judicious case selection was being practiced with a goal of improving the benefit-to-risk ratio. This transformation of ASA has now resulted in periprocedural mortality rates of <1% that closely track those seen with surgical myectomy at experienced centers [83].

During initial experience with ASA, the rates of conduction abnormalities with ASA were high, with up to 20–25% of patients receiving permanent pacemakers for complete heart block or prophylactic implantable defibrillators for the risk of sudden death [71, 84]. With refinement of ASA technique, the rates of permanent pacemaker placement in more contemporary studies are now in the 8–17% range [74, 83]. Despite significant reductions in the incidence of permanent pacemaker requirement, ASA still lags behind the ~2–3% rates of pacemaker placement seen with surgery. However, it remains unclear whether this is solely due to the procedure itself or exacerbated by the older age at which patients are preferentially offered alcohol septal ablation.

One of the challenges in the field of HCM and septal reduction therapy is the limited experience among majority of the surgeons and interventionalists in the United States. Currently, most US centers that provide septal reduction therapy perform few SM and ASA procedures, which is below the threshold recommended by the 2011 American College of Cardiology Foundation/American Heart Association Task Force Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy [85]. Low-volume septal reduction centers are associated with worse in-hospital outcomes, including higher mortality, longer length of stay, and higher hospital cost. Therefore, further efforts by the cardiology community are needed to encourage referral of patients with HCM to centers of excellence for septal reduction therapy.

The third debate, and the only one that has not been completely settled, revolves around the issue of long-term survival. Proponents of surgical myectomy have argued that ASA, by introducing transmural infarction and scar to the septum, may predispose this population to life-threatening sustained ventricular tachyarrhythmias and arrhythmia-related sudden death [86]. However, multiple meta-analyses of large observational series with up to 8 years of follow-up have failed to demonstrate even a signal of increase in death when comparing ASA with surgery [75, 77, 78, 87]. Furthermore, patients who have successfully undergone either procedure appear to have survival rates that track each other as well as a comparable non-HCM population [11, 71, 73] as mentioned above. However, some reports have suggested a higher risk of the need for additional septal reduction therapy compared with those who undergo myectomy [87]. Patients with prior ASA undergoing surgical septal myectomy represent a higher risk cohort and may be at an increased risk of cardiac death, advanced heart failure, and implantable cardioverter defibrillator discharges [88]. Myectomy has been suggested as the treatment of choice in patients with pronounced septal hypertrophy; however, ASA may be an effective treatment strategy in such patients as well [89]. Severe septal hypertrophy serves as a marker of reduced survival in HCM, and in such patients, reduced survival may not be unique to ASA or myectomy.

Noseworthy, PA et al. however have reported that among patients with an ICD or pacemaker, ASA was associated with an annual rate of VT/VF, cardiac arrest, or appropriate ICD therapy of ~4.9%/year [90]. The data from Mayo Clinic have also suggested a higher annualized rate of appropriate ICD discharges after undergoing ASA (4.3%/year) compared with 0.24%/year rate following myectomy [79]. This higher than expected rate of ICD discharges may be explained partly by intrinsic selection bias, where older patients with more comorbidities (and therefore at higher VT/VF risk in general) tend to undergo ASA. In addition, many have called into question the appropriateness of surrogate markers, such as appropriate ICD discharge, since many of these arrhythmias are not truly life-threatening and the higher prevalence of ICD implantation among ASA patients adds to a surveillance bias. And, of course, this has not translated into reduced survival as previously discussed. Nonetheless, this higher rate of monitored arrhythmias is concerning and requires further investigation.

All considered, only a prospective randomized trial could eliminate the selection bias of current clinical practice and provide the cardiovascular community with definitive comparative long-term data. Unfortunately, several obstacles make the design and performance of an appropriately powered randomized trial impossible [65]. Given relatively low event rates after either procedure, ~1200 patients with obstructive HCM and severe drug-refractory symptoms would need to be randomized, which would require screening of ~34,000 consecutive HCM patients. Such an enormous number of HCM patients could not realistically be screened even with combination of major North American and European HCM centers. Therefore, an adequately powered randomized trial comparing long-term survival of ASA and myectomy would not be feasible.

The debate regarding optimal septal reduction therapy for symptomatic medically refractory HCM patients is also evident in the dichotomy of practice between the United States and European HCM centers. In the United States, ASA is reserved for those patients who are older or with significant comorbidities, in whom surgery is either contraindicated or considered high risk. The American College of Cardiology Foundation/American Heart Association Guidelines on the diagnosis and management of HCM support this algorithm, which is largely followed at HCM treatment centers throughout the United States [39]. In contrast, in most European centers, ASA is the preferred treatment of choice, for a number of reasons, including physician and patient preference, minimally invasive nature of the procedure, an increasing sense of

equipoise, local availability of experienced ASA operators, and lack of regional surgical expertise [81, 86]. The extinction of surgical myectomy in many European countries, even from countries formerly with rich surgical traditions and experience such as Germany and Switzerland, has prompted a call to "bring septal myectomy back for European patients" [86]. And, given the frequency with which additional anatomic problems are present in patients with HCM, it would seem appropriate that both procedures be available so as to optimally treat the largest number of patients with this disease.

Future Directions

As further evidence mounts regarding improved long-term survival after ASA that appears identical to that seen with surgery, an argument could be made to change the recommendation for ASA to class IIa, making it an equivalent option to surgery in those who qualify anatomically for both procedures. In experienced HCM centers, the only meaningful difference between the two procedures might be the higher risk of permanent pacemaker in ASA patients versus the known risk of sternotomy and longer postsurgical recovery in those undergoing surgery. Recent modifications to ASA (the use of myocardial contrast echocardiography and reduction in the dosage of alcohol) as well as better patient selection have led to improvements in results and decrease in periprocedural complications.

The current challenge is to inform practitioners in the United States about the full capabilities of ASA and myectomy, to educate clinicians that experienced operators at HCM centers of excellence can perform these procedures today with similar short- and long-term outcomes, and to disseminate both techniques to larger areas of the country. In the United States, there is currently a shortage of experienced operators, both surgical and interventional, that would need to be trained in case selection, optimal technique, and longitudinal care of HCM patients. An important goal for the future may be to train more young surgeons to perform myectomy and, therefore, to provide HCM patients with access not only to ASA but also to centers with extensive experience in surgical myectomy [91].

As the ASA and myectomy procedures become safer in terms of periprocedural complications, the threshold for invasive intervention may need to be lowered in the future. Patients with NYHA class II symptoms, particularly those with syncope, near syncope, and presence of intermittent or chronic atrial fibrillation, may derive significant symptomatic improvement after septal reduction. Veselka, J et al. have reported outcomes from the Euro-Alcohol Septal Ablation Registry; 161 patients with mild symptoms (NYHA class II) had a sustained symptomatic and hemodynamic improvement after ASA, with their survival being comparable to the general population [92]. Given that septal reduction therapy may improve not only quality of life but possibly even longevity, septal reduction therapy may need to be considered earlier in life [9]. Many older patients now undergoing ASA have advanced diastolic dysfunction, giant left atria, and atrial fibrillation, all potentially avoidable by earlier septal reduction therapy.

Furthermore, should ASA be considered in patients without a confirmed diagnosis of HCM, but who instead have the favorable constellation of anatomic and physiologic features, including hypertrophy and LVOT gradient? Kovacic, JC et al. have recently demonstrated that ASA can be beneficial in terms of post-procedural gradient reduction, end-diastolic pressure improvement, and symptomatic NYHA class improvement in a wide cohort of patients with symptomatic concentric LVH and LVOT obstruction [93]. In reality, a firm diagnosis of HCM is not always possible, and a small proportion of patients without HCM have likely inadvertently been undergoing both surgical myectomy and ASA for the relief of LVOT obstruction symptoms. Therefore, it may be reasonable to offer septal reduction therapy (ASA or surgical myectomy) to patients with the pathophysiology of dynamic outflow tract obstruction, whether or not due to HCM. In addition to genetically mediated HCM, these could include hypertensive heart disease of the elderly, severe concentric hypertrophy (e.g., in patients with uncontrolled hypertension or end-stage renal disease), those with Takotsubo cardiomyopathy and outflow obstruction unresponsive to medical therapy, or those with prior mitral valve repair/replacement and iatrogenic LVOT obstruction, among other cohorts. In addition, ASA may become the first treatment option for elderly HCM patients refractory to medications, who frequently have favorable ASA anatomy with a focal "septal bulge," that may not be suited for surgery due to advanced age and concomitant comorbidities [94]. ASA has recently been described as a therapeutic option to provide acute relief of transcatheter mitral valve replacement-induced LVOT obstruction when septal hypertrophy is a contributing factor [95]. In addition, prophylactic ASA has been performed prior to transcatheter aortic valve replacement in patients with septal hypertrophy.

Future investigations regarding ASA therapy may need to focus on techniques to reduce the incidence of complete heart block, as well as longer-term follow-up to assure safety and survival outcomes. Such novel technologies may include the use of polyvinyl alcohol foam particles, microspheres, absorbable gelatin sponges, or septal coils as alternatives to alcohol, with a goal of reducing the incidence of complete heart block and pacemaker requirement [96–99]. Finally, reduction in septal mass by radiofrequency catheter ablation and cryoablation are under further investigation as well and may become complementary procedures to either surgery or alcohol septal ablation [100–102].

Clinical Pearls

- Identification of LV outflow tract obstruction with exercise echocardiography or provoking it during cardiac catheterization may help to identify symptomatic HCM patients who might benefit from therapies to relieve the obstruction, including medications and invasive septal reduction treatment.
- Cardiac catheterization may aid in assessing alternate yet treatable etiologies of the symptoms, such as obstructive coronary disease, important volume overload or depletion amenable to diuretics, or volume expansion, respectively.
- Patients should be considered for septal reduction therapy only when (a) symptoms are clearly and primarily attributed to obstructive HCM despite optimal medical therapy; (b) symptoms are severe heart failure or angina (NYHA or CCS class III/IV), recurrent obstruction-related syncope, or recurrent clinical decompensation due to refractory paroxysmal atrial fibrillation; (c) a gradient ≥50 mmHg can be documented on optimal medical therapy; and (d) obstruction is clearly dynamic and subvalvular, typically from septum-to-anterior mitral leaflet contact. Echocardiography and cardiac catheterization must confirm the anatomic and hemodynamic findings.
- An individualized approach to selection of septal reduction therapy is required, with comprehensive assessment of clinical symptoms, associated comorbidities, and echocardiographic, electrocardiographic, and angiographic features that might favor one approach over another.
- There are no randomized controlled trials comparing ASA to surgical myectomy. Evidence from nonrandomized studies suggests that ASA and surgical myectomy result in similar short- and long-term outcomes with respect to hemodynamic and functional improvements, with greater propensity for pacemaker placement with ASA. For some patients, both procedures could provide reasonable treatment options. In such cases, the principle of patient autonomy suggests that patients can choose between myectomy and ASA after a thorough discussion of the risks and benefits related to each procedure.
- It seems reasonable to limit the performance of both alcohol septal ablation and surgical myectomy to programs with sufficient experience to optimize outcomes; in particular, programs should perform 8–10 procedures per year and ideally have performed over 50 procedures.

Questions

1. Septal reduction therapy should be considered for which of the following patients?
   A. Patient with severe LV outflow tract obstruction and drug-refractory symptoms, such as severe dyspnea or chest pain (usually NYHA or CCS functional class III/IV), or other important exertional symptoms (e.g., syncope)
   B. Patients who are intolerant of optimal medical therapy
   C. Patients in whom symptoms are clearly and primarily attributed to obstructive HCM physiology
   D. Patients with septal thickness ≥ 15–16 mm at point of septal – mitral contact
   E. All of the above

   Answer: E. Patients should be considered for septal reduction therapy when (a) symptoms are clearly and primarily attributed to obstructive HCM despite optimal medical therapy; (b) symptoms encompass severe heart failure or angina (NYHA or CCS class III/IV), recurrent obstruction-related syncope, or recurrent clinical decompensation due to refractory paroxysmal atrial fibrillation; (c) a gradient ≥50 mmHg can be demonstrated on optimal medical therapy; and (d) obstruction is clearly dynamic and subvalvular, resulting mainly from septum-to-anterior mitral leaflet contact. Septal wall thickness < 15–16 mm is considered a contraindication to either myectomy or ASA due to the potential risk of septal perforation with creation of a ventricular septal defect.

2. The following features would favor the selection of myectomy over alcohol septal ablation as the septal reduction therapy of choice, except:
   A. Younger age
   B. Septal hypertrophy ≥30 mm
   C. Preexisting left bundle branch block
   D. Prior cardiac or thoracic surgery
   E. Atrial fibrillation that requires a maze procedure

   Answer: D. Myectomy surgery is preferred in younger patients; those with massive septal hypertrophy (e.g., ≥30 mm); those with diffuse rather than focal left ventricular hypertrophy that extends to the mid-ventricle or even apex; those with preexisting left bundle branch block (since ASA usually causes right bundle branch block, resulting in a high incidence of complete heart block); those with concomitant cardiac disease requiring surgical intervention: intrinsic severe mitral valve disease, presence of membranes, moderate/severe aortic stenosis, and coronary artery disease favoring coronary artery bypass grafting; and those with atrial fibrillation that might require

a maze procedure or left atrium appendage ligation. Prior cardiac or thoracic surgery (given the risks inherent to reoperation) would favor ASA over myectomy.

3. The following features would favor the selection of alcohol septal ablation over myectomy as the septal reduction therapy of choice, except:
   A. Advanced age
   B. Comorbid conditions that would increase surgical risk (e.g., pulmonary hypertension)
   C. Presence of pacemaker/ICD
   D. Absence or minimal intrinsic disease of mitral valve apparatus and papillary muscles and of other conditions for which cardiac surgery is indicated
   E. Preexisting left bundle branch block

   Answer: E. Factors that favor ASA over myectomy include advanced age (>65 years), comorbid conditions that would increase surgical risk (e.g., pulmonary hypertension or severe COPD causing significant concerns about lung or airway management), preexisting right bundle branch block (because myectomy usually causes left bundle branch block and a high incidence of complete heart block), presence of pacemaker/ICD that would substantially lower the procedural risk of ASA, prior cardiac or thoracic surgery (given the risks inherent to reoperation), and focal CAD that can be treated with stenting. Myectomy is preferred in those with preexisting left bundle branch block, since ASA usually causes right bundle branch block, resulting in a high incidence of complete heart block.

4. In patients being considered for septal reduction therapy, what LV outflow gradient should be demonstrated?
   A. LV outflow gradient of ≥30 mmHg with exertion.
   B. LV outflow gradient of ≥60 mmHg at rest.
   C. LV outflow tract gradient of ≥50 mmHg at rest, with physiologic provocation, or with exertion.
   D. No gradient needs to be demonstrated if symptoms of severe heart failure or angina (NYHA or CCS class III/IV) are present.
   E. LV outflow tract gradient of ≥60 mmHg at rest, with physiologic provocation, or with exertion.

   Answer: C. Candidates for septal reduction therapy must have an LV outflow tract gradient of ≥50 mmHg at rest, with physiologic provocation, or with exertion. While echocardiography is the gold standard, permitting evaluation of obstruction provoked by Valsalva maneuver or treadmill exercise, cardiac catheterization is frequently complementary and often necessary in patients with poor echocardiographic "windows" to evaluate or confirm the severity of LVOT gradient at rest and with provocative maneuvers.

5. If a significant resting gradient (gradient of ≥50 mmHg) is not found by echocardiography or during catheterization, the following maneuvers are recommended:
   A. Valsalva
   B. Induction of an extrasystolic beat to measure the Brockenbrough-Braunwald sign
   C. Exercise (e.g., supine bicycle exercise)
   D. Pharmacologic challenge (amyl nitrite, nitroglycerine, or isoproterenol)
   E. All of the above

   Answer: E. If a significant resting gradient (gradient of ≥50 mmHg) is not found during catheterization, provocative maneuvers such as the Valsalva or an induction of an extrasystolic beat to measure the Brockenbrough-Braunwald sign (or a combination of both maneuvers) should then be performed. If a significant gradient is still not provoked, either exercise (e.g., supine bicycle exercise) or pharmacologic challenge (amyl nitrite, nitroglycerine, or isoproterenol) is helpful when the clinical picture strongly suggests obstructive physiology. Isoproterenol hydrochloride provides direct stimulation of the β1- and β2-receptors that simulates exercise and, therefore, may uncover a labile outflow tract gradient.

6. Alcohol septal ablation results in the following:
   A. Improvement in functional class (NYHA and CCS class)
   B. Improvement in peak oxygen consumption
   C. Improvement in exercise capacity
   D. Improvements in LV synchrony, microvascular function of the subendocardium, and myocardial energetics parameters
   E. All of the above

   Answer: E. ASA results in a significant improvement in functional class (NYHA and CCS class), peak oxygen consumption, and exercise capacity for up to 8–10 years in published studies. In addition, recent studies have indicated that ASA results in improvements in LV synchrony, microvascular function of the subendocardium, and myocardial energetics parameters. HCM patients after a successful ASA procedure also appear to have long-term survival rates that are comparable to the non-HCM population.

7. Selective coronary angiography is required prior to alcohol septal ablation in order to demonstrate or exclude the following findings, except:
   A. Exclude concomitant coronary disease.
   B. Examine the size of the septal perforator arteries.
   C. Exclude collateral circulation from septal branches to other coronary segments.

D. Examine the septal thickness prior to ASA.
E. Examine the distribution of the septal perforator arteries.

Answer: D. Selective coronary angiography should be performed to exclude concomitant coronary disease. Furthermore, in those undergoing workup for septal reduction treatment, the size and distribution of the septal perforator arteries need to be carefully evaluated. In addition, septal arteries may arise from the left main, diagonal branches and even from the right coronary artery, and thus, meticulous angiography in multiple views is imperative. It is also important to exclude the presence of the collateral circulation from septal branches to other coronary segments.

8. The following recommendations for septal reduction therapy have been made by the ACCF/AHA 2011 Hypertrophic Cardiomyopathy Guidelines:
   A. In those patients who are acceptable surgical candidates, surgical myectomy should generally be preferred (class IIa).
   B. In those patients who are acceptable surgical candidates, ASA should be preferred (class IIa).
   C. In those patients who are not acceptable candidates for surgical intervention, ASA would be the favored treatment option (class IIb).
   D. Patient preference for alcohol septal ablation over surgical myectomy is reasonable after a balanced and thorough discussion (class IIa).
   E. All of the above.

   Answer: A. ACCF/AHA 2011 Hypertrophic Cardiomyopathy Guidelines recommend that in those patients who are acceptable surgical candidates, surgical myectomy should generally be preferred (class IIa) over ASA (class IIb), whereas in those patients who are not acceptable candidates for surgical intervention, ASA would be the favored treatment option (class IIa). Patient preference for alcohol septal ablation over surgical myectomy is also reasonable after a balanced and thorough discussion (class IIb). An individualized approach to selection of septal reduction therapy is commonly required, with comprehensive assessment of clinical symptoms, associated comorbidities, and echocardiographic and angiographic features that might favor one approach over another.

9. When comparing surgical myectomy to ASA, the following statements are correct, except:
   A. Myectomy and ASA achieve similar early symptomatic improvements in NYHA heart failure class.
   B. More complete gradient reduction may be achieved with myectomy.
   C. ASA is associated with higher rate of pacemaker post-ASA.
   D. Similar survival rates have been demonstrated when comparing ASA and surgical myectomy in multiple retrospective cohort studies and meta-analyses.
   E. A randomized controlled trial comparing ASA to surgical myectomy has demonstrated similar symptomatic improvements in NYHA heart failure class.

   Answer: E. The early symptomatic improvements in NYHA heart failure class, syncope, angina, and LV outflow tract gradient have been shown to be similar between myectomy and ASA. There are sufficient data from retrospective cohort studies regarding rates of acute complications, LVOT gradient reduction, and short-term symptomatic improvement; both procedures are similarly efficacious in the modern era. In most reports, more complete gradient reduction is still achieved with surgery, but the magnitude does not translate into clinically meaningful differences in outcomes. ASA still lags behind the ~2–3% rates of pacemaker placement seen with surgery. However, it remains unclear whether this is solely due to the procedure itself or exacerbated by the older age at which patients are preferentially offered alcohol septal ablation. Similar survival rates when comparing ASA and surgical myectomy in multiple retrospective cohort studies and meta-analyses, with follow-up out to 8 years, have been shown. No randomized controlled trials comparing ASA to surgical myectomy have been performed, and it is unlikely that a randomized trial comparing these two therapies in patients with anatomy favorable for both procedures will ever be performed.

10. The following factors need to be examined when deciding regarding the appropriateness of the septal reduction therapy, except:
    A. Symptoms should be clearly and primarily attributed to obstructive HCM physiology despite optimal medical therapy.
    B. Symptoms of severe heart failure or angina.
    C. Family history of sudden cardiac death.
    D. Gradient ≥50 mmHg should be documented on optimal medical therapy.
    E. Obstruction should clearly be subvalvular and dynamic.

    Answer: C. Patients should be deemed candidates for isolated septal reduction therapy when (a) symptoms are clearly and primarily attributed to obstructive HCM physiology despite optimal medical therapy; (b) symptoms are severe heart failure or angina (as measured by NYHA or CCS class, respectively), recurrent obstruction-related

syncope, or recurrent clinical decompensation due to refractory paroxysmal atrial fibrillation; (c) a gradient ≥50 mmHg can be documented on optimal medical therapy, either at rest or with provocation; and (d) obstruction is clearly subvalvular and dynamic, from septum-to-anterior mitral leaflet contact, and not due to fixed obstructive valvular disease or membranes. Family history of sudden cardiac death should only be a factor in assessing the need for ICD therapy.

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Surgical Myectomy and Associated Procedures: Techniques and Outcomes

23

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Abbreviations

AF	Atrial fibrillation
ASA	Alcohol septal ablation
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
HCM	Hypertrophic cardiomyopathy
ICD	Internal cardiac defibrillator
LV	Left ventricle
LVOTO	Left ventricular outflow tract obstruction
MVR	Mitral valve replacement
NYHA	New York Heart Association
PPM	Pacemaker
RPR	Resection-plication-release
SAM	Systolic anterior motion
SCD	Sudden cardiac death

Key Points

- Isolated septal myectomy results in a low operative mortality of <1% and excellent long-term survival when performed at experienced centers. It is the gold standard for relief of symptomatic left ventricular outflow tract obstruction in hypertrophic cardiomyopathy.
- The heterogeneity, complexity, and incidence of obstructive hypertrophic cardiomyopathy (HCM) requiring myectomy create a unique procedure in cardiac surgery that has been most successful when performed in centers with a dedicated HCM program and experienced surgeons.
- Intraoperative transesophageal echocardiography is critical in understanding the pathophysiology of HCM by demonstrating the septal size, the point of mitral-septal contact, and associated mitral valve and papillary muscle abnormalities.
- The benefits of septal myectomy include improvements in quality of life, heart failure symptoms, and long-term survival; survival after myectomy is equal to age- and sex-matched non-HCM controls.
- Complications are seen in <2% of patients after undergoing septal myectomy. Concomitant surgery such as coronary revascularization, atrial fibrillation ablation procedures, and mitral valve repair may be done safely with little additional risk.
- As long-term data is collected and analyzed, indications for septal myectomy may continue to evolve, as well as novel approaches for mid-cavity and apical disease.

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Introduction

Over the past 50 years, improvements in surgical techniques and expanded understanding of hypertrophic cardiomyopathy (HCM) and its pathophysiology have led to the current era in which septal myectomy has excellent, reproducible results. Based on formal guidelines, those patients with symptomatic obstructive HCM who have failed medical management and have left ventricular outflow gradients of >50 mmHg should be considered for septal myectomy. Better understanding of septal myectomy in terms of echocardiographic evaluation, operative techniques, and reported outcomes is critical in treating this heterogeneous and complex disease.

Surgery for HCM

Background and History

The description of an area of muscular hypertrophy causing obstruction to left ventricular outflow below the aortic valve is commonly credited to Sir Russell Brock and the pathologist, Dr. Donald Teare, in *Guy's Hospital Reports* from 1957 [1, 2]. They first elucidated the nature of the obstruction, though they offered no possibility of therapy. Since then, the complex of cardiac structural abnormalities has been given many names but is now termed hypertrophic obstructive cardiomyopathy (HOCM). Descriptions of the malady exist as early as the beginning of the nineteenth century from France to England and in a report from Germany at the beginning of the twentieth century [3, 4, 5].

With the advent of cardiopulmonary bypass and open-heart surgery, a variety of surgical techniques were promulgated as possible therapies for this disorder and first successfully accomplished by Cleland in 1958 [6]. Early procedures were associated with an extremely high mortality risk, most probably associated with the problems of myocardial protection, air embolism, and the complications secondary to an often-performed left ventriculotomy. In a study group gathering sponsored by the Ciba Foundation in 1970, the debate centered on the therapeutic success and complications of a simple myotomy versus limited myectomy and the role of the mitral valve in obstruction. Well-known surgeons of the time— John Kirklin, Brian Barratt-Boyes, Douglas Wigle, Hugh Bentall, and physician Eugene Braunwald—all proposed different approaches to surgical management, including resection of the right side of the ventricular septum through a limited right ventricular myotomy [7]. Results were mixed and fraught with complications. Dr. Andrew Morrow, working with the group at the National Heart Institute in the USA, described a transaortic approach and a left ventricular myectomy which in most cases significantly relieved the bulk of the obstruction with a reasonable operative risk. His procedure was popularly adopted after his presentation of results from 83 patients and their follow-up in 1975 [8].

Evolution of Procedure

Since the mid-1980s, given the failure of the Morrow procedure in a significant number of patients, progress in surgical therapy has been directed at those cases where simple myectomy does not adequately relieve the obstruction to flow. Improvements in operative technique related directly to a better understanding of the disease process, first by pathologic studies and later through the use of echocardiography (Table 23.1). Recognizing the role of the anterior leaflet of the mitral valve in obstruction, Cooley first proposed mitral valve replacement (MVR) for cases with severe mitral insufficiency in 1976, especially valuable in cases where the septum is relatively thin and the morphology of the anterior leaflet was especially long or broad [9]. MVR was used for treatment of HCM and data was published supporting this treatment [10, 11]. Because mitral valve replacement in a relatively young group of patients was an unattractive therapy, McIntosh and Maron subsequently promoted a vertical mitral valve plication to stiffen the leaflet and limit its excursion into the outflow tract [12]. The abnormal morphology of the mitral valve in HCM was described in detail by Klues et al. and added significantly to the expanding knowledge of this disease process [13, 14].

In 1994, Messmer and his group described a more extensive myectomy, which included thinning or remodeling of the papillary muscle including the division of abnormal lateral attachments to allow the anterior leaflet to fall into a more posterior position within the ventricular chamber [15, 16]. This "extended myectomy" is generally accepted and performed at all major HCM surgical centers. However, higher-resolution echocardiography has made clear the wider range of morphologic variations that promote obstruction. With the

Table 23.1 Evolution of surgical techniques for treatment of obstructive hypertrophic cardiomyopathy

Year	Surgeon	Procedure
1958	Cleland	Transaortic resection of muscle bar
1960	Morrow	Transaortic septal myectomy
1961	Kirklin	Transaortic/transventricular access
1964	Johnson	Myectomy combined with mitral valve replacement
1970	Cooley	Mitral valve replacement alone
1990	McIntosh	Myectomy combined with vertical plication of the anterior mitral leaflet
1990	Messmer	Extended septal myectomy
2000	Swistel	Septal resection, horizontal plication of mitral valve, and release of lateral attachments

development of HCM centers of excellence where these variations have been better understood, it has become recognized that therapy often requires individualization.

Many other groups have offered alternative variations to surgical management to accommodate the various phenotypes that represent hypertrophic cardiomyopathy [17–23]. In some circumstances, the hypertrophied muscle may be localized and dominant, basal, midventricular, or apical, and in others a more diffuse hypertrophy may be present. Furthermore, the anterior leaflet of the mitral valve may be grossly elongated and the septum minimally thickened, limiting the amount of resection that can be accomplished. Many of the variations of technique involve the mitral valve and highlight its prominent role in this disease process. These techniques include plication, retention plasty, leaflet extension, and edge-to-edge repairs [19, 20, 21, 23]. Additional morphologic variations best described by the surgeons at the Mayo Clinic include abnormal or accessory papillary muscles and subvalvular structures. Often redundant, these papillary muscles must be either resected or thinned to obliterate the outflow tract gradients [22]. More recently at the Cleveland Clinic, the anterolateral papillary muscle has been occasionally sutured posteriorly to either the posterior papillary muscle or myocardial wall to draw the anterior mitral leaflet out of the way of the dominant direction of flow toward the outflow tract and minimize the opportunity for systolic anterior motion (SAM) [24].

Analysis of the pathophysiology of the anterior leaflet of the mitral valve has led our group to conclude that a simple, reproducibly excellent result can be obtained by shortening in an anteroposterior dimension with a horizontal plication [25–28]. As opposed to a vertical plication, this preserves the coaptation zone of both leaflets and leaves their relationship intact. We termed this the *RPR* procedure, resection/plication/release: *r*esection of the hypertrophied muscle, *p*lication of the anterior leaflet of the mitral valve, and *r*elease of lateral attachments and/or the resection of the subvalvular mechanism to allow a more posterior displacement of the valve and control of any accessory structures contributing to obstruction [25]. Moreover, by placing a row of plication sutures high on the anterior curtain area of the valve, the leaflet is stiffened in exactly the right dimension to limit the possibility of bowing out into the outflow tract and meeting the contact point on the septum.

As surgical experience has grown, the many variations of morphology and pathophysiology that cause obstruction have become better understood and appreciated. A variety of surgical strategies is available and must be tailored in each case to match the particular morphology causing obstruction. In fact, variations in morphology are so common that in 1988 McIntosh and Maron noted, "it is relatively uncommon to encounter a patient with obstructive HCM at operation in whom septal hypertrophy is both particularly marked and homogeneously distributed so that the standard myotomy-myectomy can be undertaken with no preoperative deliberation regarding the pattern and magnitude of septal thickness" [29].

Operative Technique

A systematic technique is necessary to analyze the pathophysiology of obstruction in a given patient and tailor a procedure using a variety of possible methodologies to limit systolic anterior motion of the mitral leaflet (SAM), relieve obstruction, and restore mitral valve competency. Key elements of the procedure are partially determined before incision using echocardiography (Table 23.2). Echocardiographic findings are reviewed preoperatively to clarify the thickness of the septum and characterize its morphology, whether discreet or diffuse, basal, mid, or apical. The length of the anterior leaflet is measured and the point of mitral-septal contact determined. More recently, we have also noted whether the midportion of the leaflet contacts the septum or whether the leading edge is primarily involved. Although at times harder to identify, accessory papillary structures may be seen. In the operating room, all patients have a 2D/3D transesophageal echo (TEE) transducer placed, and the analysis is repeated under anesthesia. Not all patients have a resting gradient, though the general anesthetic vasodilates the patient which is gradient-provoking in itself. Rarely, inotropic agents are administered to provoke obstruction, although some centers elect for routine pre- and post-resection isoproterenol infusion to confirm no residual gradients.

A full or partial sternotomy incision is carried out. Arterial cannulation is performed through the upper ascending aorta, a single venous cannulation is utilized, and the left ventricle is vented through the right superior pulmonary vein with a 28F cannula. A coronary sinus catheter is placed, and the heart is arrested with antegrade and retrograde cardioplegia as necessary. A generous transverse aortotomy is performed.

Table 23.2 Morphologic variants of hypertrophic cardiomyopathy determined by preoperative transesophageal echocardiography

Site	Characteristics
Septum	Width measurement
	Location of hypertrophy: basal, midventricular, or apical
	Point of mitral-septal contact
Mitral valve	Degree of mitral regurgitation
	Length of anterior mitral leaflet
	Abnormal morphology/intrinsic disease of mitral leaflets
Papillary muscles	Location and size
	Presence of lateral attachments
Subvalvular apparatus	Thickened chords contributing to obstruction

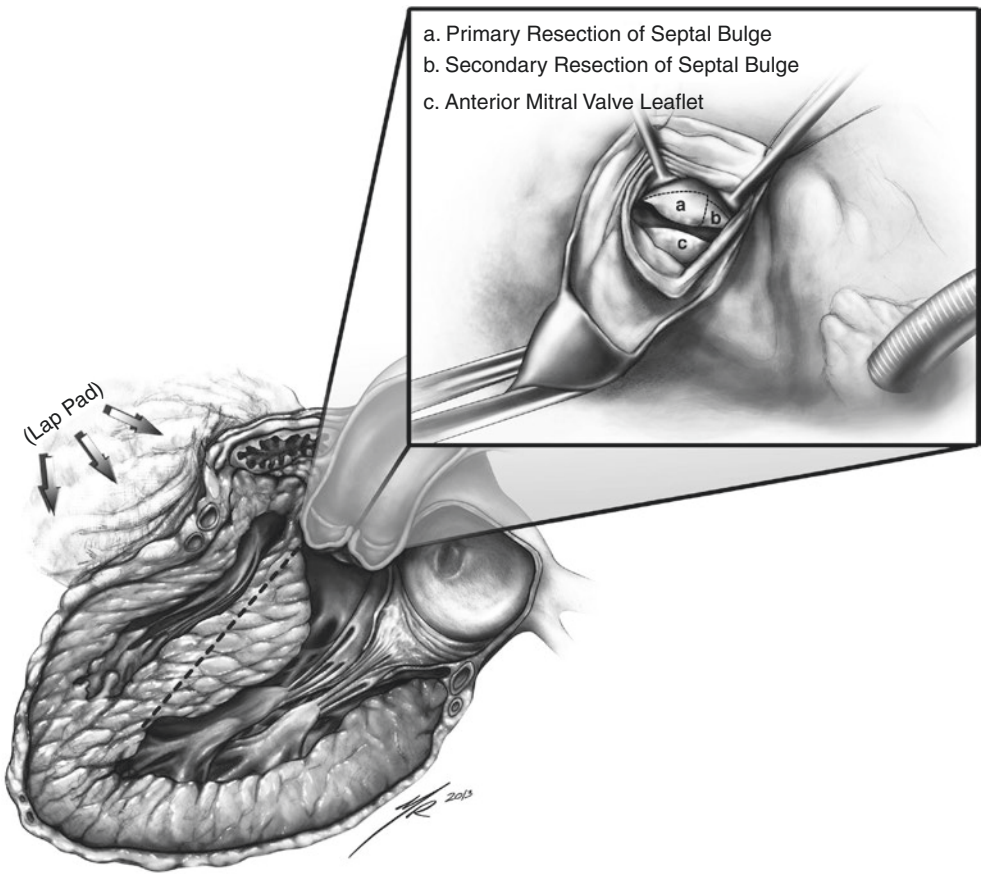

Fig. 23.1 Surgeon's view of the heart as visualized through a transverse aortotomy. Myectomy is performed to include sections "a" and "b" and begins below the annulus of the aortic valve. An icy laparotomy pad placed between the right ventricle and chest wall may assist in bringing the septum further into view. The incision is begun 3–5 mm below the aortic annulus, depending on the site of mitral-septal contact as determined by echocardiography

In general, extreme retraction of the anterior septum is required, especially in cases where the septum has extensive thickening and fibrosis, and we have found it preferable to nearly transect the aorta distal to the sino-tubular junction rather than the tearing that usually occurs with attempts at a limited aortotomy. Leaflet retractors are placed to protect the aortic valve leaflets and the left ventricle is examined. Thickened, fibrotic scar tissue is almost always present at the area of mitral-septal contact. It is often helpful to place an icy pad over the left ventricle to help place posterior pressure on the anterior septum (Fig. 23.1). A three-pronged hook is placed between the right coronary ostia and the commissure of the left and right aortic leaflets and engaged into the septal muscle beyond the area of mitral-septal contact as calculated from the preoperative transesophageal echo. The myectomy is performed with a long-handled, 45-degree, #15 knife blade (Fig. 23.2). The incision is started at least 3–5 mm from the aortic annulus. This area is not involved in the pathogenesis of SAM, preserves the A/V node to limit the incidence of postoperative complete heart block, and lessens the possibility of an iatrogenic ventricular septal defect. Depending on the predetermined thickness of the septum, anywhere from 1.0 to 1.5 cm of muscle thickness is resected. Once the first few millimeters of muscle is cut, the hook is released, and the myectomy segment is grasped with a very long forceps, and the resection is continued. The medial border of the resection is usually just lateral to the right coronary ostia and extends laterally almost to the lateral commissure of the mitral valve. This yields a segment about 3 or 4 cm in width. In typical cases of basal hypertrophy, the resection extends into the ventricle just beyond the midportion of the anterolateral papillary muscle. The segment is then an approximate square: 3.0–4.0 cm on each side and 1.0–1.5 cm thick. This is a so-called extended myectomy. In cases where the obstruction is more midventricular, additional muscle can be removed up to the junction of the papillary muscles and medially deeper within the chamber avoiding the area where the conduction system is known to reside. In general, the portion of muscle is resected in the first attempt. Thereafter, the muscle tends to shred, and it is more difficult to get a purchase on additional segments. Irregular areas are often smoothed out with an angled pituitary rongeur.

With sufficient experience in this procedure, we have been able to extend this resection to the apex of the ventricle for patients with apical obstruction without resorting to an apical myotomy. An apical myotomy is most useful when the patient already suffers from an apical aneurysm. In apical obstruction without aneurysmal formation, it is very difficult to identify the papillary muscles and differentiate them from hypertrophied resectable muscle. Treatment for apical HCM

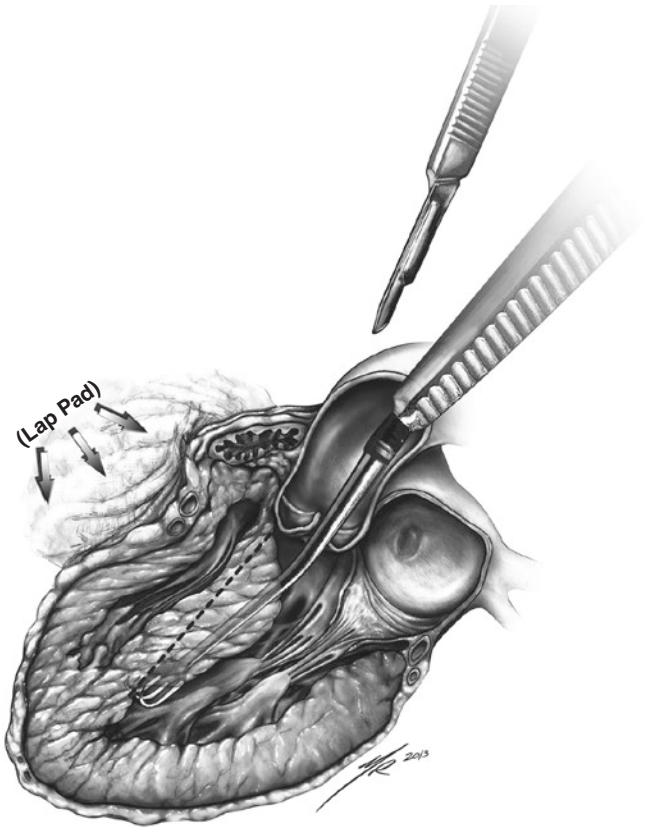

Fig. 23.2 Characteristic outflow tract morphology with basal septal hypertrophy. Insertion of the hook allows the surgeon to stabilize the septum while using the knife to excise a wide portion of muscle that begins just past the bundle and continues across to the far side, often extending to both trigones. Depending on the predetermined thickness of the septum, anywhere from 1.0 to 1.5 cm. of muscle thickness is resected

and midventricular obstruction has recently been described via a transapical approach. These procedures are limited to very few specialized centers with limited data. In this technique, both the mitral valve apparatus and the papillary muscles must be carefully avoided with the opening and enlarging of the left ventricular (LV) cavity [30–33]. In our center, if transaortic visualization is deemed inadequate for an appropriate and complete resection, we start the resection through the standard aortotomy, then perform an apical myotomy, and find the partial myectomy. In this manner we are assured of completing the myectomy in a safe location, minimizing the risk of damage to the papillary muscles or veering posteriorly where there could be less septal thickening and there is danger of creating an iatrogenic ventricular septal defect.

Once the myectomy is complete, it is usually much simpler to visualize the interior of the left ventricle and examine the mitral subvalvular structures and identify any lateral attachments of the anterolateral papillary muscle and the LV free wall. Often, these lateral attachments are already resected with the myectomy segment, but additional thinning of the junction of the anterolateral papillary muscle with the LV free wall can be easily accomplished with a medium-sized pituitary rongeur (Fig. 23.3). This muscle will then fall more posteriorly into the LV chamber and draw the anterior leaflet of the mitral valve with it. Overly aggressive resection here, however, may lead to antero-apical free wall rupture.

Attention is now directed to the anterior leaflet of the mitral valve itself. If there are abnormal papillary muscles attached directly, careful analysis of other underlying chords is necessary to decide whether the muscle here can be completely resected or whether only some degree of thinning can be accomplished. If there are no other supporting structures, resection may lead to a flail segment and postoperative central insufficiency. In many instances where accessory attachments exist, it is possible to resect a portion of the muscle or chord involved in obstruction and leave a more apical portion intact that retains additional attachments to the leading edge of the leaflet. Occasionally, upon analysis of the anterior leaflet on preoperative TEE, a certain degree of tenting of the anterior mitral leaflet is identifiable. In these cases, there may be limited if any mitral insufficiency, but an outflow tract gradient will exist secondary to mid-leaflet chordal SAM. Upon gross examination at operation, one or two culprit fibrotic secondary chords can be identified. Numerous primary chords are usually present, and these secondary chords can be safely resected with restoration of a more typical mitral valve orientation and relationship to both the left atrium and the outflow tract [88]. The anatomy here can be extremely variable, and it is difficult to generalize any approach to systematic resection.

It is relatively simple, however, to deal with an extremely long anterior leaflet. Preoperative echo analysis yields information on the total length of the anterior leaflet and directs the amount of plication, which can be from as little as 2 or 3 mm to as much as 5 or 6 in cases where the total leaflet length may exceed 4.0 cm [25]. From the left side of the patient, the surgeon can easily place four or five vertical mattress sutures of 5.0 prolene in a horizontal line to shorten the leaflet from anywhere between 3 and 6 mm depending on the previously calculated overall length of the leaflet. This leaves the coaptation zone of the leaflets intact and limits the capacity for mitral-septal contact by stiffening the leaflet to minimize bowing out in addition to shortening (Fig. 23.4). In general, we shorten any leaflet that is longer than 2.5 cm in overall length, not including any chordal tissue that may confound the measurements [28].

More recently, we have added another technique to deal with severe anterior leaflet elongation in cases where the preoperative TEE reveals leading edge contact with the septum during systole. On occasion, the leading edge of the A2 segment has a protruding lip with extreme laxity of its chordal attachments. This portion, termed the

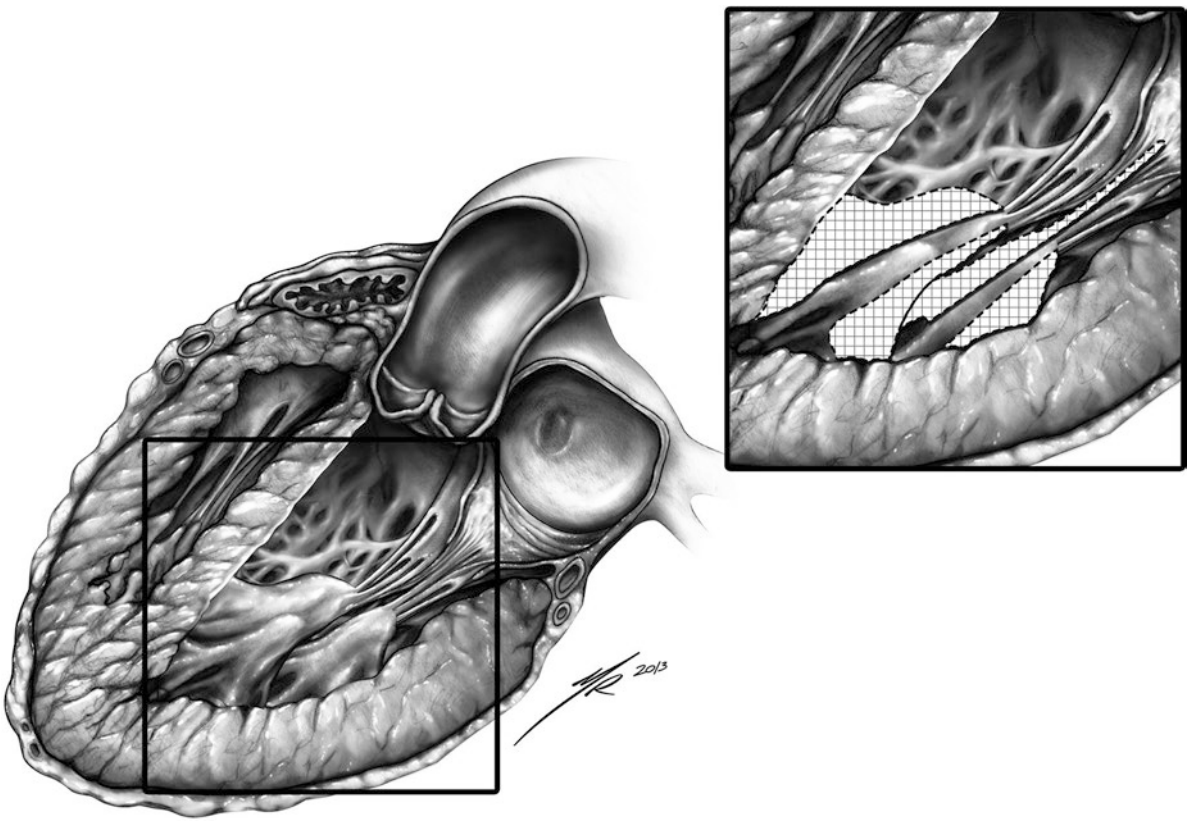

Fig. 23.3 Diagram showing the operative approach for resection and thinning of the papillary muscles as well as release of abnormal lateral attachments between papillary muscles and ventricular free wall that allow the anterior leaflet to fall more posteriorly

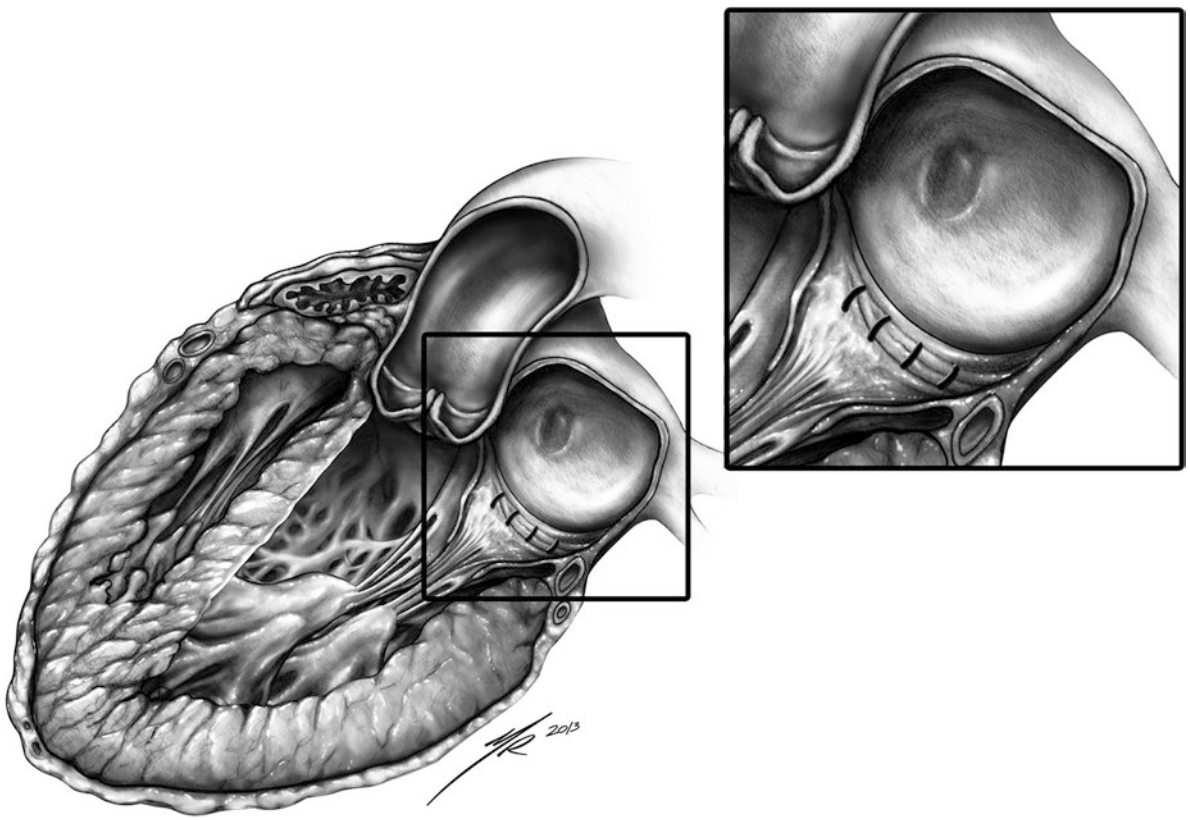

Fig. 23.4 Diagram of the horizontal mitral valve plication technique: placing sutures on the aortic side of the anterior mitral leaflet in order to shorten and stiffen the leaflet, thereby preventing systolic anterior motion in the setting of an elongated, redundant anterior mitral leaflet

"residual leaflet", can be measured at TEE as well and may be anywhere from 4 to 10 mm in length. It is the extreme laxity of the associated chords that suggests they are functionless in controlling prolapse, and we have found residual leaflet resection an additional strategy in resolving obstruction. However, care must be utilized. If the degree of laxity is misjudged and an overly aggressive resection is undertaken, central mitral insufficiency may result. As in many of these techniques, experience is extremely important in making judgments regarding any resection and manipulation. In general, any decision to resect or shorten the anterior leaflet of the mitral valve or resection of secondary chords is driven by the preoperative TEE analysis, while resection or thinning of the papillary muscle heads is decided more by gross examination.

The area is examined, and usually it is quite clear that the possibility of mitral-septal contact is limited compared to the preresected and plicated condition. The LV cavity is copiously irrigated and suctioned to remove any residual debris, examined for any loose sections of partially resected muscle, and the heart allowed to fill passively as the aortotomy is closed. Standard deairing is undertaken before the cross-clamp is removed. After separation from heart-lung bypass, and the initial echocardiographic examination for adequacy of the procedure, enough of an inotropic agent is administered, usually at least 10μgm/kg of dobutamine, to stimulate the myocardium. As described above, some institutions will use isoproterenol here and compare to any pre-procedure intraoperative measurements. The outflow tract area is examined for any residual mitral-septal contact, color flow turbulence, and gradient. A gradient above 20 mmHg under provocation, turbulence, or more than trace to 1+ mitral insufficiency generally requires a reassessment of the procedure. A decision would be required whether additional muscle could be resected, the condition could be rectified with postoperative β-blockade and/or disopyramide, or to proceed with mitral valve replacement as a last resort. Although we have rarely had to place the patient back on heart-lung bypass to resect additional segments of muscle, we have never left the operating theater with an unacceptable gradient on provocation or more than trivial mitral insufficiency. Mitral valve replacement has never been necessary unless there is severe mitral annular calcification or pre-existing mitral stenosis, and in these instances mitral valve replacement has been the predetermined procedure [28, 34, 35]. If the mitral valve has been plicated, occasionally there may be small jets of insufficiency secondary to needle holes left by the plication sutures. This has never persisted once the heparin has been reversed with protamine. Almost all the patients have a new left bundle-branch conduction block and are temporarily dependent on an external pacemaker.

Postoperative Management

Postoperative critical care management after septal myectomy is similar to other open cardiac surgical procedures. The first step begins with transfer of the patient to the intensive care unit during which a system-based evaluation is performed assessing respiratory status and hemodynamics. Next, standard postoperative laboratory studies, chest X-ray, and electrocardiograms are obtained.

The cardiovascular system is closely monitored particularly in terms of intravascular fluid status. Patients initially often have a period of further rewarming that results in vasodilation and may require additional colloid or crystalloid to maintain filling. Optimization of preload is obtained using information from pulmonary artery monitoring and continuous mixed venous saturations. Occasionally, alpha-adrenergic agents are used. The use of inotropes is discouraged in these patents postoperatively and is rarely necessary given the normal left ventricular function.

HCM patients have varying degrees of myocardial fibrosis and consequent diastolic dysfunction. This may manifest itself more severely after heart-lung bypass and moderate hypothermia during surgery. Not infrequently, for several hours postoperatively, the cardiac output and index may be depressed, but the temptation to use inotropic support should be resisted as this may provoke obstruction in these patients who may be additionally vasodilating and relatively hypovolemic. The myocardium relaxes after several hours, and the cardiac output and index revert to normal levels.

Patients are monitored for coagulopathy and postoperative bleeding. Rarely, blood transfusion is necessary and usually required only in older patients with multiple concomitant procedures and/or comorbidities. Atrial fibrillation may occur and is treated with amiodarone, beta-blockade, and cardioversion if necessary. Some institutions elect to place all patients on amiodarone postoperatively to prevent atrial fibrillation and discontinue the medication at 3 months as an outpatient. Patients are typically extubated within 6 h of surgery and remain in the hospital an average of 5 days. Increased length of stay correlates directly with age, comorbidities, and associated procedures. More often than not, the only medication used postoperatively is beta-blockade, and possible amiodarone and anticoagulation as discussed previously. Calcium channel blockers and disopyramide are almost never required. Standard nursing, physical therapy, and respiratory therapy continue during the recovery period. During the acute hospitalization, repeat echocardiography is done only for symptoms or clinical concerns.

Once patients are discharged from the hospital, they follow up with both their surgeon and cardiologist. All patients are followed within a formal hypertrophic cardiomyopathy program and receive an echocardiogram at 3–6 months and then yearly thereafter.

Outcomes

Improvements in technique and better understanding of HCM pathophysiology have resulted in surgical treatments that have become refined over the past 50 years. In 2003, a specialized consensus panel published guidelines formally recommending septal myectomy as the gold standard therapy for those patients with symptomatic obstructive HCM refractory to medical management [36]. This was restudied more recently in 2011 by the ACCF/AHA Consensus panel report, which further reinforced the importance of surgical therapy [37].

It is important to remember that the majority of patients with HCM are treated medically, which may include the use of beta-blockers, verapamil, or disopyramide [38–41]. Despite this treatment, approximately 10% of patients with obstructive HCM will continue to have symptoms, which may include chest pain, dyspnea, syncope, or exercise intolerance. Patients with obstructive HCM and persistent symptoms despite medical management with a resting or provoked gradient of >50 mmHg should be referred for septal myectomy [36, 37].

Multiple large retrospective studies have reported long-term data and demonstrated excellent outcomes after septal myectomy [28, 43–51] (Table 23.3). Yet myths about surgical myectomy such as surgical risk, the potential for ventricular septal defect (VSD), and the need for postoperative pacemaker implantation still exist [52]. Regional referral patterns are highly influenced by knowledge and biases regarding therapy. The absence of formal randomized trials for surgical myectomy due to practical and ethical issues complicates definitive answers regarding survival benefits [53].

Operative Mortality

Operative mortality and the risk of serious complications influence referral for treatment and are required knowledge when counseling patients. During the early years of septal myectomy, operative mortality of 2.9–6.0% was reported [42–46]. As techniques have advanced, the risk of surgery in the current era has decreased significantly. This marked improvement is a result of many factors: better understanding of the disease, focused use of intraoperative echocardiographic guidance, improved myocardial protection, and advances in postoperative care. Recent data from experienced centers, as summarized in Table 23.1, demonstrates an overall mortality for isolated myectomy in high-volume centers of 0.0–0.8% [28, 32, 47–51].

Significant mortality predictors reported by the Toronto group include age > 50, female gender, preoperative atrial fibrillation, concomitant coronary bypass grafting (CABG), and preoperative left atrial size of 46 mm or greater [48] (Table 23.4). Female gender has specific correlations in HCM surgery including underrepresentation, diagnosis at an older age, and delays in diagnosis that may make the risk greater for women [54]. After surgery, they have lower functioning status and a higher risk of cardiovascular events and death [48]. It has been suggested that women may have a more aggressive form of the disease or be more prone to disease progression [48, 54, 55]. A more recent study of 699 patients at the Cleveland Clinic looked specifically at predictors of long-term survival and found that age > 50 and postoperative atrial fibrillation were independent predictors of lower long-term survival by multivariate analysis [51].

Conflicting literature exists regarding the addition of concomitant surgery that initially was found to increase the mortality of myectomy by up to threefold [46]. Although these additional procedures have been identified as univariate risk factors for surgery, they do not portend a significantly shorter survival than those with myectomy alone and are not considered a significant risk factor after multivariate analysis [51, 56]. Recent studies have shown no significant difference between short- and long-term survival in the two cohorts

Table 23.4 Risk factors for septal myectomy [48]

Age > 50
Female gender
Preoperative atrial fibrillation
Left atrial enlargement > 46 mm
Concomitant coronary artery bypass grafting

Table 23.3 Mortality and long-term survival after septal myectomy

Year	Series	Patients (*n*)	Operative mortality (%)	5-year survival (%)	10-year survival (%)
1993	Schulte et al. [43]	364	2.9	92	88
1995	Heric et al. [44]	178	6	86	70
1996	Robbins and Stinson [45]	158	3.2	5.4	71.5
1998	Schonbeck et al. [46]	110	3.6	93	80
2005	Ommen et al. [47]	289	0.8	96	83
2005	Woo et al. [48]	388	1.5	95	83
2007	Dearani et al. [49]	1134	0.8	N/A	N/A
2012	Balaram et al. [28]	132	0.0	99	92
2013	Desai et al. [51]	699	0.0	N/A	N/A

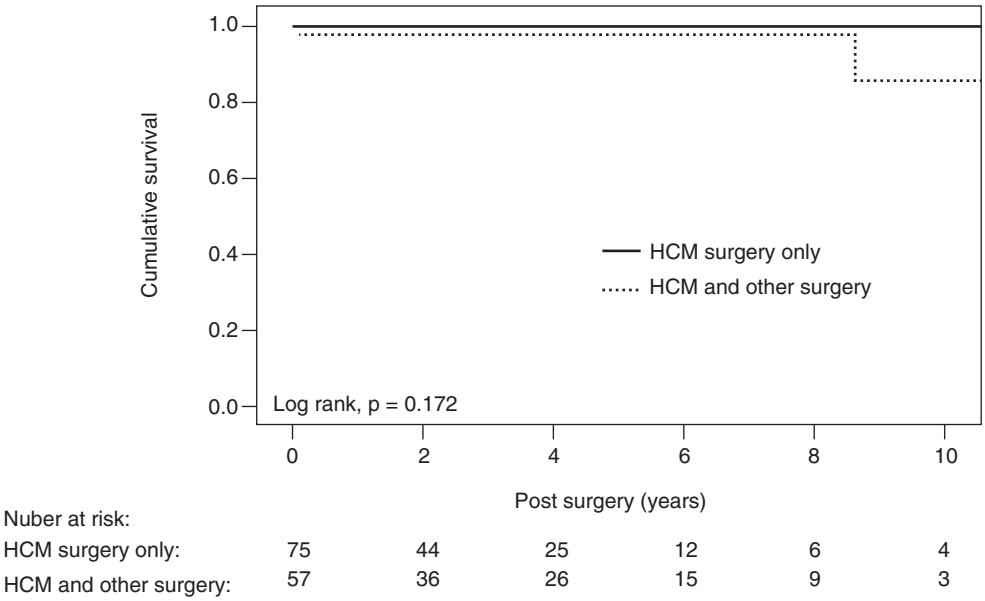

Fig. 23.5 Survival free from all-cause mortality for patients who underwent operations for hypertrophic cardiomyopathy (HCM) only ($n = 75$) and those who underwent operations for HCM and a concomitant cardiac procedure ($n = 57$). No statistically significant difference is seen for short- and long-term survival. (Permission obtained from Elsevier Ltd. Balaram et al. [28])

(Fig. 23.5). While recent mortality for isolated myectomy ranges from 0.0% to 1.5% [28, 47–51], in other studies the addition of concomitant procedures can increase this risk to 2.1–3.4% [48, 49]. In the current era, many patients are older with complex pathology, and it is accepted that there will be a slight difference in risk between isolated myectomy and the addition of concomitant procedures.

Short- and Long-Term Outcomes

Septal myectomy results in both immediate and long-term gradient reduction in obstructive HCM. Immediately after myectomy, postoperative gradients of 0–10 mmHg are expected in the operating room and remain low over time [36]. At many centers, resting and dobutamine-stimulation (or isoproterenol) gradients are checked intraoperatively to assess for the presence of hemodynamic significance. Patients may require additional myectomy for significant gradients with stimulation persistent systolic anterior motion (SAM) and/or mitral regurgitation (MR). Gradients can be expected to fall in the first 3 months after myectomy and may continue to decline [50]. Long-term follow-up confirms gradients of <30 mmHg in up to 98% of patients [28, 48–51].

Improvement in heart failure symptoms post-myectomy is of critical importance. Left ventricular outflow tract obstruction (LVOTO) has been shown to be a strong predictor of heart failure progression and death, and an independent risk factor for HCM-related mortality [57, 58]. Surgically managed patients undergo immediate relief of obstruction and show a reversal of heart failure progression and significantly better HCM-related survival [47] including those having no or mild symptoms [57].

From a physiologic perspective, the relief of obstruction results in a clear decrease in wall stress, left ventricular end-systolic and diastolic pressures, and ischemia [18, 36, 47, 48, 59–61]. After myectomy, improvements of left ventricular end-systolic and end-diastolic pressures occur in >90% of patients [9]. A decrease in the risk of atrial fibrillation and in the size of the left atrium has also been reported and is likely secondary to the improvement in chronic mitral regurgitation after relief of obstruction [48, 59, 61, 62].

Mitral regurgitation, as associated with obstructive HCM and SAM, improves after septal myectomy. The change from the Morrow procedure to Messmer's extended myectomy reduced the appearance of residual mitral regurgitation first described in the literature [63]. Some have argued that extended myectomy alone is adequate for the resolution of SAM [64]. However, the heterogeneity of HCM presents multiple variables in terms of mitral valve pathology. Mitral abnormalities may be secondary to Venturi forces with obstruction alone [65, 66], the pushing force of flow [18], or be related to mitral leaflets with or without papillary muscle abnormalities [13, 14, 67]. Obstruction has frequently been described secondary to SAM without septal hypertrophy of any degree and with the presence of extreme elongation of either the anterior leaflet or both the anterior and posterior leaflet alone. It is imperative to understand that both intrinsic and functional mitral valve abnormalities may be present and contributing to obstruction. The addition of required mitral valve surgery has been shown in multiple studies with excellent results [12, 28, 34, 51].

Marked clinical improvements of heart failure symptoms are seen with relief of obstruction that correlate with physiologic changes. After myectomy, patients report improvements in quality of life in all large series [28, 46–51].

More than 90% of patients will improve at least two functional classes after surgery [32]. In multiple studies, advanced NYHA classes comprise <10% of patients in the post-myectomy population [32, 47, 51].

Prognosis and Survival Benefit

The variability of HCM in terms of genetic penetration and clinical presentation can complicate the issue of prognosis. In early publications, the referral bias of symptomatic patients relegated to experienced tertiary care centers translated into a reported annual HCM-related mortality rate as high as 3–5% [68, 69]. With time, variability in clinical presentation has made clear that up to two-thirds of individuals with HCM have either minimal or no disability [41]. With these cohorts included, the annual mortality rate of HCM is now estimated to be approximately 1%, similar to that of the general adult population [38, 70, 71]. Without prospective randomized trials, the question of whether myectomy improves long-term prognosis has been delegated to large retrospective reviews.

What is known is that significant obstruction affects both morbidity and mortality due to the supply-demand mismatch that occurs in the face of increased ventricular wall tension, hypertrophied myocardium, and myocardial ischemia [58, 72, 73]. High gradients decrease left ventricular ejection velocity and flow in obstructive disease [65, 74]. A resting LVOT gradient >30 mmHg results in a fourfold higher risk of heart failure, stroke, or death [58].

Septal myectomy, with relief of obstruction, is an independent predictor of survival. Multiple studies have shown strong evidence that surgical relief of obstruction improves long-term survival [47, 49, 51, 75]. Data shows that those patients who undergo myectomy have a significantly lower risk for all-cause mortality and HCM-related death compared to those patients with obstruction who did not undergo surgery [58] (Fig. 23.6). Follow-up data up to 15 years after surgery shows excellent survival that has been shown when age- and gender-matched to be equivalent to the general population [47].

Data also suggests a decrease in the incidence of sudden cardiac death after myectomy although the risk is not completely abolished [47]. The need for placement of a ICD must be considered separately from the need for myectomy, and based on the individual family history, previous arrhythmias, and the presence of massive LVH [72, 76]. Myectomy has been shown to be particularly beneficial for patients of younger age who do not have significant comorbidities that could affect their survival [47]. Referral, patient selection, and bias can make these data hard to interpret, particularly when comparing to nonsurgically treated patients who have comorbidities that may contribute to a worse prognosis regardless of treatment. One study did demonstrate the incidence of appropriate ICD firing occurred at a rate of 0.24% per year after myectomy as opposed to 4.5% per year in a nonsurgical group ($p = 0.004$) [77]. This strong presumptive evidence is encouraging but must be tempered with the knowledge that HCM is a disease of the myocardium, and relief of obstruction alone will not change the underlying substrate.

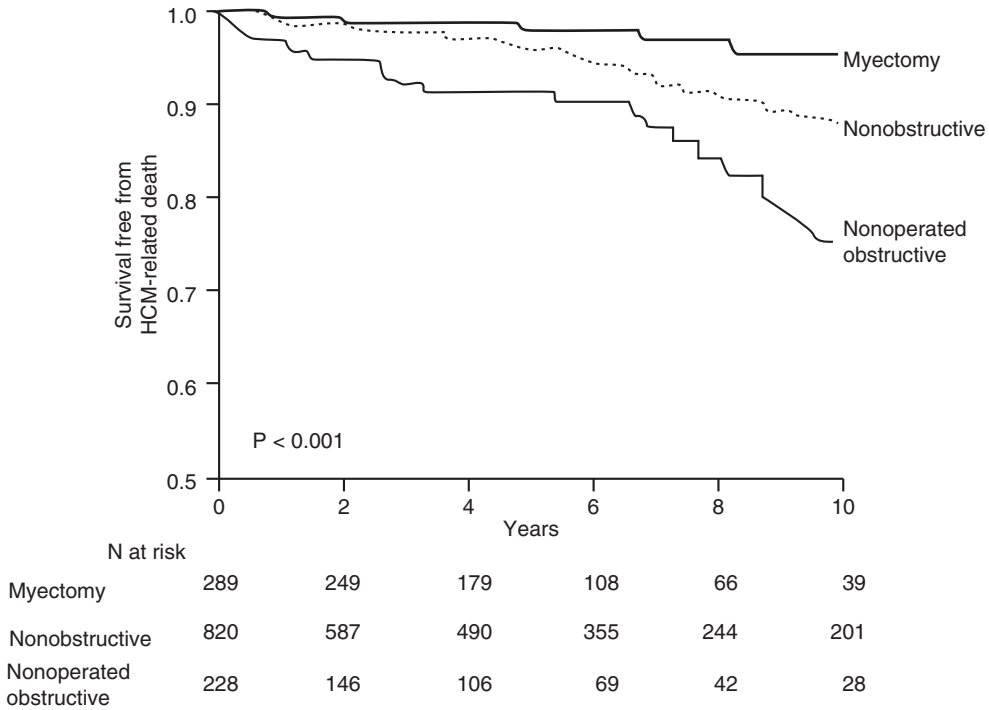

Fig. 23.6 Survival free from hypertrophic cardiomyopathy-related death among patients in three hypertrophic cardiomyopathy (HCM) subgroups: surgical myectomy ($n = 289$), nonoperated with obstruction ($n = 228$), and nonobstructive ($n = 820$). Overall log-rank, $p = 0.001$; myectomy versus nonoperated obstructive hypertrophic cardiomyopathy, $p = 0.001$; myectomy versus nonobstructive hypertrophic cardiomyopathy, $p = 0.01$. (Permission obtained from Elsevier Ltd. Ommen et al. [47])

Complications

The morbidity of septal myectomy has, along with mortality, decreased over recent years. Overall, significant complications can be expected in <2% of all patients undergoing septal myectomy [32]. Common complications include postoperative atrial fibrillation with an incidence of up to 30%, similar to other cardiac surgeries [28, 48, 50]. Myectomy or postoperative edema that occurs near the location of the conduction tissue within the septum may result in heart block requiring permanent transvenous pacing. The septal area of concern is at the base of the ventricular septum to the right of the nadir of the right coronary cusp. The requirement for a postoperative pacemaker ranges from 1% to 7% and is most common in patients with pre-existing conduction abnormalities such as a complete right bundle brand block [28, 32, 47, 48, 49, 50].

A potentially devastating complication of myectomy is an iatrogenic postoperative ventricular septal defect (VSD). The area most commonly injured is the lateral septum inferior to the right coronary cusp and close to the annulus of the aortic valve. Injury may occur if too much septum is removed close to the annulus of the aortic valve; it may be more common in those patients with a relatively thin septum (<2.0 cm). This area of the septum is not involved with the pathogenesis of obstruction and should theoretically be left alone during the myectomy. On the other hand, during an extended myectomy procedure, if muscle is resected too far on the posterior septum, a VSD can be inadvertently created here. This can occur even if an appropriate amount of muscle is resected in patients with a lesser degree of myocardial fibrosis. When full cardiac function is restored after the termination of heart-lung bypass, the muscle in this area can shred and tear. The reported incidence of VSD ranges from 0.7% to 2.0%. This has been treated with patch repair of the septum with good results [28, 48, 56]. Repair of posterior VSDs is difficult and usually requires access through the right atrium and the tricuspid valve.

Other complications include cerebrovascular accidents (0.6–1.9%) that are typically the result of embolic events [50, 51]. Pericardial effusion or late pericardial tamponade can occur in the postoperative period. This may be seen particularly in those patients who require anticoagulation such as for chronic atrial fibrillation or concomitant MAZE procedures (1.0–2.3%) [28, 50].

Rarely, patients may present with recurrent LVOTO after myectomy. The incidence of this, based on data from large centers, is approximately 2.0–3.4% [50, 51, 78]. The most common mechanisms for recurrent symptoms are incomplete myectomy, midventricular obstruction, or anomalous mitral valve anatomy [78].

The specific circumstance of septal myectomy that occurs after unsuccessful alcohol septal ablation (ASA) has been associated with higher complication rates including operative mortality (13%), postoperative arrhythmias, and PPM/ICD implantation (36%) [79]. However, this group has also had good relief of symptoms with gradient reduction after myectomy and could benefit greatly from surgical intervention. Although this data is from a small series, it is important to note that these patients are unique and worthy of increased vigilance in the postoperative period.

Concomitant Surgery

CABG

Coronary artery bypass grafting (CABG) is the most common concomitant surgical procedure in these patients, performed in 10–15% of individuals undergoing septal myectomy [28, 47–51]. As older patients are now referred for surgery, the need for CABG may increase in the future. HCM patients with coronary artery disease have other sources of myocardial ischemia added to the supply and demand mismatch from the increased wall stress that may adversely affect outcomes. As a result, concomitant CABG has been found to be a risk factor for mortality [48].

The Cleveland Clinic group showed that obstructive CAD and concomitant surgery are both risk factors by univariate analysis but have not been shown to increase risk for myectomy by multivariate statistics [51]. Minami et al. studied concomitant procedures compared to isolated myectomy and found a slight increase in early mortality that was not statistically significant (2.0 vs. 1.3%) [56]. This was accompanied by divergent Kaplan-Meier curves for long-term survival that also did not reach statistical significance (80 vs. 87%) [56]. Overall, good long-term results can be expected with septal myectomy in terms of gradient reduction, clinical improvement, and long-term results, even if concomitant CABG is performed.

Arrhythmia Surgery

The association between obstructive HCM and atrial fibrillation is well-described [3, 80–84]. Increases in left ventricular end-diastolic pressures in the setting of diastolic dysfunction result in increased left atrial size and places patients with HCM at risk of atrial fibrillation. Chronic mitral regurgitation, systolic motion, and disease severity also play a role. Surgical myectomy alone has not definitely been shown to decrease atrial fibrillation and left atrial size [36]. Most experienced centers therefore add concomitant arrhythmia surgery to myectomy for patients with preoperative atrial fibrillation. Although the lesion set for HCM patients in particular is not well described, many groups perform standard pulmonary vein isolation with radio frequency or cryo-ablation, while others use the biatrial Cox-Maze II or IV [32, 85]. Left atrial appendage ligation is

typically always performed with intraoperative ablation procedures. These procedures can be performed with no significant increase in operative risk [85].

With myectomy alone the Toronto group showed that nearly half (46%) of patients who were in preoperative AF remained in normal sinus rhythm (NSR) in the postoperative period, with age and left atrial size playing a significant role in these patients. Of those patients who were in NSR preoperatively, up to 21% developed late AF [48]. After myectomy, patients who remained in sinus rhythm showed a decrease in left atrial diameter versus those that developed new postoperative AF who had no significant change in LA size [48, 86]. Although atrial fibrillation may present several years after surgery, it may perhaps be considered as one of the contributing indications for myectomy in the future.

Mitral Valve Surgery

As previously stated, mitral valve abnormalities and HCM have a strong correlation [13, 14, 18, 67, 87]. Mitral valve repair or replacement may be required along with septal myectomy. Historically, MVR was considered an alternative treatment to myectomy. Mitral valve repair is currently much preferred to avoid problems of chronic anticoagulation such as embolization or bleeding, increased morbidity, and the potential need for reoperation in young patients. Anterior mitral leaflet plication techniques have been used with good success, but intrinsic mitral valve disease may require more complex repairs such as chordal transposition, synthetic chord placement, annuloplasty rings, or other techniques [28, 32, 34, 35]. Intrinsic calcified disease of the mitral valve, such as rheumatic disease, is the most common reason for mitral valve replacement [6, 34]. Other indications include previous attempted myectomy congenital mitral valve abnormalities and septal measurement of less than 2 cm [34, 51]. A recent study found that up to 23% of patients may require dedicated mitral valve surgery at the time of septal resection [51]. The addition of separate mitral valve surgery as a concomitant procedure does increase the risk of surgery to approximately 4.6% [34].

Future Directions

The predominant goals for HCM surgery over the next several years are to continue to gain understanding and spread knowledge regarding the complex genetics and pathophysiology involved in this disease process. It is important that the outcomes in both low- and high-volume centers remain good and that more surgeons are educated on this specialized technique in order to increase patient access to care. Data regarding late survival and the risk of sudden death after surgery will continue to be evaluated and weighed against data from less-invasive treatments. Evaluation of information from large multicenter databases may expand indications for surgery to those who are asymptomatic with obstructive gradients or others with complications such as atrial fibrillation. Technical advances for difficult problems such as midventricular and apical obstruction will continue to evolve. Advances in pharmacologic treatment and ultimately the manipulation of the genome encoding for the muscle fiber disarray that leads to hypertrophy and obstruction may eventually make surgery obsolete. But until then, surgical management will continue to strive for further enhancements to improve results for all the variations of pathophysiology leading to obstruction.

Clinical Pearls

- Surgical strategies must be uniquely tailored to match the particular morphology causing obstruction.
- Although extended septal myectomy may be adequate in many patients for relief of mitral regurgitation, intrinsic abnormalities of the mitral valve must be addressed at the time of initial surgery.
- The use of dobutamine or isoproterenol in the operating room to stimulate gradients is helpful to determine adequacy of septal resection.
- Mitral valve replacement should be considered mainly for severe primary mitral valve pathology such as rheumatic disease that is not amenable to repair.
- Septal thickness of <1.8 cm needs to be approached carefully with a complete evaluation and precise plans for resection, so as to minimize the risk of ventricular septal defect. Mitral valve plication may be particularly beneficial for these patients.
- When there is minimal septal thickening (<1.8 cm), the anterior, posterior, or both mitral leaflets are usually severely elongated. Resection of the residual leaflet portion is another option to obliterate the outflow tract gradient. Careful assessment is necessary so as not to disrupt the coaptation zone of the leaflets which would cause central mitral insufficiency.
- A transapical approach may be considered for the difficult problem of midventricular or apical obstruction, or apical aneurysm.
- The need for placement of an ICD in the postoperative period should be individualized based on patient risk.

Questions

1. A 60-year-old man undergoes an uneventful septal myectomy and requires pacing while separating from bypass. The following day he is found to have third-degree heart block. What preoperative factor confers the highest risk for permanent pacemaker after septal myectomy?
   A. AICD placement within 6 months prior to surgery
   B. Septal thickness less than 20 mm on transesophageal echocardiogram
   C. Right bundle-branch block on ECG
   D. Paroxysmal atrial fibrillation
   E. Family history of HOCM associated sudden death

   Answer: C. The incidence of permanent pacemaker requirement after septal myectomy is about 2–3%. In patients with relatively modest septal thickening, it may be advantageous to resect a shallow but broader segment of septum and even some posterior septum. That may predispose to complete heart block. However, since left bundle-branch block is almost always a consequence of septal myectomy, if the patient has a pre-existing right bundle-branch block, complete heart block and a requirement for a permanent pacemaker is almost a certainty.

2. A 54-year-old woman with LVOT gradient of 60 mmHg and septal thickness of 1.9 cm undergoes septal myectomy and resection of excess tissue at the base of her anterolateral papillary muscle. While separating from bypass, TEE demonstrates a significant left to right shunt. What is the most likely site of injury?
   A. The distal point of septal resection
   B. Below the right coronary cusp of the aortic annulus
   C. Base of the anterolateral papillary muscle
   D. Proximal aspect of myectomy along the anterior leaflet of mitral valve
   E. Posterior septum at attachment to free left ventricular wall

   Answer: B. Although it is possible to disrupt the ventricular wall with resection of muscle at the base of the anterolateral papillary muscle, that would lead to a free wall rupture into the pericardium. On the other hand, if the septum is minimally thickened and a broader myectomy is performed, it may extend into the membranous portion of the septum under the right coronary leaflet which is invariably very thin. This is the most common location for a VSD.

3. A 58-year-old man arrives in the recovery room following septal myectomy and has a new left bundle-branch block with heart rate 70 and blood pressure 90/40 mmHg, CVP 5, PA 25/15, and cardiac index 1.6. What is the best approach to initial management?
   A. Contact electrophysiology for urgent permanent pacemaker.
   B. Bedside echocardiogram to assess for ventricular septal defect.
   C. Initiate inotropic support with dobutamine.
   D. Trial of pacing via temporary wires at rate of 90.
   E. Administer 1 L crystalloid and initiate phenylephrine drip.

   Answer: E. Patients with HCM suffer with varying degrees of diastolic dysfunction due to myocardial fibrosis. It is not uncommon to have a low cardiac output state in the immediate post-op period. It is critical not to administer any inotropic support as this will further limit ventricular filling. Likewise, pacing at a faster rate would have the same effect. The PA pressure is too low to be consistent with a VSD. These patients almost invariably require higher filling pressures, especially in the immediate post-op period.

4. A 54-year-old woman with history of persistent atrial fibrillation and left atrial diameter of 52 mm and septal thickness of 20 mm. Which of the following is not a risk factor for mortality after isolated septal myectomy?
   A. Female gender
   B. Age 54
   C. Preoperative atrial fibrillation
   D. LA diameter 52 mm
   E. Septal thickness 20 mm

   Answer: E. Age, gender, and atrial fibrillation are all risk factors for mortality in open-heart surgery in general. A dilated left atrium is usually the consequence of the atrial fibrillation. Although modest septal thickening may seem like a risk factor for creation of a VSD, that has not been shown to be true.

5. Which of the following best describes the role of AICD for patients undergoing septal myectomy?
   A. AICD placement is recommended in all patients with EF <60% at time of septal myectomy.
   B. After septal myectomy, AICD firing rate decreases to <0.5% per year.
   C. Septal myectomy obviates the need for subsequent AICD placement.
   D. Most AICD should be explanted at time of septal myectomy.
   E. Patients with preoperative AICD have a threefold increase in the risk of postoperative VSD complicating septal myectomy.

Answer: B. The need for AICD in patients with HCM is decided by predetermined criteria. Recent follow-up information would suggest that although there is a decrease in the firing of an AICD after a properly performed surgical myectomy, because myocardial fiber disarray persists in the remainder of the muscle, ventricular tachyarrhythmias can still occur with deadly consequences. Therefore, the current recommendation is to keep the AICD in these patients who fulfill criteria for their original implantation. A LVEF of <60% is not criteria, and there is no relationship between AICD placement and subsequent VSD.

6. A 60-year-old man with LVOT gradient of 60 mmHg, septal thickness of 26 mm, and class III heart failure undergoes septal myectomy. Five years later he is seen in follow-up with an LVOT gradient of 15 mmHg and class I heart failure. Which of the following is not an expected long-term benefit following septal myectomy compared to medical treatment?
   A. Decreased risk of atrial fibrillation and left atrial size
   B. Decrease in risk of sudden death to age- and sex-matched controls
   C. Improvement in functional heart failure class
   D. LVOT gradient <30 mmHg
   E. Improved survival compared to asymptomatic or minimally symptomatic HOCM patients

   Answer: B. A properly performed septal myectomy with resolution of a resting and provocable gradient to near normal gives the patient a normal life expectancy. It would not improve the life expectancy beyond age- and gender-matched controls, nor would it eliminate the risk of sudden death from a ventricular tachyarrhythmia. That risk does, however, match a control population.

7. A 39-year-old woman undergoes septal myectomy and plication of the anterior leaflet of her mitral valve for LVOT gradient of 65 mmHg with septal thickness of 24 mm. A TEE is performed during weaning from bypass. Which of the following scenarios would be the least likely to prompt further investigation?
   A. New onset mild tricuspid regurgitation
   B. Inotrope-provoked gradient of 30 mmHg
   C. Turbulent LVOT flow
   D. 2+ mitral regurgitation
   E. Left to right shunt at level of midventricular septum

   Answer: A. After septal myectomy, there should no longer be a resting or provocable gradient above 20 mmHg. Mitral insufficiency should also not be tolerated since that would be a consequence of either an inadequate operation or damage to the supporting mitral valve substructure. A VSD would also not be tolerated. Mild tricuspid insufficiency, on the other hand, may be a consequence of some RV dysfunction secondary to heart-lung bypass and usually is self-limiting in the postoperative period.

8. Which of the following is correct regarding anterior mitral leaflet plication during septal myectomy?
   A. Most successful when redundant anterior leaflet height is less 20 mm in length.
   B. Vertical plication is more technically challenging but allowed for greater reduction in postoperative SAM.
   C. Horizontal plication preserves the zone of coaptation between leaflets.
   D. Easiest to perform prior to distortion of anatomy resulting from septal myectomy.
   E. Contraindicated in patients undergoing concomitant coronary artery bypass grafting.

   Answer: C. Although vertical plication has been described to be a useful tool in the surgical treatment of HCM, it has also been found to cause central mitral regurgitation in some cases due to malcoaptation of the leaflets. Horizontal plication is most easily accomplished after the myectomy, since visualization in the LV chamber is greatly improved. The anterior leaflet is usually in excess of 3.5 cm in length in cases where plication would be useful.

9. A 58-year-old man has severe midventricular obstruction from septal hypertrophy. Which of the following is correct regarding approach to this lesion?
   A. Apical myotomy is a useful approach in patients with apical aneurysm.
   B. Using a ventriculotomy approach, the septal wall can easily be distinguished from papillary muscles by identifying cordal attachments.
   C. Midventricular obstruction cannot be fully resected via aortotomy.
   D. Multiple layers of septal resection allows for the most accurate depth of resection.
   E. Successful resection of midventricular hypertrophy prevents SAM without the need for additional mitral intervention.

   Answer: A. Although it is possible, it can be extremely challenging to resect adequate septal muscle in cases of midventricular obstruction through an aortotomy. If an apical aneurysm is present, it is helpful to approach these resections from both the apex and the aortotomy. In the approach through the apex, unless the aneurysm is very large, differentiating the septum from hypertrophied papillary muscle can be difficult. It is useful to do as much of a resection as possible through the aortotomy, then open the apex, and locate

the site of resection and complete it apically. In general, patients with midventricular obstruction do not have SAM.

10. Which of the following patients would least likely benefit for septal myectomy?
    A. A 50-year-old man with resting gradient 48 mmHg and recurrent syncope on disopyramide
    B. A 60-year-old man with provoked gradient of 45 mmHg and resolution of chest pain on verapamil
    C. A 72-year-old woman with provoked gradient of 55 mmHg and persistent dyspnea on metoprolol
    D. A 26-year-old woman with exercise intolerance and resting gradient of 50 mmHg
    E. A 45-year-old man on verapamil with intermittent chest pain that resolves with rest and a provoked gradient of 60 mmHg

    Answer: B. Patients undergoing surgical management for HCM must fulfill certain criteria. They must have a resting or provocable gradient of at least 50 mmHg, and they must be symptomatic. Control of symptoms and gradient with medication is not an indication for surgical management.

11. Known mitral valve anomalies in HCM do not include:
    A. Anomalous papillary muscles
    B. Elongated anterior mitral leaflet
    C. Elongated posterior mitral leaflet
    D. Thickened or fibrotic leaflets
    E. Cleft leaflets

    Answer: E. A wide variety of mitral valve abnormalities can be present along with septal hypertrophy that can contribute to obstruction. Although some advocate for minimizing mitral valve manipulation in the surgical treatment of obstruction, some patients have such minimal septal hypertrophy that without addressing the mitral valve pathologies, obstruction and mitral regurgitation are likely to persist to a significant degree. Cleft leaflets, however, are not part of this pathology.

12. The "extended myectomy" includes all of the features except:
    A. Wide resection of the basal septum
    B. Shaving of papillary muscle heads
    C. Removal of lateral attachments
    D. Transaortic exposure
    E. Simple trough-like removal of septum

    Answer: E. The classic "morrow" myectomy traditionally consists of a trough resection roughly 1 cm wide, 1 cm deep, and about 3–4 cm long. As our understanding of the pathophysiology of obstruction has progressed, it is clear that a large proportion of patients require a wider and more extensive resection in order to allow for a more linear stream of outflow, thereby minimizing the risk of the "pushing force of flow" that catches the anterior leaflet of the mitral valve and propels it into the outflow tract.

13. Absolute indications for surgery for HCM include:
    A. Enlarged LA and atrial fibrillation
    B. Persistent symptoms despite maximal medical therapy
    C. Gradient >30 mmHg
    D. Severe mitral regurgitation
    E. Moderate aortic insufficiency

    Answer: B. There are clear published indications for surgical management of outflow tract obstruction in the treatment of hypertrophic cardiomyopathy. There must be a gradient, either at rest or on provocation of >50 mmHg, and symptoms.

14. Absolute proven benefits of septal myectomy include:
    A. Improved quality of life
    B. Improved ejection fraction
    C. Prevention of arrhythmias
    D. Better long-term survival
    E. Prevention of sudden death

    Answer: A. Although mid- to long-term follow-up would suggest that a well-performed surgical septal myectomy dramatically lowers the risk of sudden death, because muscle fiber disarray persists in the rest of the unresected myocardium, a risk of sudden death persists. These patients, in general, all have normal ejection fractions already, and unless a concomitant ablation procedure is indicated and performed, septal myectomy on its own does not limit atrial fibrillation.

15. The most common complication after myectomy surgery is:
    A. Death
    B. VSD
    C. Pacemaker
    D. Atrial fib
    E. Stroke

    Answer: D. The risk of permanent pacemaker implantation after septal myectomy varies from 2% to 5% in published reports. Death, stroke, and VSD are extremely rare when myectomy is performed in referral center programs with large volumes. Atrial fibrillation occurs after septal myectomy in roughly the same incidence as any other open-heart surgical procedure – anywhere from 20% to 45%.

16. Common acceptable medications to be used after myectomy for HCM include:
    A. Beta-blockers
    B. Epinephrine
    C. Norepinephrine
    D. Dobutamine
    E. Milrinone

    Answer: A. As these patients already have a degree of diastolic dysfunction from varying amounts of fibrosis and since the ejection fraction is almost always hyperdynamic, any inotrope (epinephrine, norepinephrine, dobutamine) administered in the immediate postoperative period would further limit ventricular filling and cardiac output. The same would be true for a peripheral vasodilating medication (milrinone) which would reduce afterload and promote ventricular emptying. Beta-blockade is usually always necessary after myectomy surgery both to improve ventricular relaxation and limit postoperative atrial fibrillation which tends to be poorly tolerated by HCM patients.

17. Surgical options in the presence of abnormal papillary muscles include:
    A. Resection
    B. Thinning
    C. Repositioning within the left ventricle
    D. Replacement of chordae
    E. Cutting of chordae

    Answer: A. Although a great deal of procedures have been described to aid in moving the anterior leaflet of the mitral valve out of the outflow tract, the papillary muscles themselves cannot be completely resected without ultimately causing prolapse. Accessory attachments, however, can be considered for resection if there are other supporting structures.

18. The main difference between the lateral and horizontal plication of the AML is:
    A. Number of stitches
    B. Location of stiches
    C. Shortening of the leaflet
    D. Postop MR
    E. Long-term changes to the valve

    Answer: C. Both lateral and horizontal plication have been described as successful ancillary procedures to help in gradient reduction in HCM surgery. Whereas lateral plication is thought to limit billowing into the outflow tract, horizontal plication both limits billowing and also shortens the leaflet in the A/P dimension, further limiting the leaflets' ability to have SAM and subsequent obstruction. The number of stiches and location are inconsistent in both cases.

19. All of the following are related to transmitral resection techniques except:
    A. Can be done minimally invasively
    B. Require AML dislocation and resewing
    C. Risk long-term changes to AML
    D. Provide exposure to septum
    E. Can cause aortic insufficiency

    Answer: E. Some have advocated transmitral access to the septum for myectomy and in small series published to date have shown good results. Others have not adopted this approach because septal access is relatively limited, and the current extended myectomy would be somewhat limited as a consequence. Additionally, this procedure requires dislocation of the entire anterior mitral leaflet. This has apparently not been a problem in short-term follow-up. However, given the relative young age of most patients, the concern remains that there may be long-term sequelae to this degree of manipulation of the AML. Since there is no transaortic access, there should not be any complications with the aortic valve in this approach.

20. Large retrospective studies have suggested that risk factors for HCM surgery include all of the following except:
    A. Women
    B. Age > 50
    C. Atrial fibrillation
    D. Concomitant surgery
    E. Mitral regurgitation

    Answer: E. As is known in most other open-heart procedures, age, female gender, multiple procedures, and atrial fibrillation all increase the risk of surgery. Since almost all of these patients (HCM) have mitral insufficiency, that would not be an additive risk factor.

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Alcohol Septal Ablation: Technique and Outcome

24

Paul Sorajja and Sherif Nagueh

Key Points

- Alcohol septal ablation may be considered for patients with drug-refractory, severe symptoms due to obstructive hypertrophic cardiomyopathy.
- While the procedure shares conventional techniques with percutaneous coronary intervention, the outcome of alcohol septal ablation is heavily dependent on appropriate patient selection, longitudinal and multidisciplinary care, and operator and institutional expertise. Alcohol septal ablation should only be performed in specialized centers.
- In selected patients treated at highly experienced centers, the outcome of alcohol septal ablation can approach and match that of surgery. Patients who are young (aged <65 years) appear to have better long-term symptom relief with surgical myectomy, especially those <40.
- In general, most long-term data have not confirmed early concerns of potential proarrhythmic effects. However, due to relative uncertainty, alcohol septal ablation still is not recommended for patients aged <21 years and generally should also be avoided in those aged <40 years.
- The major complication of alcohol septal ablation is pacemaker dependency, which is related to baseline conduction disease. Patients at greater risk of pacemaker dependency are those with left bundle branch block (~50%), while dependency still occurs in patients with a normal electrocardiogram (~6–10%).

Introduction

For patients with drug-refractory symptoms due to dynamic left ventricular outflow tract (LVOT) obstruction in hypertrophic cardiomyopathy (HCM), catheter-based alcohol septal ablation emerged over two decades ago as an effective therapy. Alcohol septal ablation (ASA) entails percutaneous injection of alcohol into one or more septal perforator arteries, leading to a controlled myocardial infarction of the ventricular septum and relief of the dynamic LVOT obstruction [1]. The success of ASA is dependent on appropriate patient selection, operator experience, and clinical expertise, with care delivered in the setting of a center dedicated to the comprehensive and longitudinal care of the HCM patient.

Patient Selection

The therapeutic goal of ASA is to treat symptoms by reducing systolic thickening of the ventricular septum that is responsible for dynamic LVOT obstruction and associated mitral regurgitation in the majority of patients. Patients who may be candidates for the procedure therefore are those with (1) severe, drug-refractory cardiovascular symptoms, which is defined as New York Heart Association class III/IV dyspnea, Canadian Cardiac Society angina class III/IV, or disabling presyncope or syncope; (2) dynamic LVOT obstruction due to systolic anterior motion of the mitral

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valve (gradient ≥30 mmHg at rest or ≥ 50 mmHg with provocation); (3) ventricular septal thickness ≥ 15 mm; (4) no significant intrinsic mitral valve disease; (5) absence of need for concomitant cardiac surgical procedure (e.g., valve replacement, bypass grafting); (6) suitable coronary anatomy; and (7) informed patient consent. In general, patients with severe myocardial hypertrophy (e.g., septal thickness > 25 mm) should not be treated with ASA due to the large doses of alcohol required and more variable outcomes. When obtaining informed consent, a shared decision-making process should be utilized with a comprehensive discussion of all of the therapeutic options, including ASA, medical therapy, and surgical myectomy. In this discussion, it is important to note the gold standard of surgical myectomy, which is associated with relief of symptoms in >90%, an operative mortality of <1%, and life expectancy comparable to the general population when performed on acceptable surgical candidates in experienced centers [2]. Risks of ASA, including pacemaker dependency and other catheter-based complications, should be discussed in detail.

Comprehensive imaging with two-dimensional and Doppler echocardiography is elementary to the ability to appropriately select patients for alcohol septal ablation. In order for the procedure to be effective, LVOT obstruction should be *dynamic*, arising due to systolic thickening of the ventricular septum, and accompanied by systolic anterior motion of the mitral valve at rest or with provocation. Mitral regurgitation associated with dynamic LVOT obstruction is posterior and lateral in direction; the presence of central or anterior mitral regurgitation should raise the suspicion of intrinsic mitral valve disease (e.g., myxomatous degeneration) (Fig. 24.1). In patients with posteriorly directed mitral regurgitation, excessive leaflet tethering from secondary causes (e.g., ischemic cardiomyopathy) should be excluded. For determining the LVOT gradient, particular care should be undertaken to distinguish the Doppler envelope of dynamic LVOT obstruction from that of mitral regurgitation. For challenging cases

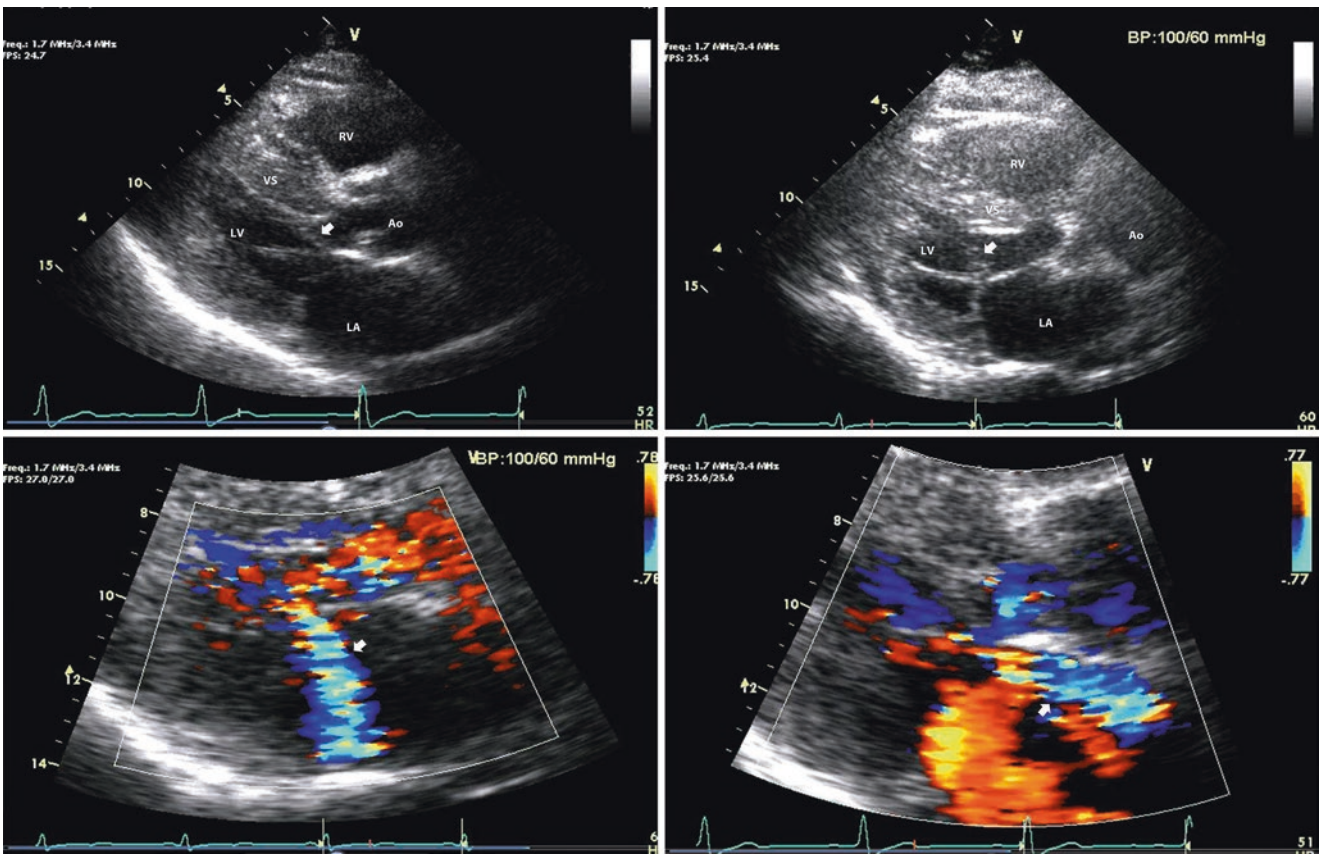


Fig. 24.1 Dynamic left ventricular outflow tract (LVOT) obstruction and associated mitral regurgitation in hypertrophic cardiomyopathy (HCM). *Left*, parasternal long-axis view from transthoracic echocardiography showing dynamic LVOT obstruction with systolic anterior motion of the mitral valve (*top*, arrow) and mitral regurgitation, which is characteristically posterior in direction (*bottom*, arrow). *Right*, parasternal long-axis view from transthoracic echocardiography in a patient with both HCM and degenerative mitral valve disease. In this patient, there also is septal hypertrophy and systolic anterior motion of the mitral valve (*top*, arrow). However, the direction of the mitral jet is anterior, demonstrating the presence of intrinsic mitral disease that would not benefit from alcohol septal ablation (*bottom*, arrow). Ao ascending aorta, LA left atrium, LV left ventricle, RV right ventricle, VS ventricular septum

Table 24.1 National guidelines for patient selection for alcohol septal ablation

Class I
Alcohol septal ablation should be performed only by experienced operators in the context of a comprehensive HCM clinical program and only for the treatment of eligible patients with severe drug-refractory symptoms and LVOT obstruction.
Class IIa
Consultation with centers experienced in performing both surgical septal myectomy and alcohol septal ablation is reasonable when discussing treatment options for eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction.
When surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LVOT obstruction and severe drug-refractory symptoms.
Class IIb
Alcohol septal ablation, when performed in experienced centers, may be considered as an alternative to surgical myectomy for eligible adult patients with HCM with severe drug-refractory symptoms and LVOT obstruction when, after a balanced and thorough discussion, the patient expresses a preference for septal ablation.
The effectiveness of alcohol septal ablation is uncertain in patients with HCM with marked septal hypertrophy (i.e., >30 mm), and therefore the procedure is generally discouraged in such patients.
Class III: Harm
Alcohol septal ablation should not be done for patients who are asymptomatic with normal exercise tolerance or whose symptoms are controlled or minimized on optimal medical therapy.
Alcohol septal ablation should not be done unless performed as part of a program dedicated to the longitudinal and multidisciplinary care of patients with HCM.
Alcohol septal ablation should not be done in patients with HCM with concomitant disease that independently warrants surgical correction (e.g., coronary artery bypass grafting for CAD, mitral valve repair for ruptured chordae) in whom surgery can be performed as part of the operation.
Alcohol septal ablation should not be done in patients with HCM who are less than 21 years of age and is discouraged in adults less than 40 years of age if myectomy is a viable option.

Modified from Gersh et al. [3]

where the severity of the LVOT gradient cannot be determined from echocardiography, an invasive assessment should be performed. During coronary angiography, suitability of coronary anatomy should be determined from studies of not only the left but also the right coronary artery, from which proximal septal perforators occasionally can arise.

National guidelines have outlined specific recommendations for ASA in regard to patient selection, emphasizing the importance of expertise of the operator and institution, preference of the procedure for patients who are either at high risk or inoperable with surgical myectomy, and avoidance in patients who either have massive hypertrophy or who are relatively young (Table 24.1) [3]. In these guidelines, an experienced operator is defined as a person with a cumulative case volume of ≥20 procedures or one who is working in a dedicated HCM program with a cumulative experience of ≥50 procedures. The operator must have comprehensive skills in interpretation of echocardiographic findings of HCM for both planning and execution of the procedure, as well as the postoperative care.

Procedural Technique

ASA may be performed with the patient under conscious sedation or general anesthesia. Some operators elect no sedation to avoid sedation-induced mitigation and/or resolution of gradients, since pre- and post-procedure gradients are often utilized to judge acute procedural success. Conscious or no sedation, with echocardiography performed using transthoracic imaging, has the advantages of expediting patient recovery while avoiding the need for intubation. With conscious sedation, patients may be able to perform the Valsalva maneuver for assessing the dynamic nature of the LVOT obstruction. For general anesthesia, the primary advantage is excellent visualization of the proximal or basal ventricular septum with transesophageal echocardiography, which occasionally can be obscured during contrast echocardiography using transthoracic imaging. General anesthesia also facilitates patient analgesia for discomfort related to the iatrogenic myocardial infarction as well as imaging for accurate transseptal puncture and catheterization. However, general anesthesia may obscure resting and provoked gradients and entails additional risks to the patient.

Temporary Pacemaker Placement

Due to the potential for complete heart block, all patients without prior permanent pacemaker implantation should undergo temporary placement prior to ASA, typically via internal jugular venous access to enable both backup pacing in the postoperative period and patient ambulation. The incidence of pacemaker dependency from alcohol septal ablation varies according to the baseline conduction abnormalities. The area of infarction from septal ablation usually courses from the junction of the anterior and inferior septum, proceeding inferiorly toward the right ventricular side of the ventricular septum [4]. This area frequently contains the right bundle branch, whose block occurs in ~50% of cases of alcohol septal ablation [5]. Thus, for patients with baseline abnormalities of left bundle branch block, severe left axis deviation, or a very wide QRS interval, the rate of pacemaker dependency with septal ablation approaches 50%, prompting consideration of permanent pacemaker placement pre-procedure in such patients. However, permanent pacemaker dependency from complete atrioventricular block still occurs in ~6–10% of patients with a normal electrocardiogram.

Conventional 5 or 6 Fr temporary pacemakers frequently are utilized. These devices, however, have been associated

with cardiac perforation due to their relative stiffness, the potential for movement, and the long dwelling time in the post-procedural care of these patients. Our favored approach has been to use active fixation leads. Importantly, the temporary pacemaker lead should be implanted distal or away from the target site of ablation to ensure continuous capture during and after the septal infarction.

Hemodynamics

While Doppler echocardiography is highly accurate for the calculation of the LVOT gradient in HCM, comprehensive invasive hemodynamic studies should be performed in all patients before and after alcohol septal ablation. These studies determine the acute effectiveness of the procedure, which is a strong predictor of long-term clinical outcome, and if additional septal reduction therapy is needed prior to discharge of the patient from the cardiac catheterization laboratory [6].

LVOT obstruction in HCM is dynamic and exquisitely sensitive to ventricular loading conditions and contractility. The operator should be cognizant of this sensitivity when examining hemodynamic data from both echocardiography and invasive catheterization. Special attention must be given not only to the initial LVOT gradient observed at rest but all dynamic and provocable gradients observed during the procedure (e.g., variation with respiration, post-PVC accentuation, or change with Valsalva maneuver or amyl nitrate inhalation). Notably, even mild variation in intrathoracic pressure during quiet respiration can result in large changes in the LVOT gradient (Fig. 24.2).

Transseptal catheterization is the most accurate method for the invasive evaluation of LVOT obstruction in HCM. In this approach, a balloon-tipped catheter with side holes (e.g., 7 Fr Berman catheter, Arrow International Inc., Reading, PA) and filled with carbon dioxide can be positioned at the left ventricular inflow region. A pigtail catheter is placed retrograde in the ascending aorta for simultaneous sampling for the LVOT gradient. The transseptal approach helps to avoid catheter entrapment, which can be difficult to distinguish from changes in left ventricular pressure that occur due to the highly dynamic nature of LVOT obstruction. The use of a sheath with a sidearm port (e.g., 8 Fr Mullins) for the transseptal access also enables simultaneous recording of left atrial pressure for assessment of concomitant diastolic dysfunction and the impact of mitral regurgitation (Fig. 24.3).

Alternatively, left ventricular pressure can be assessed with a 5 or 6 Fr catheter placed retrograde across the aortic valve. In this technique, a pigtail catheter with shaft side holes should not be used because some or all of the holes will be positioned above the level of subaortic obstruction, leading to erroneous measurements of left ventricular pressure and the LVOT gradient. Catheters that may be used for this purpose are a multipurpose with side holes at the catheter tip or a Halo pigtail. Single end-hole catheters (e.g., Judkins right) are not recommended due to the propensity for entrapment. In the retrograde approach, absence of catheter entrapment should be confirmed with hand contrast injections or demonstration of pulsatile flow from the catheter during disconnection from the tube extenders used for pressure transduction.

Coronary Angiography

The primary goal of coronary angiography is to determine the most appropriate septal artery for the procedure. As stated previously, both the left and right coronary arteries should be studied, as basal septal branches occasionally arise

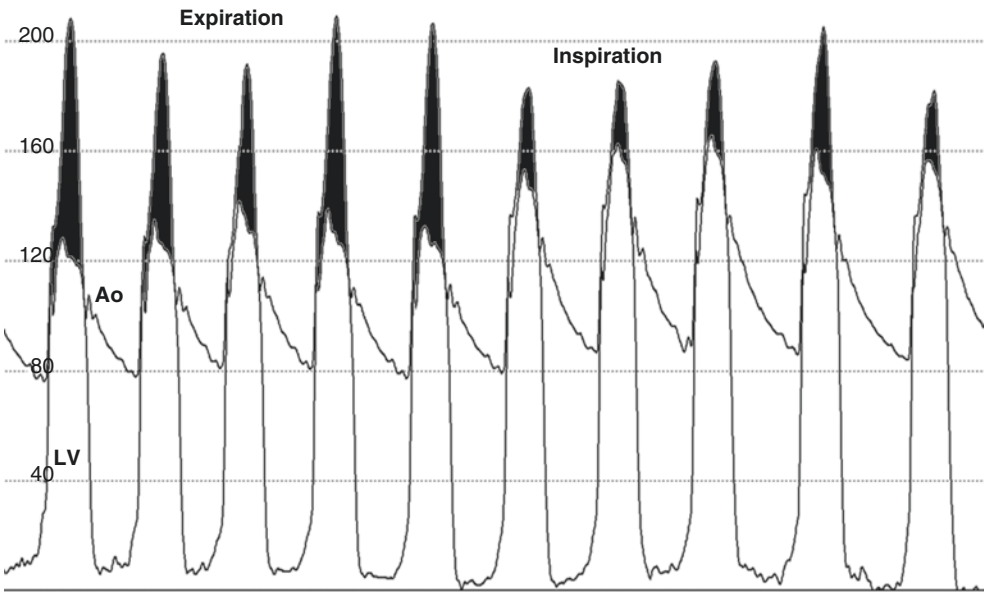


Fig. 24.2 Respiratory variation in left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. These hemodynamic tracings were taken from a patient during quiet respiration. Note the marked variability in the LVOT gradient (shaded), which is greatest during expiration due to the respiratory decrease in ventricular afterload (arrow)

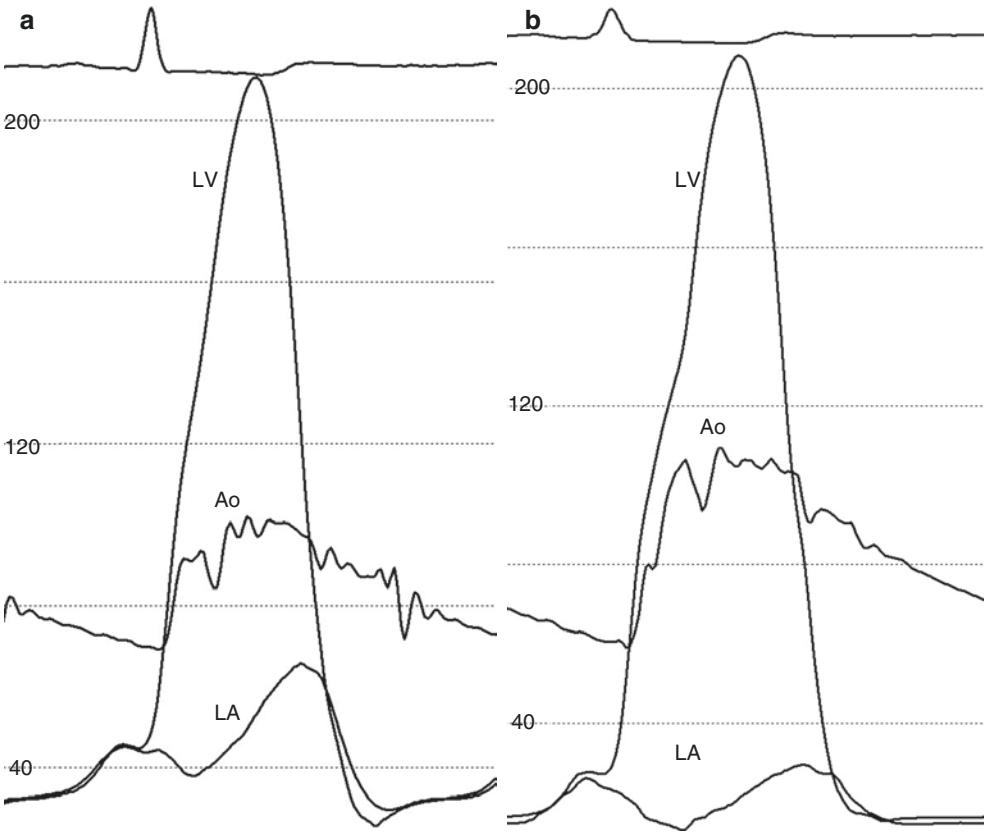


Fig. 24.3 Invasive hemodynamics in hypertrophic cardiomyopathy. Simultaneous recording of left atrial (LA) pressure can be beneficial as the LA pressure may vary despite the presence of severe left ventricular outflow tract (LVOT) obstruction. A, severe LVOT obstruction with high LA pressure. B, severe LVOT obstruction with normal LA pressure

from the proximal right coronary artery. In addition, appropriate septal arteries may arise from the ramus intermedius or diagonal branches. With right anterior oblique views, straight and caudal projections of the left coronary artery help to examine the angulation of the origin of the septal artery, while cranial projections can assist with the length of the vessel. The course of the artery in the ventricular septum should always be demonstrated using the left anterior oblique projections. It is important to note that the length of the septal artery may not be entirely visible on angiography and appear short, but the vessel often can still be wired distally for support. A small dose (100 mcg) of intracoronary nitroglycerin may aid in dilation of the septal perforators for easier visualization and determination of their diameter, although care must be taken to avoid provocation of gradients in the hypovolemic patient. Taken together, the most important factors for choosing a candidate septal perforator artery are location (i.e., proximity to basal septum or myocardial area targeted for ablation), width, and angulation, rather than length of the vessel.

Alcohol Septal Ablation

While a 6 Fr guide can be used to engage the left coronary artery, larger (i.e., 7 Fr) catheters are sometimes recommended to facilitate high-quality contrast injections. These high-quality injections, performed with a well-seated, coaxial guide, are essential to ensure no communication between the septal artery and epicardial vessel during balloon occlusion. Standard procedural anticoagulation (e.g., heparin 70–100 units/kg) is given. Both a primary and a large secondary bend should be placed on the tip of a long 0.014″ guidewire to facilitate entry into the candidate septal artery. The wire should be carried considerably distal to ensure the stiff portion is at the occlusion site, helping to facilitate balloon delivery and minimize balloon movement during the procedure. In some instances, septal wires may be utilized (e.g., Fielder XT). A slightly oversized (e.g., 2.0 mm balloon for a 1.5 mm vessel), short-length (e.g., 9 mm), over-the-wire balloon is placed entirely into the septal artery, typically >10 mm past the ostium, using standard catheter techniques. In shorter septal arteries, this degree of distance from the left anterior descending may not always be possible, however. Oversizing of the balloon allows occlusion of the septal artery at low pressures (3–4 atm), which permits easy injection of material through the wire lumen of the catheter with minimal risk of distal septal artery dissection or trauma. Following inflation of the balloon catheter, the guidewire is withdrawn.

Coronary angiography then is performed to demonstrate no communication between the septal perforator and left

anterior descending artery during balloon inflation in the right anterior oblique view and then repeated to confirm the course of the balloon in the target vessel through the ventricular septum in the left anterior oblique view. Next, using undiluted contrast (approximately 1 ml), angiography of the septal artery through the balloon catheter confirms patency of the vessel for ablation and localization (i.e., no untoward collateralization). This injection should be done gently as a forceful one can result in vessel dissection and opening of distal collaterals, the significance of which can be difficult to determine. Angiographic contrast can be visible on echocardiography for identification of the perfusion bed, though some operators also prefer to additionally inject dedicated echocardiographic contrast (e.g., 0.5 ml Definity or Optison) (Fig. 24.4). Multiple echocardiographic views are used to confirm enhancement of the septal hypertrophy intimately related to LVOT obstruction and the absence of undesirable locations, such as the free walls, thinner areas of the septum more distal or proximal to the target region, right ventricle, moderator band, or papillary muscles (Fig. 24.5). After delineation of the targeted myocardium, 1–3 ml of desiccated ethanol is infused slowly over a period of 3–5 min followed by ~0.3–0.5 cc of slow normal saline flush to eliminate any remaining alcohol in the balloon catheter lumen. In general,

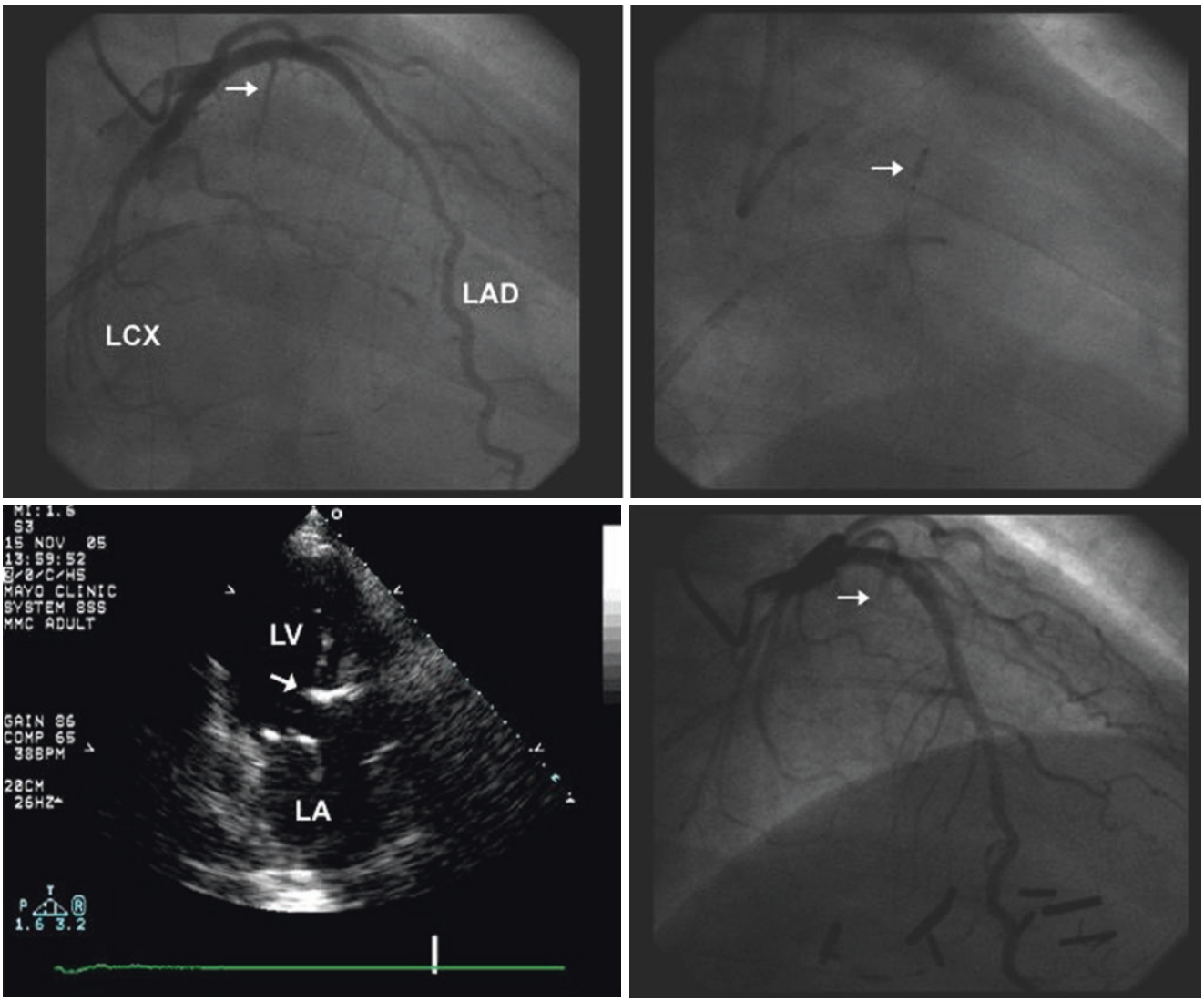
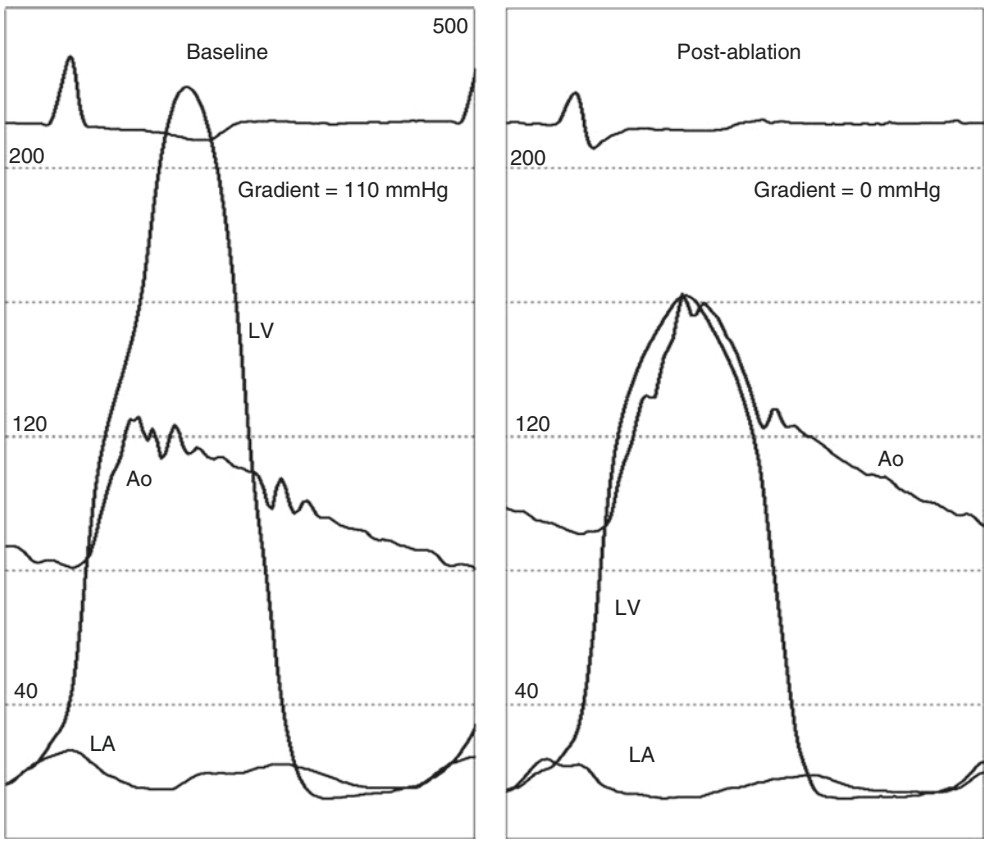


Fig. 24.4 Alcohol septal ablation procedure. *Top left*, left coronary angiography demonstrates a large proximal septal perforator artery arising from the left anterior descending (arrow). *Top right*, echocardiography demonstrates ventricular septal hypertrophy and outflow tract obstruction due to systolic anterior motion of the mitral valve (arrow). *Middle left*, with contrast injection through the septal artery, the myocardium intimately involved with obstruction is highlighted (arrows). *Middle right*, following administration of alcohol, there is obliteration of the septal artery due to infarction. *Bottom left*, baseline hemodynamic study demonstrates a gradient of 83 mmHg across the left ventricular outflow tract. *Bottom right*, following septal ablation, the gradient is 0 mmHg. Ao ascending aorta, LA left atrium, LAD left anterior descending, LV left ventricle, RV right ventricle

Fig. 24.4 (continued)



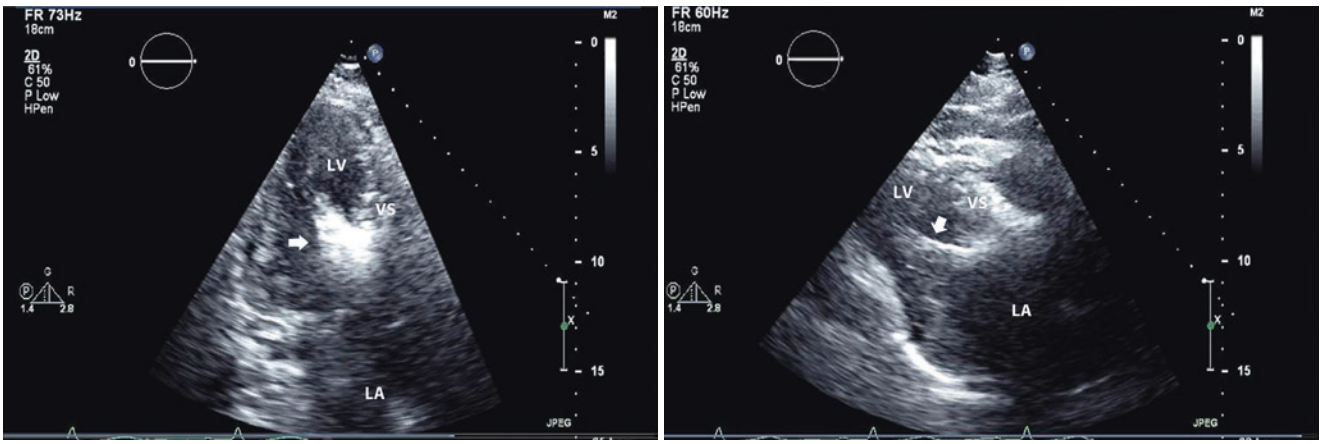


Fig. 24.5 Contrast enhancement of papillary muscles (arrows) in patient with hypertrophic cardiomyopathy during an attempt at alcohol septal ablation. Top, apical long-axis view; bottom, parasternal long-axis view. LA left atrium, LV left ventricle, VS ventricular septum

the dose of alcohol is 0.8 ml per 10 mm of septal wall thickness with a maximal limit of 3 ml. The use of alcohol is preferred because this agent immediately results in a discrete myocardial infarction. In other percutaneous methods (e.g., vascular coiling, covered stent placement), adequate septal infarction may not result due to extensive septal collateralization that is either pre-existing or develops during follow-up.

The balloon should be left inflated following saline flush for 5–10 min to reduce likelihood of alcohol extravasation into the epicardial vessel. For patient comfort, intravenous sedation or analgesia (e.g., morphine 2–4 mg, or fentanyl 25–50 mg) frequently is given prophylactically or as needed. For patients without significant reduction of either the resting or provoked LVOT gradient, other septal perforator arteries can be targeted and treated in similar fashion, with the echo findings determining choice of subsequent septal perforators. Of note, the residual LVOT gradient is a strong predictor of poor clinical outcome in patients who undergo alcohol septal

ablation [6]. When assessing the acute result of the procedure, it is important to repeat hemodynamic evaluation with large lumen catheters devoid of the ablation equipment, as the balloon catheters will lead to pressure dampening. The LVOT gradient should also be assessed at rest and after provocative maneuvers (e.g., post-ectopic accentuation). In general, residual peak gradients <30 mmHg and preferably <10 mmHg are desired, prompting termination of the procedure. While some operators choose to terminate the procedure following a 50% reduction in pre-procedural peak gradients, we have found the former criteria to lead to more consistent outcomes in long-term follow-up.

Clinical Outcomes

Acute Procedural Success

Overall, ASA typically results in an 80% reduction in the LVOT gradient. Results similar to surgery for acute procedural success, with a final residual resting gradient of ≤10 mmHg, occur in 80–85% of patients [6, 7]. Factors associated with higher likelihood of acute hemodynamic success include relatively less septal hypertrophy, lower LVOT gradients, and greater operator experience [8]. It is important to note that myocardial edema from the infarction can lead to recurrent LVOT obstruction in the subacute period and can be a source of confusion regarding the acute effect of the procedure but that this edema subsides with time and ventricular remodeling. Ventricular remodeling and basal septal thinning leads to further reduction in the LVOT gradient over a period of 3–6 months after the procedure. Of note, regression of myocardial hypertrophy at the site of LVOT obstruction from the infarction and also remotely from the ventricular septum has been demonstrated in studies using cardiac magnetic resonance imaging and may be responsible for improved diastolic function and further reductions in symptoms out to 2 years [9].

Procedural failure most frequently results from the lack of an appropriate septal artery, which may be absent in up to 20% of patients [10]. The most common complication of alcohol septal ablation is temporary or complete atrioventricular block. Conduction abnormalities usually present during the procedure but can occur subacutely due to edema from the infarction with late heart block being rare. Other potential complications are cardiac tamponade, ventricular tachycardia or fibrillation, dissection of the left anterior descending artery, ventricular septal defect, and free wall myocardial infarction. For these reasons, patients should be observed in an intensive care setting for at least 2–3 days after the procedure. Overall, the published periprocedural mortality rates for alcohol septal ablation are 1–2%, with contemporary observational series in the United States and Europe reporting mortality rates <1%.

Symptom Improvement

The clinical efficacy of alcohol septal ablation has been demonstrated with improvements in both subjective reporting of New York Heart Association functional class and objective testing, such as treadmill exercise time and peak exercise myocardial oxygen consumption. The clinical efficacy of alcohol septal ablation is related to the degree of reduction in severity of the LVOT gradient. Overall, alcohol septal ablation typically results in a ~25% increase in objective measures of functional capacity.

Repeat procedures occasionally may be required (~5% of cases). Shadowing of the basal septum from echocardiographic contrast can occur with imaging from the transthoracic apical windows, leading to the false impression of successful ablation of the most proximal portion and resulting in residual obstructive hypertrophy. Stunning of the ventricular septum from balloon occlusion may occur without complete infarction, leading to recovery of septal function and recurrent LVOT obstruction in follow-up. While several studies have shown clinical improvements comparable to that of myectomy, symptom relief may be greater with surgery in younger patients (Fig. 24.6). The reasons for this observation are not clear, but may be related to the residual gradients present after ablation (typically 10–20 mmHg) that are consequently higher than those after surgical myectomy (typically <10 mmHg). These relatively higher residual gradients may be less tolerated by younger, more active individuals. In addition, younger patients more often have more massive septal hypertrophy, anatomy that is less likely to be completely resolved by alcohol septal ablation.

Survival

Several single-center studies have compared the results of ASA to surgical myectomy with follow-up extending 8–10 years [6, 7, 11–16]. Overall survival has been comparable to that of surgery in several series, although the total number of patients in these comparative analyses remains relatively small.

In a study of 177 patients, 8-year survival free of all-cause mortality (including appropriate defibrillator discharge) after alcohol septal ablation was 79% and similar to that of matched patients who had surgical myectomy (79%) as well as the expected survival of a similar US general population of individuals (79%) [6]. For the combined endpoint of sudden death, appropriate defibrillator discharge, and unknown cause of death, the incidence was 1.41% (95% confidence interval, 0.67–2.52%). In the Baylor Medical University of South Carolina study (n = 629), overall survival was 89% after 8 years of follow-up. While this study lacked a comparison group, the incidence of sudden cardiac death was low (n = 7 or 1.1%) [17]. In a separate study of 55 patients

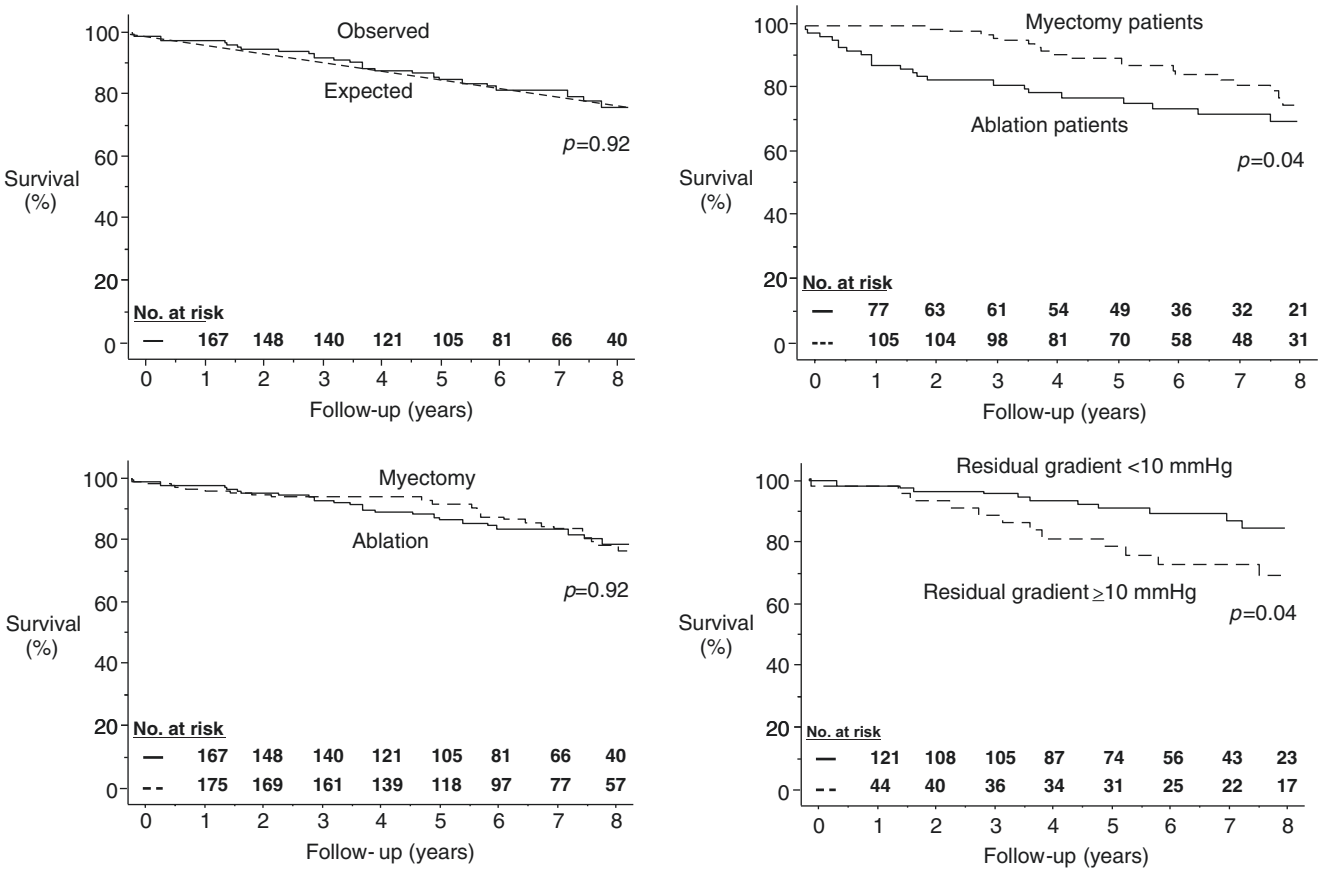


Fig. 24.6 Survival free of death or severe symptoms in patients with hypertrophic cardiomyopathy after alcohol septal ablation. *Top left*, observed survival for the ablation patients vs. expected survival, which was calculated using US population death rates for year of entry into study, age, and gender. *Bottom left*, comparison of survival free of all-cause mortality for the ablation patients vs. survival of age and sex-matched myectomy patients. *Top right*, for patients aged <65 years, survival free of all-cause mortality and severe symptoms was better for surgery than the ablation patients. *Bottom right*, survival free of all-cause mortality for the ablation patients according to residual left ventricular outflow tract gradient. (Reproduced with permission from Sorajja et al. [6])

who underwent alcohol septal ablation at Cleveland Clinic, 76% of patients survived at 10 years of follow-up [18]. In an analysis of 321 patients over a mean follow-up of 7.6 years, Vriesendorp et al. reported outcomes of ASA patients comparable to both myectomy patients ($n = 253$) and those with nonobstructive HCM ($n = 349$). The annual incidence of sudden cardiac death for the ASA patients was low at 1.0% per year, though numerically higher than the rate observed with myectomy (0.8% per year) [19].

A notable exception for these favorable outcomes is an early study of 91 patients treated at Erasmus MC, Rotterdam. In this analysis, sudden cardiac death (or appropriate defibrillator discharge, $n = 4$) occurred in 19 patients (or 21%) during a mean follow-up period of 5.7 years [20]. While these results raised concern regarding potential for arrhythmias after ablation, the study was noteworthy for a relatively higher average alcohol dose (3.5 ± 1.5 ml) among their patients, including a mean dose of 4.5 ± 1.2 ml in the first 25 patients, consistent with the early experience of alcohol septal ablation when such higher doses of alcohol were used. In other studies, where long-term survival was not impaired, the mean alcohol dose was only 1.8 ml, and the septal wall thickness was similar to the patients in the Rotterdam study (23 ± 5 mm vs. 23 ± 5 mm). Of note, early studies of alcohol septal ablation, where contrast echocardiography was not routinely performed, were associated with higher volumes of alcohol utilized, consequently larger infarct size, a greater risk of complications, and poorer clinical outcome [21].

In a multicenter registry of 874 alcohol septal ablation patients that included patients from aforementioned studies, there was significant improvement in functional status (~5% with residual severe symptoms). Overall survival was 74% at 9 years of follow-up with predictors of death being lower baseline ejection fraction, fewer number of arteries treated, larger number of ablation procedures, and higher septal thickness post-ablation [22]. Several large-scale registries and meta-analyses have examined the outcome of patients undergoing alcohol septal ablation in comparison to surgery [23, 24] [Veselka Euro-ASA registry]. Taken together, the aforementioned studies suggest that efficacious and

comparable outcomes can be achieved with appropriate patient selection, use of lower doses of alcohol, and greater operator and institutional experience in the comprehensive care of patients with HCM.

Conclusions and Future Directions

Although septal ablation has established itself as an efficacious therapy in selected HCM patients, its introduction has been met with controversy about its appropriate role in the management of these patients. These concerns have arisen primarily because of the established safety and durable efficacy of surgery at experienced centers; potential procedural morbidity of septal ablation (e.g., pacemaker dependency), particularly in its early experience; and possible long-term deleterious effects of the therapeutic infarction.

The selection of alcohol septal ablation or surgical myectomy will continue to rely on carefully performed observational data and expert consensus, as randomized clinical trials in this field have been deemed to be not feasible [25]. For some patients, alcohol septal ablation may be the only option for definitive relief of LVOT obstruction due to poor candidacy for surgery. In others, alcohol septal ablation can be offered as an alternative treatment after the risks of the procedure and the aforementioned concerns have been discussed fully with the patient. Without the need for general anesthesia and open surgery, the relatively less invasive aspects of alcohol septal ablation are its principal advantages. Hospital stay (typically 3–5 days) and physical rehabilitation is also relatively shorter. These issues are particularly relevant for elderly patients or those with morbidities that significantly increase the risk of open surgical repair. Of note, among patients who underwent alcohol septal ablation in one study, 20% of these patients were believed to be at significantly increased operative risk for myectomy due to patient age (≥75 years) or presence of severe comorbidities (e.g., end-stage renal disease, porcelain aorta, morbid obesity, cor pulmonale) [7].

Importantly, even though alcohol septal ablation uses conventional coronary angioplasty equipment, the procedure is complex with a steep learning curve and unique complications [8]. Recent data have highlighted the beneficial effects of ASA for relatively younger patients, though a balanced discussion must still be undertaken when counseling patients [26, 27]. In addition, patients with HCM are uniquely complex in terms of diagnosis and management, with many factors that should be taken into account when considering septal reduction therapy. Thus, national guidelines recommend that these management considerations be made in a tertiary center with a dedicated HCM program, where expertise in both percutaneous and surgical options can be offered [3].

Clinical Pearls

- Patient selection is key to the success of the procedure. Ensure that the procedure is performed only for *dynamic* LVOT obstruction and systolic anterior motion of the mitral valve, with predominantly *posterior and lateral* mitral regurgitation.
- Comprehensive cardiac imaging performed preprocedurally and careful invasive hemodynamic studies during the procedure are needed to ensure success of the procedure.
- Basal septal shadowing occurs frequently with apical echocardiographic views. Thus, always start with the most proximal septal artery for interrogation of the perfusion bed. Injection of distal or mid-ventricular arteries first will make it difficult to determine contrast enhancement proximally unless transesophageal echocardiography is used.
- Temporary pacemakers with small profile, active fixation leads reduce the risk of cardiac perforation and may allow for prolonged monitoring.
- Imaging with gadolinium and cardiac MRI helps determine the anatomic effect of the procedure and feasibility of repeat procedures.

Questions

1. A 45-year-old woman with diagnosis of obstructive HCM has hypertension. Echocardiogram shows asymmetric septal hypertrophy with basal septal thickness of 2.5 cm and posterior wall thickness of 1 cm. There is SAM with LVOT gradient of 60 mmHg. The patient has dyspnea with daily activities. She is on the following medications: metoprolol at 50 mg twice daily and valsartan at 320 mg daily. Heart rate is 75/min and BP = 130/80 mmHg. What would you recommend now?
   A. Surgical myectomy.
   B. Alcohol septal ablation.
   C. Disopyramide.
   D. Long-acting verapamil.
   E. Stop valsartan and increase metoprolol dose.

   Answer: E. The patient is in NYHA class III, and there is severe dynamic obstruction. Before considering septal reduction therapy, medical treatment should be maximized. Given the vasodilator properties of valsartan and its adverse effect of increasing LVOT obstruction, this drug should be stopped. To help maintain BP control, metoprolol dose should be increased as there is room given heart rate of 75/min.

2. A 35-year-old man has obstructive HCM and has dyspnea with daily activities. Echocardiogram shows asymmetric LV hypertrophy with septal thickness of 2 cm and posterior wall thickness of 1.3 cm. There is SAM and LVOT gradient is 64 mmHg. Heart rate is 78/min and BP = 138/74 mmHg. The patient is on metoprolol at 50 mg every 12 h. What would you recommend now?
   A. Surgical myectomy.
   B. Alcohol septal ablation.
   C. Disopyramide.
   D. Long-acting verapami.l
   E. Increase metoprolol to 100 mg every 12 h.

   Answer: E. The patient is in NYHA class III, and there is severe dynamic obstruction. Before considering septal reduction therapy, medical treatment should be maximized. The beta blocker dose should be increased, and there is room given his heart rate of 78/min and BP = 128/74 mmHg.

3. Which of these LV and LA changes is *not* seen after alcohol septal ablation?
   A. LV end-diastolic volume increases.
   B. Basal septal thickness decreases.
   C. LV mass decreases.
   D. LV EF increases.
   E. LA maximum volume index decreases.

   Answer: D. LV remodeling takes place after alcohol septal ablation. LV diastolic dimensions and volumes increase, and LV mass decreases. The decrease in LV mass is due not only to decreased septal thickness after ablation but also to regression of LV hypertrophy in remote regions. LA volumes decrease due to the improvement in LV diastolic function and the decrease in the severity of mitral regurgitation. Long-term follow-up studies have shown a significant decrease in LV EF, albeit it remains in the normal range.

4. Which changes in LV filling and LA function are seen after alcohol septal ablation?
   A. LA contribution to LV filling increases.
   B. LA minimum volume increases.
   C. LV passive filling volume increases.
   D. LV end-diastolic volume decreases.
   E. LA maximum volume increases.

   Answer: C. Due to an improvement in LV diastolic function, LV passive filling volume increases, and the LA contribution to LV filling decreases. LV remodeling takes place after alcohol septal ablation. LV diastolic dimensions and volumes increase. LA volumes (maximum and minimum) decrease due to the improvement in LV diastolic function and the decrease in the severity of mitral regurgitation.

5. A 40-year-old man presents with dyspnea on his daily activities. Peak oxygen consumption is 18 mL/kg/min. The patient has obstructive HCM and SAM with LVOT gradient = 80 mmHg. Septal thickness is 3 cm, and he is on metoprolol at 100 mg twice daily with heart rate of 60/min and BP = 90/60 mmHg. Which of the following treatment options would you recommend at this time?
   A. Increase metoprolol dose to 150 mg every 12 h.
   B. Add long-acting verapamil at 180 mg/day.
   C. Permanent pacemaker implantation.
   D. Surgical myectomy.
   E. Alcohol septal ablation.

   Answer: D. The patient is on maximum medical therapy given his heart rate and blood pressure. Therefore, septal reduction therapy should be considered given the options presented in this question. Randomized controlled studies have not shown a beneficial effect of RV pacing on exercise tolerance and LVOT gradients in young patients. Given his young age and severe septal hypertrophy, surgical myecytomy is the best option.

6. A 65-year-old woman with COPD and obstructive HCM is seen for progressive dyspnea and chest pain with exertion. She does not have CAD. Her serum creatinine is 2.1 mg/dL. The patient uses O_2 at night. Septal thickness is 1.8 cm with LVOT gradient of 68 mmHg due to SAM. Heart rate is 62/min and BP = 90/60 mmHg. She is on diltiazem long-acting preparation at 360 mg/day. Which of the following treatment options would you recommend at this time?
   A. Add metoprolol at a dose of 50 mg every 12 h.
   B. Increase diltiazem to 480 mg/day.
   C. Permanent pacemaker implantation.
   D. Surgical myectomy.
   E. Alcohol septal ablation.

   Answer: E. The patient is on maximum medical therapy given her heart rate and blood pressure. Therefore, septal reduction therapy should be considered given the options presented in this question. Randomized controlled studies have not shown a beneficial effect of RV pacing on exercise tolerance and LVOT gradients. Given her age and the presence of comorbidities, alcohol septal reduction therapy is the better option.

7. Which finding poses the highest risk for complete heart block after alcohol septal ablation?
   A. Female sex
   B. Age > 65 years

C. Left bundle branch block
D. Peak CK after ablation of 600 units/liter
E. Septal thickness of 2 cm

Answer: C. Risk factors for complete heart block after alcohol septal ablation include female sex, large infarctions, and left bundle branch block. The latter finding poses the highest risk as alcohol septal ablation causes RBBB in 60–70%, and thus a pre-existing LBBB is associated with a high risk of complete heart block.

8. Which of these would favor against recommending alcohol septal ablation?
   A. Septal thickness of 1.8 cm
   B. SAM
   C. LVOT gradient of 55 mmHg
   D. Moderately severe MR with posterolateral jet
   E. NYHA class I

   Answer: E. All of the findings, except E, are findings that should be present before recommending alcohol septal ablation. LVOT gradient and MR severity both decrease with successful alcohol septal ablation. The patient should be symptomatic despite maximum tolerated medical therapy before undergoing septal ablation.

9. Which symptoms have been shown to improve after alcohol septal ablation?
   A. Dyspnea
   B. Angina
   C. Syncope
   D. All of the above
   E. None of the above

   Answer: D. Virtually all observational studies have shown significant improvement in all symptoms after successful alcohol septal ablation. The symptomatic improvement is accompanied by an improvement in objective measurements of exercise tolerance that were still observed at long-term follow-up.

10. In comparing alcohol septal ablation with surgical myectomy, which of these statements is true?
    A. Alcohol septal ablation more frequently leads to LBBB.
    B. Alcohol septal ablation more frequently leads to progressive MR.
    C. Alcohol septal ablation more frequently leads to higher risk of sudden cardiac death.
    D. Alcohol septal ablation more frequently leads to permanent AV block.
    E. Alcohol septal ablation more frequently leads to mild aortic regurgitation.

    Answer: D. Alcohol septal ablation more frequently leads to RBBB and advanced AV block and hence the need for pacing. However, the incidence of complete AV block has decreased dramatically since the initial studies and is around 5–8%. Alcohol septal ablation leads to a decrease in LVOT gradient and MR severity. Surgical myectomy is associated with mild AR. Recent studies have shown a similar incidence of sudden cardiac death after surgery and after alcohol septal ablation.

11. Which of these findings would favor surgical myectomy?
    A. Septal thickness = 1.8 cm
    B. Single vessel CAD
    C. LVOT gradient = 55 mmHg
    D. Moderately severe MR with anteromedially directed jet
    E. Moderately severe MR with posterolaterally directed jet

    Answer: D. Alcohol septal ablation can be recommended in the presence of all options, except D. The presence of an anteromedially directed MR jet indicates the presence of intrinsic mitral valve pathology that needs correction by surgery.

12. Mechanical complications of alcohol septal ablation include except:
    A. LAD dissection
    B. Pericardial tamponade
    C. Ventricular septal defect
    D. Left atrial rupture
    E. Cerebrovascular events

    Answer: D. All except left atrial rupture are rare mechanical complications of alcohol septal ablation.

13. The use of myocardial contrast echocardiography during alcohol septal ablation is associated with which of the following:
    A. Shorter intervention time
    B. Shorter fluoroscopy time
    C. Smaller infarct size
    D. Lower LVOT gradient
    E. All of the above

    Answer: E. In comparison with alcohol septal ablation without contrast echocardiography, the use of intracoronary contrast injection is associated with shorter intervention time, shorter fluoroscopy time, small size of septal infarction, and lower LVOT gradient.

14. Septal perforator arteries originate from:
    A. LAD
    B. Diagonal branch of LAD

C. Ramus intermedius
D. Left main
E. All of the above

Answer: E. Septal perforator arteries can take origin from all of these vessels. The use of intracoronary contrast echocardiography can help determine the myocardial territories of the cannulated arteries.

15. A 65-year-old woman with previous alcohol septal ablation is presenting with recurrent dyspnea and angina. Echocardiography showed septal thickness of 1.7 cm at the site of septal ablation. LV EF is >70%. SAM is present and LVOT gradient at rest is 64 mmHg. The patient is on metoprolol at 100 mg every 12 h, and heart rate is 55/min and BP = 116/70 mmHg. Which of the following would you recommend next?
A. Increase metoprolol to 150 mg every 12 h.
B. Add verapamil long acting at 240 mg/day.
C. Disopyramide 150 mg every 8 h.
D. Repeat alcohol septal ablation.
E. Surgical myectomy.

Answer: C. The patient is left with significant symptoms, and thus additional treatment is indicated. While increasing beta blockers and adding long-acting verapamil are not good choices given resting bradycardia, it is reasonable to try disopyramide and assess the response to the drug. For patients who remain symptomatic with severe obstruction on the drug, repeat septal reduction therapy is needed.

16. A 25-year-old male with obstructive HCM seeks advice about primary prevention for sudden cardiac death. He has a positive family history of HCM, but not sudden death. He is asymptomatic without symptoms of near syncope or syncope. Maximum wall thickness is 2.3 cm. There is no obstruction at rest. Holter recordings showed isolated ventricular ectopic beats. What advice would you give this patient?
A. No further testing is needed.
B. Needs additional evaluation with event recorder, before making a recommendation.
C. Needs CMR for scar before making a recommendation.
D. Needs EP study to assess for inducible ventricular arrhythmias, before making a recommendation.
E. Needs stress echocardiogram for provocable obstruction, before making a recommendation.

Answer: A. The patient does not have risk factors for sudden cardiac death. There is no need for additional testing at this time, including CMR. In borderline cases, the presence of a large scar burden by CMR can be discussed with the patient and considered in reaching a recommendation for ICD. In asymptomatic patients, treatment of rest or provocable gradients is not indicated.

17. Which of these predicts the need for repeat alcohol septal ablation?
A. CK leak after of the procedure of 1500 Units/liter
B. Female sex
C. Age < 50 years
D. Residual gradient of 50 mmHg in the catheterization laboratory
E. High-grade AV block

Answer: D. The presence of a large residual gradient after alcohol septal ablation predicts a higher likelihood of repeat septal reduction therapy.

18. A 54-year-old man is referred for evaluation of possible HCM. There is positive family history of sudden death. The patient is asymptomatic. There are no other medical problems. EKG shows sinus rhythm and non-specific ST-T changes. Echocardiogram is technically difficult, and basal septal thickness is 1 cm with posterior wall thickness of 0.9 cm. EF is 75%. There is no SAM or dynamic obstruction. Which of these would you recommend?
A. No further testing
B. Stress echocardiogram for provocable obstruction
C. Holter recording for 48 h
D. Event recorder for 30 days
E. CMR

Answer: E. Additional imaging with CMR is needed, given the technically difficult echocardiographic images. In some patients, hypertrophy is present in segments other than the septum which can be readily detected by CMR. This has been shown to be the case for the anterolateral wall. The presence of arrhythmias or provocable obstruction in the absence of LV hypertrophy is not enough to establish the diagnosis.

19. A 63-year-old woman is referred for evaluation of dynamic obstruction. She has dyspnea with her daily activities. Echocardiography shows asymmetric LV hypertrophy with septal thickness of 1.3 cm. She has SAM with dynamic gradient at 64 mmHg. LV EF is 70%. She is already on metoprolol at 100 mg twice daily with heart rate of 60/min and BP = 90/60 mmHg. EKG shows sinus rhythm, PR interval of 220 ms, and QTc interval of 560 ms. Which of these would you recommend?
A. Increase metoprolol to 150 mg every 12 h.
B. Disopyramide 150 mg every 8 h.
C. MitraClip implantation.

D. Alcohol septal ablation.
E. Surgical myectomy.

Answer: C. The patient is symptomatic despite maximal medical therapy. Given her heart rate and BP, there is no room to increase metoprolol dose. Given her QTc interval, disopyramide should not be started at this time. Since septal thickness is only 1.3 cm, septal reduction therapy is not the safest option. Percutaneous MV repair with the Clip resulting in reduced motion of anterior mitral valve and thus reduced SAM and dynamic gradient is the best option.

20. During alcohol septal ablation, a 60-year-old man reports chest pain and develops hypotension with BP = 80/50 mmHg. EKG shows complete AV block with heart rate of 45/min. RV pacing is started. During RV pacing, heart rate is up to 70/min with successful capture, but BP is unchanged. What is the definitive treatment for hypotension?
A. Increase the pacemaker rate to 80/min, and gradually increase the rate till SBP = 100 mmHg.
B. Administer 500 mL of 0.9% NaCl as an intravenous bolus, followed by a drip.
C. Administer intravenous epinephrine and then isoproterenol.
D. Temporary lead placement in RA with AV sequential pacing.
E. Proceed to perform urgent alcohol injection into the target septal perforator artery.

Answer: D. LV filling is heavily dependent on synchronized LA contraction due to LV diastolic dysfunction. With RV pacing only, LA contribution to LV filling is lost for several cycles, and this leads to reduced LV stroke volume, cardiac output, and blood pressure. Thus, AV sequential pacing is the best treatment option for this patient. Increasing the heart rate can reduce the diastolic filling period and further reduce LV end-diastolic volume and stroke volume. Administration of fluids is reasonable while preparations are taking place for RA lead placement. However, this is a temporary measure and not definitive treatment. Administration of inotropes can increase LVOT obstruction and does not correct the problem stemming from RV pacing. It is most appropriate to attend to the problem of AV block and hypotension before proceeding to completing the procedure.

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Managing the High-Risk Patient: Critical Care, TAVR, MitraClip, Pressors, and Cardiac Assist Devices

25

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Key Points

- Early recognition of left ventricular outflow tract obstruction in the critical care setting helps guide management and improve outcomes for patients with the HCM phenotype.
- Medical and interventional therapies are available to assist in stabilizing the critically ill HCM patient, both those with LVOT obstruction as well as those who have progressed to systolic heart failure.
- The expanding field of percutaneous intervention for structural heart disease includes the HCM patient, particularly those at high risk for traditional surgical techniques.

Care of the Critically Ill Hypertrophic Cardiomyopathy Patient

Common indications for intensive care unit referral include hypotension, refractory heart failure signs and symptoms, and/or arrhythmia. For the patient with known HCM, accurate characterization of the outflow tract physiology as well as recognition of the potential for diastolic dysfunction without outflow obstruction is key to successful resuscitation. A focused history and physical examination, as well as a low threshold to perform echocardiography to confirm suspected findings, are helpful for initial evaluation. Furthermore, left ventricular outflow tract obstruction (LVOTO) may occur in a variety of scenarios beyond typical HCM, and we will briefly review the literature. We will then discuss medical and other therapies of LVOTO.

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Initial Evaluation

The goal of a focused history and physical examination is to rapidly determine key data elements which inform the treating team as to potential primary diagnoses as well as relevant contributing factors. Determining the history of known LVH (or common systemic causes of LVH such as aortic stenosis or hypertension) or documented HCM, recent fluid intake and output, and recent clinical course are a reasonable beginning. Physical examination should focus on volume status, perfusion status, as well as auscultation for outflow tract murmurs and/or significant regurgitant lesions. Finally, echocardiography will be useful to help confirm the initial assessment. A key diagnostic inflection point is determining whether LVOTO is present or absent, as therapies are highly divergent. Key echocardiographic findings supporting severe LVOTO include hypertrophy of the basal interventricular septum, systolic anterior motion of the mitral valve apparatus, hyperdynamic LV systolic function, peak LVOT gradient by continuous wave Doppler of at least 30 mm Hg with a characteristic late-peaking waveform suggestive of dynamic (and not fixed) obstruction [1]. See Fig. 25.1.

Etiologies of LVOTO in the ICU Patient

The typical phenotype of HCM which predisposes to LVOTO includes basal septal hypertrophy and mitral valve abnormalities including leaflet elongation as well as papillary muscle derangements which displace the mitral

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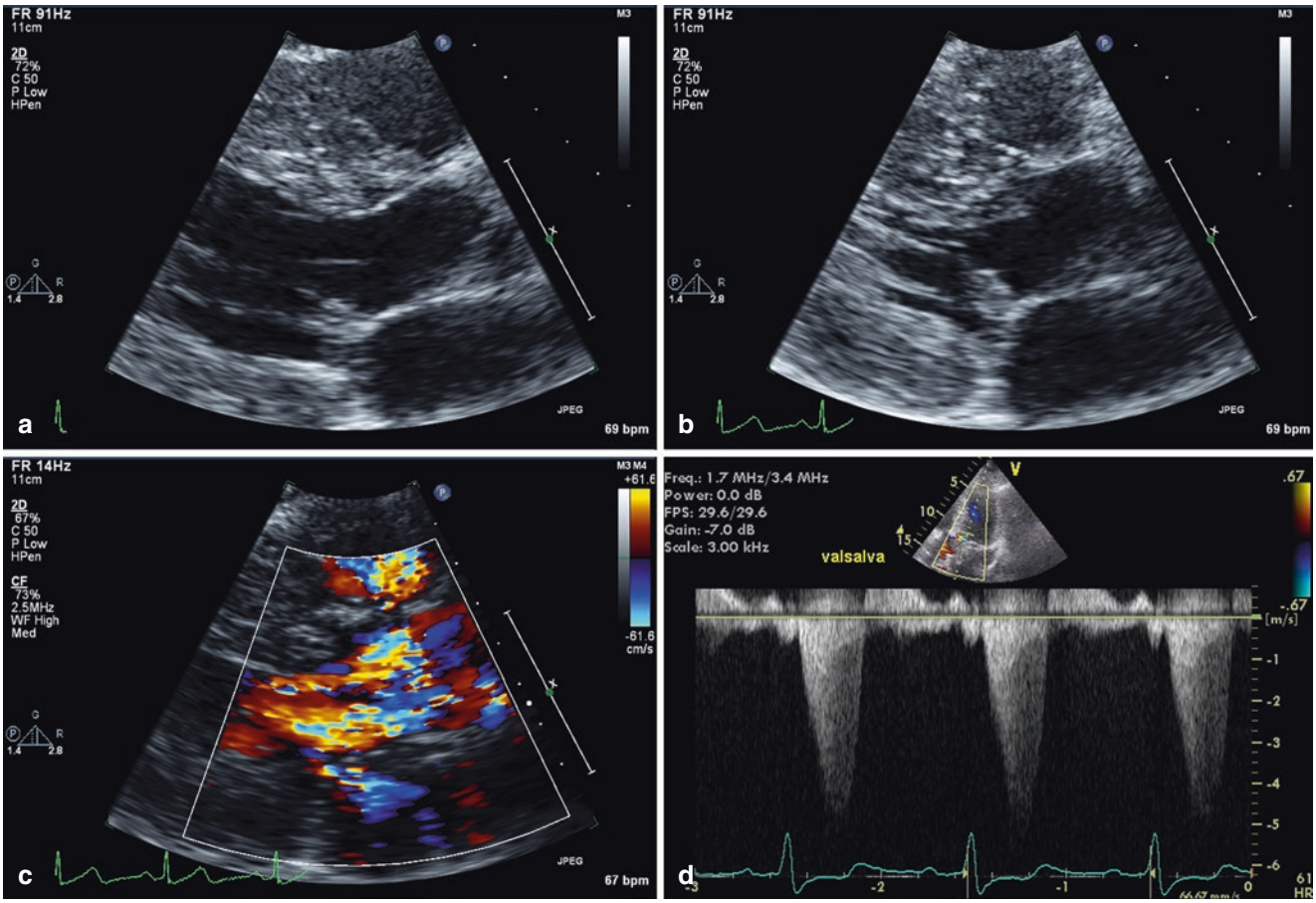

Fig. 25.1 Example of HCM patient with LVOT obstruction. Panels A and B show diastolic and systolic imaging, respectively, demonstrating systolic anterior motion of the mitral valve in the setting of septal hypertrophy. Panel C shows LVOT obstruction and turbulence by color Doppler, along with posteriorly directed mild mitral regurgitation due to systolic anterior motion of the mitral valve. Panel D demonstrates a late-peaking outflow tract velocity of approximately 5 m/s, corresponding to a gradient of 100 mm Hg

apparatus further into the LVOT space than usual. However, many other scenarios beyond typical HCM may also contribute to LVOTO, and these are briefly listed below.

- Sepsis and accompanying vasodilatory shock may lead to LVOTO (or mid-ventricular obstruction) in both anatomically predisposed hearts as well as among those with normal structure [2].
- The perioperative period is associated with hyperdynamic LV contractility, vasodilatory effects of anesthesia, and hypovolemia secondary to blood loss – all of which favor obstruction. Such predisposing factors may persist postoperatively as well. One subset of surgical patients at risk for LVOTO includes those undergoing direct intervention to the mitral or aortic valves. LVOTO and systolic anterior motion of the mitral valve occur in approximately 5% of mitral repair procedures, likely due to technical factors within the procedure such as utilization of a rigid annuloplasty ring for support which alters the geometry of the outflow tract [3].
- Hyperkinetic myocardial segments remote from a region of acute injury may obstruct the LVOT. One scenario involves acute myocardial infarction (often within the left anterior descending artery vascular territory) in which distortion of normal geometry as well as compensation by the unaffected segments leads to LVOTO. Along similar lines, stress (Takotsubo) cardiomyopathy with apical dyskinesis but preserved basal contractility may also provoke a dynamic LVOTO situation. Indeed, approximately 15% of patients with stress cardiomyopathy demonstrate severely elevated outflow gradients [4], which typically normalize as the apical ballooning resolves.
- Atrial fibrillation is the most common arrhythmia in patients with HCM, affecting up to one in five patients. HCM patients who develop atrial fibrillation with rapid ventricular response may develop significant hemodynamic instability as loss of atrial-dependent LV filling and tachycardia result in increased LVOTO and systemic hypotension. Prompt recognition, early restoration of sinus rhythm with cardioversion and/or use of disopyramide or amiodarone, avoiding use of inotropes to support blood

pressure, and stroke prevention with timely anticoagulation are all warranted [5]. Further discussion of atrial fibrillation management in patients with HCM is covered in Chap. 21.

- Acute pulmonary embolism may result in dynamic LVOTO. Large pulmonary emboli may result in reduced pulmonary circulation, decreased LV filling, and leftward septal shift, all culminating in LVOTO especially in patients with pre-existing HCM [6]. Prompt recognition, volume resuscitation, avoidance of inotropes, prompt anticoagulation, and (if clinically indicated) surgical or catheter-based direct intervention are necessary to stabilize and treat such patients.

Management of LVOTO in the Acute Setting

Minimizing the LVOT gradient may be accomplished by addressing some or all of the following factors: reducing LV contractility, slowing the heart rate, as well as increasing afterload and preload. Initial maneuvers include bolus IV fluid infusion to rapidly raise preload and increase LV chamber size. Cautious use of non-vasodilating beta-blockers may assist with increasing diastolic filling time, reducing LV contractility, and blunting the effect of circulating catecholamines. Morelli and colleagues demonstrated that in patients with sepsis, preserved LV function, and tachycardia (some of whom likely have LVOTO given a one in five prevalence reported by others) [2], beta-blockers improved outcomes [7]. Additionally, a case report describes the use of disopyramide in an ICU patient with LVOTO [8]. Should initial medical therapy be unsuccessful, the use of pure alpha agonists for increasing afterload – such as phenylephrine – may also be helpful. Pressors with sympathomimetic or inotropic properties may worsen LVOTO and are contraindicated. Certain mechanical support devices may also be indicated in severe, refractory cases and will be discussed separately.

Management of Advanced Heart Failure in the Acute Setting

Only a minority of HCM patients will progress to LV dilation, myocardial thinning, and reduced systolic function – typically considered an end-stage phenotype in which advanced heart failure intervention may be required [9, 10]. Additionally, some patients with a nonobstructive HCM phenotype may also develop refractory heart failure symptoms. In the acute setting, mechanical assist devices may play a role in this high-risk HCM subgroup. An in-depth discussion of the role of medical therapy and heart transplantation in the management of the HCM patient with end-stage heart failure or other advanced disease is provided in Chap. 30, so only a brief discussion is provided in this chapter.

Advanced Heart Failure in Hypertrophic Cardiomyopathy

A small proportion of patients (<20%) with hypertrophic cardiomyopathy (HCM) proceed toward advanced heart failure [10]. In a series of 277 consecutive patients from the Minneapolis Heart Institute, 5 patients (2%) developed refractory end-stage heart failure leading to heart transplantation with 9% experiencing severe symptoms of New York Heart Association class III or IV [11]. In another study of 293 consecutive patients from the Padua University HCM Center, 17% ($n = 50$) developed severe progressive heart failure, of which 18 were transplanted or died. In this heart failure cohort, three profiles of heart failure were identified: end-stage systolic dysfunction (30%), left ventricular outflow obstruction at rest (22%), and nonobstruction with preserved systolic function (48%) [12]. There is growing recognition of advanced heart failure in nonobstructive HCM patients with preserved systolic function. In a more recent study of 2100 patients from 2 referral centers (Tufts Medical Center and the Minneapolis Heart Institute), 46 nonobstructive HCM patients (2.2%) received or were listed for heart transplant, including 20 with normal systolic function. This under-recognized cohort was marked by the following characteristics: NYHA functional class III/IV, mean left ventricular ejection fraction (LVEF) 62 ± 7%, non-dilated left ventricle (end-diastolic dimension, 39 ± 7 mm), none or minimal fibrosis by cardiovascular magnetic resonance in 10 (of 15), and elevated left ventricular end-diastolic or pulmonary capillary wedge pressure. In the preserved systolic function cohort, 10% died (compared with 23% in end-stage HCM LVEF <50% cohort, $p = 0.26$) demonstrating the mortality in this patient subtype [13].

Heart Transplantation

Heart transplantation is recommended for patients with advanced disease[Gersh] [1]. Late referral may be associated with end-organ damage and pulmonary hypertension. Co-management with an HCM Center of Excellence and Advanced Heart Failure program may be beneficial to ensure optimal transition and consideration of advanced heart failure therapies, particularly in under-recognized phenotypes. A small proportion of HCM patients advance to heart transplantation. In the largest series to date, 303 HCM patients (1%) of 26,706 underwent heart transplantation between January 1990 and December 2004 in the United States (UNOS Registry). The 1-, 5-, and 10-year overall survival for HCM patients was 85%, 75%, and 61%, respectively. Propensity-matched, covariate-adjusted, Cox regression model analysis demonstrated better survival over time among the HCM patients ($p < 0.01$). During this time period, HCM

patients were less likely to be listed for transplant at the highest urgency status (Status 1) compared to non-HCM patients (61% vs. 67%, $p = 0.035$) [14]. However, this study accounts only for those who are successfully transplanted. In another analysis of the UNOS Registry, VanderPluym et al. assessed the outcomes in patients removed from the waiting list before receiving a transplant. Of 15,061 patients, 1871 (12%) were removed before receiving a heart transplant. Of these patients, 692 (37%) were removed due to clinical deterioration and 560 (30%) due to clinical improvement with the remainder for other reasons. Multivariable predictors of death after delisting were removal due to clinical deterioration (hazard ratio (HR) 14.1 [95% confidence interval (CI) 10.7–18.7]), hypertrophic (HR 2.2 [95% CI 1.4–3.7]) or restrictive cardiomyopathy (HR 2.0 [95% CI 1.3–3.0), Status 1 listing, and renal dysfunction [15]. Hypertrophic cardiomyopathy patients have acceptable or better survival than non-HCM patients; however, HCM patients seem to face increased mortality in the waiting period for transplant. It remains to be seen how impending changes to UNOS heart allocation policy will impact this cohort.

Mechanical Circulatory Support

Mechanical circulatory support (MCS) has not been well studied in patients with HCM. Recent left ventricular assist device (LVAD) trials focused on end-stage dilated and ischemic cardiomyopathy. Patients with HCM were not well represented in these trials. There are technical challenges with LVAD implantation in patients with thickened left ventricular walls and small left ventricular chamber size. As discussed, heart transplantation significantly improves survival for HCM patients with advanced heart failure. However, due to increasing waiting times on the transplant list, patients may deteriorate or develop irreversible pulmonary hypertension with increased mortality which may necessitate bridging to heart transplantation with MCS.

Two small series have reported on outcomes in HCM patients who underwent durable LVAD implantation. In a series from the Mayo Clinic, 83 consecutive patients received continuous axial flow LVAD support (HeartMate II, Abbott, Pleasanton, CA) between February 2007 and May 2010, of which 4 had HCM as well as 4 with restrictive cardiomyopathy (RCM). Surgical technique was modified to allow for additional left ventricular myectomy ($n = 2$) as needed to create adequate space for the inflow cannula and to allow for positioning with the long axis of the left ventricle aimed toward the mitral valve. No difference in early mortality (12.5% vs. 9.3%, $p = 0.57$) or 1-year survival (87.5% vs. 73.2%, $p = 0.77$) was demonstrated between HCM/RCM patients and non-HCM/RCM patients. However, right heart failure, prolonged inotropic use, and central venous catheter infection were more common in the HCM/RCM group. Observed right heart failure may be secondary to primary myopathic involvement of the right ventricle and pre-existing pulmonary hypertension. In this patient cohort, right ventricular function improved as inotropes were successfully discontinued with improvement in right atrial pressures and without need for right ventricular assist device support [16].

In another series from St Vincent's (Sydney, Australia), of 39 patients implanted with centrifugal flow LVADs (HeartWare HVAD, Medtronic, Minneapolis, Minnesota; VentraAssist, Ventracor, Sydney, Australia), 3 had hypertrophic cardiomyopathy. All three HCM patients were implanted with the HeartWare HVAD. There was no difference in surgical technique between HCM and non-HCM patients. No difference in early mortality at 3 months was observed between the HCM and non-HCM groups (0% vs. 9%, $p = 0.60$). However, veno-pulmonary arterial extracorporeal membrane oxygenation (ECMO) was initiated in 1 HCM patient (with preoperative use of ECMO prior to LVAD placement) and 4 of 36 in the non-HCM group. Improvement in mean pulmonary arterial and right atrial pressures was demonstrated in both groups (HCM group: mean right atrial pressure, 18 ± 7.8 to 11.3 ± 5.1 mmHg; mean pulmonary arterial pressure, 43.3 ± 4.9 to 22.3 ± 2.8 mmHg, $p < 0.01$). At the time of publication, one patient was successfully transplanted, one continued on LVAD support (744 days), and one died (due to intraventricular clot with inlet obstruction) [17].

Durable mechanical circulatory support has the potential to improve survival in the HCM population particularly when timely heart transplantation is not feasible. Caution is advised, however, as the data to date is limited to small series. Multidisciplinary management is critical to the care of this patient population. Surgical considerations in addition to ventricular assist device and medical management are important as left ventricular hypertrophy extent and chamber size likely impact the care of HCM patients.

Temporary Ventricular Assist Devices

Limited data exists for use of the CentriMag (Abbott, Pleasanton, California), a surgically implanted extracorporeal continuous-flow ventricular assist device use, in patients with HCM. It can be used for both left and right ventricular support. In a case series of four patients, there was one HCM patient implanted with the CentriMag ventricular assist device. This 58-year-old patient underwent septal myectomy, ventricular septal defect closure, and tricuspid valvuloplasty. The patient required intra-aortic balloon pump and multiple inotropes to wean from cardiopulmonary bypass. However, acute kidney injury and pulmonary dysfunction

necessitated hemodialysis and mechanical ventilation, and this patient underwent biventricular assist device (BIVAD) placement with CentriMags as well as listing for heart transplantation. The patient underwent reoperation on postoperative day 3 for bleeding. This patient was successfully bridged to transplant following 4 days of BIVAD support. Posttransplant course was complicated by mediastinitis and septicemia with unremarkable course following discharge 2 months later. The reported experience with temporary CentriMag support is very limited. This may be a feasible option to allow for recovery following a definitive corrective surgery (i.e., myectomy) or as a bridge to durable MCS or heart transplantation [18]. However, caution is advised given the paucity of data and the complex management (medical and surgical) of these patients.

There is limited data for use of percutaneous ventricular assist devices in hypertrophic cardiomyopathy. In a case report, a 69-year-old woman underwent TandemHeart (Cardiac Assist, Pittsburgh, Pennsylvania) placement for cardiogenic shock as a bridge support device until septal myectomy could be performed safely. Initiation of percutaneous ventricular assist device support improved the patient's hemodynamics with concomitant decrease in vasopressor requirements. Ultimately, the patient was successfully bridged to myectomy the following day [19]. To our knowledge, there are no reported cases with other percutaneous ventricular assist devices, although use of the Impella (Abiomed, Inc.) makes theoretical sense given its ability to bypass the outflow tract obstruction and can be instituted rapidly. Further data is needed to understand whether these therapies can benefit HCM patients. As with durable MCS, this therapy may indeed benefit HCM patients, but caution is warranted as the effectiveness and management of these devices are likely impacted by the degree and location of left ventricular hypertrophy.

Structural Heart Disease Intervention and the HCM Patient

Transcatheter Aortic Valve Replacement

The expanding indications for transcatheter aortic valve replacement (TAVR) along with a high prevalence of septal hypertrophy in aortic stenosis (AS) patients necessitate consideration by the critical care specialist of left ventricular outflow tract obstruction (LVOTO) as a potential cause of post-procedural hypotension during recovery in the ICU. The etiologic distinction between septal hypertrophy secondary to familial hypertrophic cardiomyopathy versus that due to AS and aging is beyond the scope of this chapter, which is focused on critical care issues relevant to the high-risk patient with obstructive HCM phenotype.

Preprocedural assessment should ideally address whether septal hypertrophy and/or concomitant LVOTO should be managed as part of the TAVR preprocedural evaluation [20]. Careful echocardiographic imaging with spectral Doppler and, if needed, meticulous localization of the gradient between the left ventricle and ascending aorta via left heart catheterization are helpful. However, initial assessment may not always predict development of LVOTO after the AS is treated, and more thorough invasive hemodynamics may be helpful. A review of the several cases published to date provides perspective regarding the clinical course following LVOTO development. Most recently, Krishnaswamy et al. report a case of a TAVR patient with severe asymmetric septal hypertrophy (basal septum 2.0 cm, posterior wall 1.3 cm) but without demonstrable LVOTO at rest or with Valsalva maneuver [21]. Yet, following aortic bioprosthesis deployment, hypotension developed in the context of severe mitral regurgitation due to systolic anterior motion of the mitral valve with peak-to-peak LV-Ao gradient of 120 mm Hg. Alcohol septal ablation was immediately performed with subsequent improvement of blood pressure and near resolution of LVOTO. Similarly, Takeda et al. report a TAVR case involving septal hypertrophy without LVOTO under resting conditions abruptly developing SAM, severe mitral regurgitation, and LVOTO following transapical deployment of the prosthesis [22]. Beta-blockade and cibenzoline (a class Ia antiarrhythmic with anti-inotropic effects) were administered without clinical improvement. Subsequent pacemaker implantation was associated with resolution of SAM and LVOTO. Finally, Suh et al. describe a case of transapical TAVR where a bioprosthesis was successfully placed, but the patient developed low urine output the following morning. It was noted that following loop diuretic administration to augment urine output, the patient became hypotensive, and the addition of norepinephrine decreased the blood pressure further. Coronary angiography did not identify flow-limiting lesions, but mid-cavitary obstruction was noted during ventriculography. Echocardiography demonstrated systolic anterior motion of the mitral valve. The patient improved with intravenous fluids and escalating doses of beta-blockade and did not require any further invasive intervention [23].

The three cases highlight the importance of identifying the cause of post-TAVR hypotension, especially since the treatment of LVOTO is confounded by therapy for alternative causes, such as pressors for vasodilatory shock. Indeed, a recent review describing the role of echocardiography in identifying complications associated with TAVR suggests specific assessment for LVOTO in cases of hypotension [24]. Predictors of post-procedural LVOTO are likely similar to those previously identified for outflow obstruction following surgical AVR: small ventricular size, hyperdynamic systolic function, high interventricular septum to posterior wall thickness ratio, high transvalvular gradients, and small LV mass [25]. Successful management of post-procedural

LVOTO ranges from medical therapy to increase preload and reduce myocardial contractility to invasive therapy such as urgent alcohol septal ablation or pacing or mechanical support. Finally, two of the three cases cited specifically mentioned preprocedural concern for LVOTO following TAVR which raises the concept of prophylactic intervention to septal hypertrophy implicated in obstruction. Shenouda and Naidu present a series of three cases of LVOTO and aortic stenosis in which two patients underwent alcohol septal ablation to treat severe obstruction *prior to* TAVR [20]. Neither case developed post-procedural LVOTO. Further work remains to identify more specific criteria for patients most likely to benefit from pre-TAVR septal reduction therapy.

Percutaneous Therapy for LVOTO and Associated Mitral Regurgitation: MitraClip

As an alternative to alcohol septal ablation for LVOTO therapy, an initial experience utilizing percutaneous mitral valve plication has recently been reported in a cohort of patients considered too frail or inappropriate anatomy for surgical myectomy, mitral valve repair, or alcohol septal ablation. Sorajja and colleagues successfully placed the MitraClip (Abbott, Abbott Park, Illinois) device across the A2-P2 leaflets of the mitral valve in six symptomatic patients with LVOTO, SAM, and mitral regurgitation [26]. No adverse events were observed, and mitral regurgitation and heart failure symptoms were improved in all patients at 1.5-year follow-up. While three patients did demonstrate residual elevated LVOT gradients, the clinical significance of the finding is uncertain and has been postulated to potentially reflect a pressure recovery phenomenon. Potential advantages of this technique over alcohol septal ablation include the avoidance of septal scar creation (with associated risks of ventricular septal defect, arrhythmia, and heart block) and the ability to perform the procedure independent of coronary artery or basal septal anatomy. Of note, anecdotal experience suggests that once the MitraClip has been permanently deployed, future mitral valve repair is likely not feasible, and replacement may be the only surgical option should intervention be required.

Clinical Case Examples

To provide real-world context to several of the concepts discussed in this chapter, we present two cases which highlight the importance of identifying the presence of LVOTO in the setting of acute hypotension as well as initial management of patients with complex hemodynamics due to both dynamic and fixed outflow obstruction.

Evaluation and Management of Acute Hypotension

A 70-year-old woman presented to the emergency department with abdominal discomfort, nausea, and vomiting and developed chest discomfort while undergoing evaluation. A loud systolic murmur was auscultated at the right upper sternal border and across the precordium. EKG demonstrated sinus tachycardia with nonspecific ST-T wave changes; initial troponin was 0.75 (normal <0.10) and subsequently rose to 5.3 several hours later. Abdominal CT imaging demonstrated jejunal inflammation. Although no ST elevations were noted on repeat EKG, the persistence of her symptoms as well as tachycardia (HR 120 bpm) and hypotension (100/60; baseline 140/85) led the ED team to consult cardiology for urgent coronary angiography. Findings included angiographically normal-appearing coronary arteries and a peak-to-peak gradient of 140 mm Hg across her LV outflow tract. She was then transferred to the cardiac ICU for further care. Subsequent transthoracic echocardiography demonstrated severe anterior and apical hypokinesis with hyperdynamic function in the remaining segments. A sigmoid septum phenotype was observed with the basal anterior septum measuring 1.5 cm. Moderate to severe, posteriorly directed mitral regurgitation with systolic anterior motion of the mitral valve was observed, with Doppler estimates of an outflow tract gradient of 169 mm Hg (Fig. 25.2a). She was treated with aggressive IV fluids and a test dose of IV metoprolol tartrate which was associated with increase in blood pressure. She was then started on escalating doses of metoprolol tartrate for relief of LVOT gradient. Her chest pain, hypotension, and tachycardia resolved over the next 3 days, and she was discharged home in good condition, as her stress cardiomyopathy resolved. At outpatient follow-up 1 month later, treadmill stress echocardiography demonstrated complete resolution of wall motion abnormalities as well as no dynamic LVOTO under resting or exercise conditions (Fig. 25.2b).

Discussion This case highlights the importance of correctly identifying the primary cause of hypotension. We hypothesized that the initial GI symptoms led to severe dehydration and subsequent stress (Takotsubo) cardiomyopathy. In the setting of baseline sigmoid septal hypertrophy, the reduced preload and hyperdynamic basal segments led to severe LVOTO. Medical therapy to increase preload (IV fluids) and reduce contractility (beta-blocker initiation and uptitration) proved adequate to support her through the acute decompensation until the hypokinetic and hyperdynamic wall motion abnormalities resolved.

Acute Management of LVOTO and Aortic Stenosis

A 75-year-old woman was transferred from an outside hospital for worsening chest and jaw pain and dyspnea with minimal exertion to the cardiac step-down unit. Her history was notable for previously identified severe aortic stenosis (AS) for which eventual referral for TAVR was planned, given multiple comorbidities of pulmonary embolism 3 months prior, history of cerebral hemorrhage in 2011, arthritis, and overall frail state. A transesophageal echocardiogram was performed to further characterize her valvular heart disease, which identified hyperdynamic LV function, severe septal hypertrophy of 2.1 cm, LVOT obstruction secondary to systolic anterior motion of the mitral valve with a late-peaking gradient of up to ~100 mm Hg, and severe mitral regurgitation (Fig. 25.3a). A second mechanism of mitral regurgitation was identified as well with significant prolapse of the tip of the P1 leaflet. The aortic stenosis severity was characterized as severe with a peak velocity of 4.1 m/s. Left heart catheterization demonstrated minimal coronary artery disease and a Brockenbrough-Braunwald sign suggestive of severe, dynamic LVOT obstruction. The proceduralist noted that passing a catheter across the aortic valve could be easily accomplished during several attempts. The patient was stabilized with beta-blockade as well as a non-dihydropyridine calcium channel blocker but remained symptomatic with minimal activity. A heart team evaluation favored cardiac surgery for mitral valve repair, septal myectomy, and aortic valve replacement. However, a colonoscopy was performed

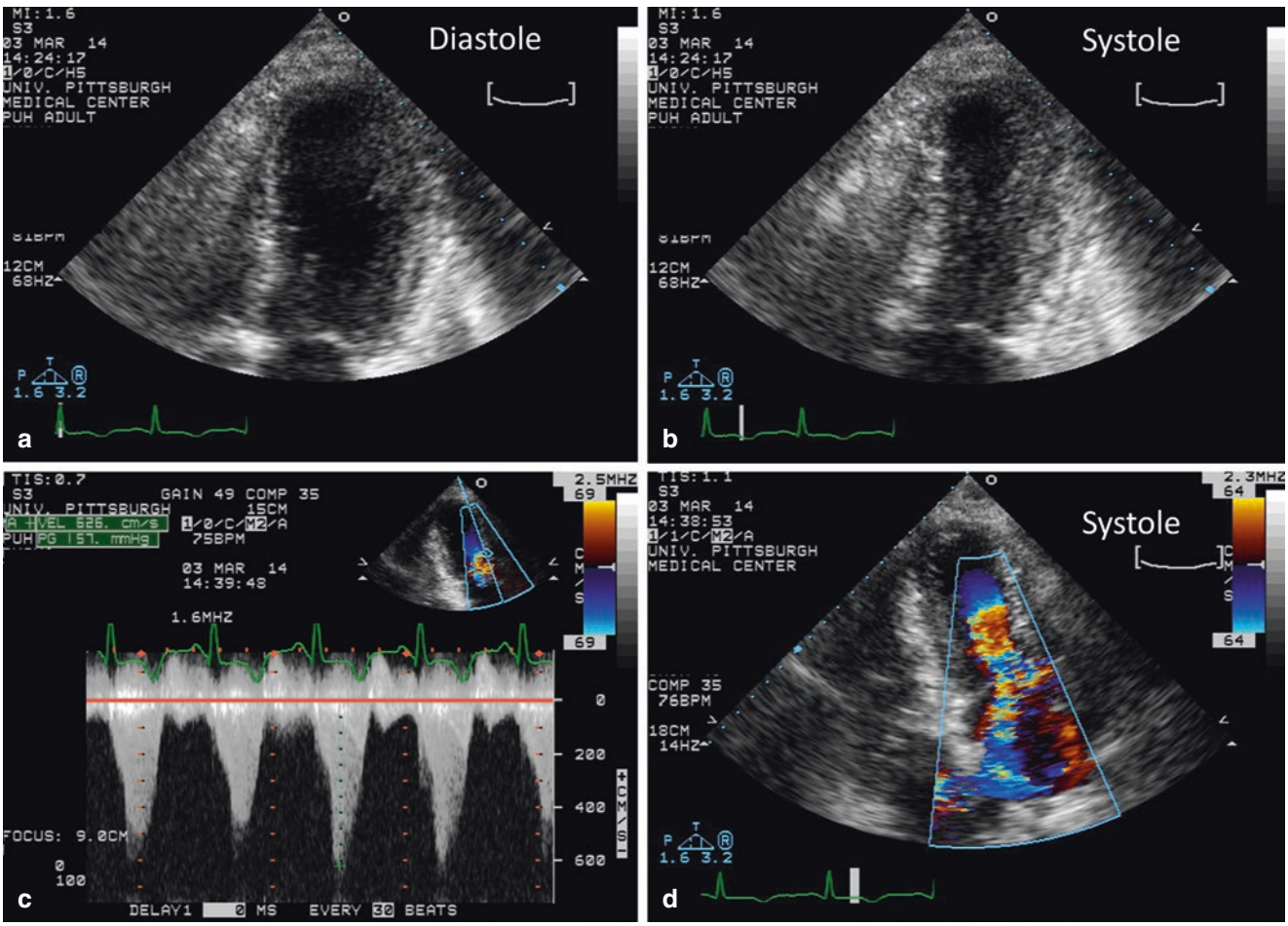

Fig. 25.2 (**a**) Example of patient with stress cardiomyopathy and LVOT obstruction. Panels A and B show diastolic and systolic imaging in the apical four-chamber view, respectively, demonstrating severe apical hypokinesis but hyperdynamic contractility at the base. Panel C shows spectral Doppler in the apical three-chamber view demonstrating severe LVOT gradient with corresponding color Doppler imaging in Panel D demonstrating severe LVOT turbulence as well as severe, posteriorly directed mitral regurgitation. (**b**) Follow-up transthoracic echocardiography demonstrating near resolution of the apical hypokinesis (panels A and B). Spectral Doppler interrogation of the outflow tract (panel C) shows complete resolution of the outflow gradient. Mitral regurgitation was reduced as well (not shown)

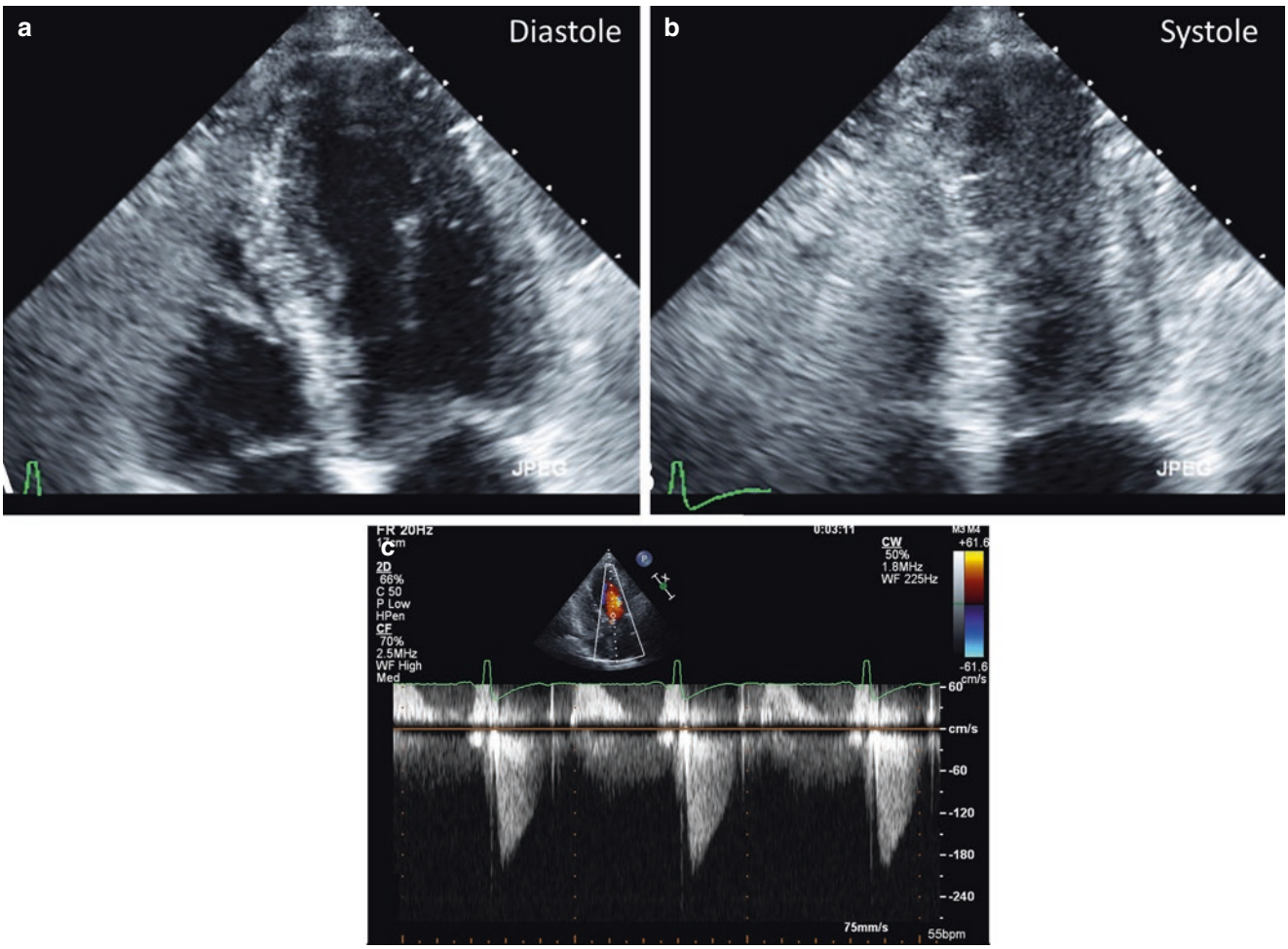

Fig. 25.2 (continued)

because of recent worsening anemia (Hg 7 mg/dL) which revealed a large adenocarcinoma. At this point, the heart team discussion focused on acute management of the severe LVOTO, and a trial of disopyramide therapy was started. The patient's LVOT gradient decreased from 100 mm Hg down to 9 mm Hg (Fig. 25.3b) by careful assessment to isolate the outflow velocity from the transvalvular velocity. The patient's symptoms improved, and she was discharged home and underwent uneventful colectomy (on disopyramide therapy) with plans for elective surgical AVR, myectomy, and mitral valve repair after 3 months of recovery.

Discussion This case also demonstrates the importance of identifying the underlying cause of acute decompensation in a patient with stable (albeit severe) valvular heart disease – in this case the possibility of concomitant LVOTO and AS. We hypothesized that the occult GI malignancy led to pulmonary embolism. Subsequent anticoagulation therapy likely accelerated worsening of her initially mild chronic anemia and unmasked significant LVOTO given her baseline septal hypertrophy. Identification of the dynamic LVOT obstruction in addition to her fixed valvular stenosis allowed specific therapy to be directed to reduce the risk of worsening obstruction and/or shock. While various strategies were discussed including alcohol septal ablation and MitraClip, her frail state led to the initial choice of disopyramide, a potent anti-inotropic agent with demonstrated efficacy in the relief of LVOTO and associated symptoms [27]. Of note, immediate release disopyramide was used in this case with good effect due to the national shortage of the extended release form.

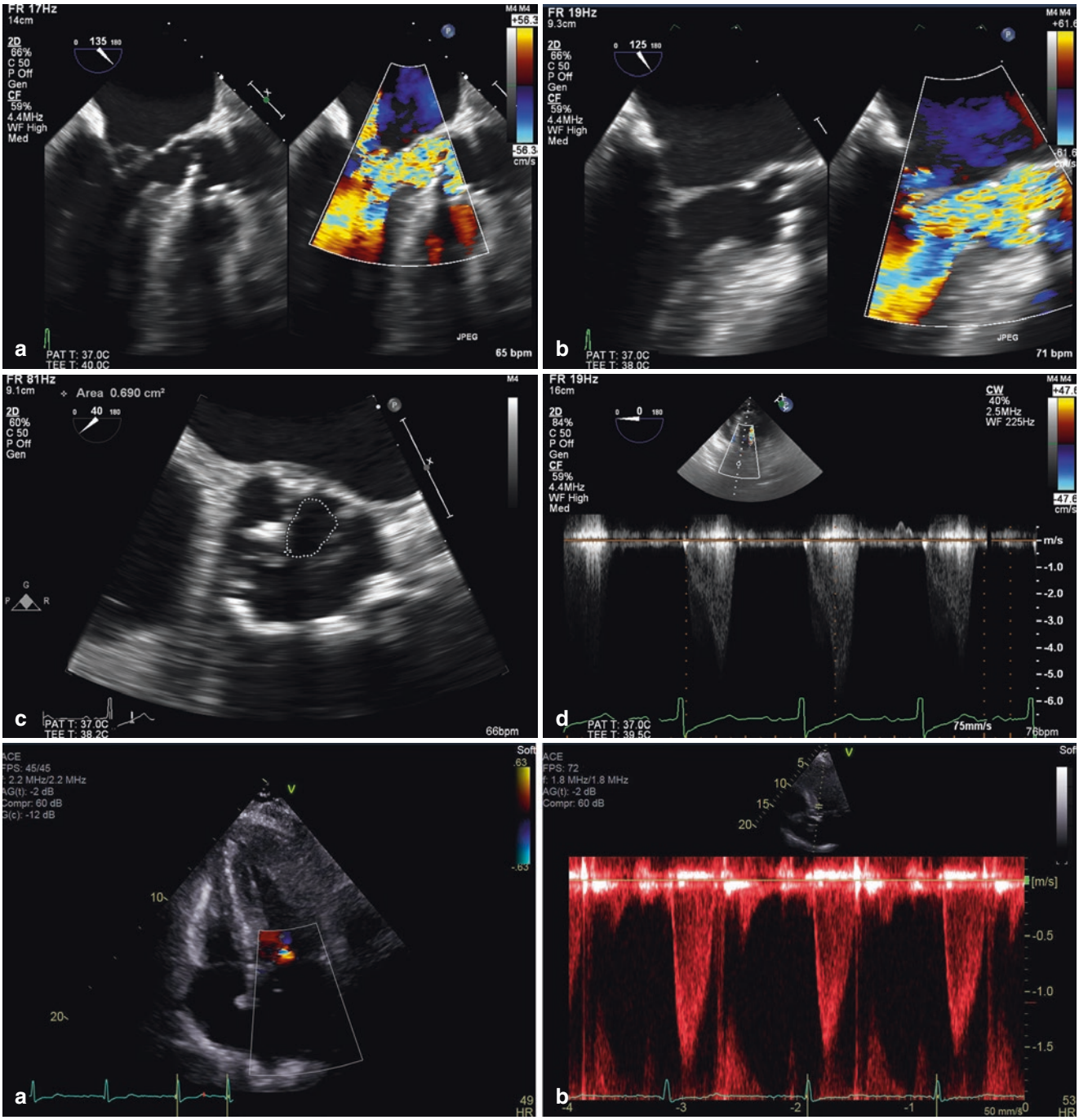

Fig. 25.3 (**a**) Example of patient with combined LVOT obstruction and aortic stenosis. Panels A and B show two views of transesophageal echocardiography in the mid-esophageal ~130 degree view (panel B is zoomed in) demonstrating septal hypertrophy, calcified aortic valve, and LVOT turbulence. Panel C shows a calcified aortic valve with significantly stenotic valve area by planimetry. Transgastric evaluation of the LVOT by spectral Doppler demonstrated severe late-peaking LVOT gradient. (**b**) Follow-up transthoracic echocardiography following disopyramide initiation shows minimal LVOT turbulence in the apical five-chamber view (panel A) with normalization of the LVOT gradient by spectral Doppler (panel B)

Conclusions

Patients with hypertrophic cardiomyopathy, with or without obstruction, are not infrequently present in critical status, with acute pulmonary edema, hypotension, and even frank shock. Rapid assessment of such patients to determine the presence or absence of obstruction, magnitude and etiology of obstruction, and extent of decompensation are paramount to planning a course of treatment. In such patients, treatment may include fluids, diuresis, pure pressors, intubation, use of right heart catheterization, beta-blockers or disopyramide, or advanced therapies such as urgent or emergent alcohol septal ablation or implantable assist devices. Keys to management include a thorough assessment and reassessment and likely a team approach including HCM specialists, critical care specialists, and surgeons.

Clinical Pearls

- Refractory LVOT obstruction that does not respond adequately to medications, fluids, or IV pressors may require temporary cardiac assist devices; in this regard, the Impella device is the most rapid and likely to benefit the patient by directly bypassing the obstruction.
- IABP must be avoided in cases of obstruction, as the reduction in afterload may paradoxically increase obstruction and further reduce blood pressure and cardiac output.
- Phenylephrine is the pressor of choice, and digoxin, dopamine, dobutamine, and other inotropes should be avoided whenever possible in the patient with LVOTO.
- Right heart catheterization may be very useful for titrating volume status to avoid congestion but maintain adequate filling in the obstructed or non-obstructed patient with diastolic dysfunction.
- The best treatment for post-AVR (TAVR or surgical) or post-MVR LVOTO is to predict the development of this complication and treat prophylactically either with medications or preferably with durable therapy such as alcohol septal ablation or via concomitant surgical myectomy. A careful preprocedural hemodynamic and anatomic assessment can often predict when this complication is likely.

Questions

1. A 79-year-old woman with a past history of hypertrophic cardiomyopathy is admitted to the ICU after presenting to the emergency department with shortness of breath, with subsequent evaluation notable for multilobar pneumonia associated with hypotension (60/40 mm Hg) and tachycardia (115 bpm). A loud systolic murmur is heard at the cardiac base which augments with Valsalva maneuver. Her blood pressure remains unchanged after a 2 L IV bolus of normal saline. She reported taking her usual metoprolol succinate dose that morning. Which of the following agents would be MOST appropriate to support her blood pressure?
   A. Dobutamine
   B. Milrinone
   C. Phenylephrine
   D. Norepinephrine
   E. Dopamine

   Answer: C. Acute management of LVOTO following IV fluids and medical therapy with an anti-inotropic agent includes the use of a pure alpha agonist such as phenylephrine. The remaining agents may augment contractility and/or heart rate and worsen LVOT obstruction.

2. Which of the following scenarios would be least likely to cause left ventricular outflow tract obstruction in a patient presenting to the ICU?
   A. Acute MI of the anterior wall
   B. Stress cardiomyopathy (Takotsubo syndrome)
   C. Mitral valve repair surgery using a rigid ring for support
   D. Trauma surgery with 5 L estimated blood loss
   E. Dilated cardiomyopathy patient in acute HF

   Answer: E. Acute MI, stress cardiomyopathy, MV repair, and hypovolemia have all been associated with LVOTO (even in patients without significant LVH). Typically, patients with DCM have thinned, dilated ventricles with reduced systolic function and are not prone to LVOTO.

3. Which of the following temporary mechanical support devices is contraindicated in patients with HCM, LVOTO, and cardiogenic shock?
   A. ECMO
   B. Impella 2.5
   C. Impella CP
   D. IABP
   E. TandemHeart

   Answer: D. IABP is contraindicated in patients with LVOTO, as the reduction in afterload may worsen obstruction and paradoxically further reduce blood pressure and perfusion. Impella is theoretically favored in this setting, although data are limited.

4. A patient with long-standing HCM and obstructive physiology goes into atrial fibrillation with rapid ventricular response, followed by syncope. Upon awakening, she is

in respiratory distress and emergently intubated for pulmonary edema. Heart rate is 145 and irregular, and blood pressure is 80/60. Her EF is known hyperdynamic. Which of the following is contraindicated?

A. Trial of rate control with beta blockers followed by cardioversion if patient remains hypotensive
B. IV neosynephrine to maintain MAP > 65
C. Anti-arrhythmic therapy with amiodarone
D. IV fluid boluses to maintain blood pressure
E. Dopamine infusion to maintain blood pressure

Answer: E. Dopamine is contraindicated in patients with LVOT obstruction, as although it will raise blood pressure, it will also increase the obstruction. The combination will require escalating doses of dopamine which promotes progression to cardiogenic shock.

5. A patient is referred to the TAVR clinic for worsening AS. On echocardiographic evaluation there is calcified aortic valve and a pressure gradient (mean) of 50 mm Hg. There is also a basal septum of 1.7 cm and turbulence both across the outflow tract and the aortic valve. A meticulous hemodynamic assessment reveals a resting gradient of 30 across the aortic valve and 20 across the outflow tract, but the peak pressure gradient goes from 50 to 150 with Brockenbrough. What is a reasonable course of action?

A. Reassessment of surgical candidacy and consider surgical AVR and myectomy
B. Alcohol septal ablation and reevaluation of AS gradient
C. Alcohol septal ablation followed by TAVR once septum regresses
D. Medical management with beta blockers and/or disopyramide
E. All of the above

Answer: E. This patient has moderate AS and severe LVOTO obstruction physiology. All of the above options are reasonable in this patient.

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End-Stage Diastolic and Systolic Heart Failure: Evaluation and Timing of Heart Transplantation

26

Eric D. Popjes and Anjali Tiku Owens

Key Points

- End-stage HCM can present as systolic or diastolic heart failure.
- LV cavity enlargement with regression of wall thickness is the classic remodeling phenotype.
- Once heart failure symptoms are present with LVEF <50%, standard heart failure therapies should be instituted including ACE inhibitor, beta-blocker, loop diuretics, and aldosterone antagonists if indicated.
- End-stage restrictive HCM presents a treatment dilemma but often requires advanced therapies.
- Patients with end-stage HCM are at risk for sudden cardiac death and should have an ICD placed for primary prevention.
- Patients with end-stage dilated HCM are potential candidates for mechanical circulatory support.
- Heart transplant is a viable option for patients with advanced HCM, and early referral should be made to a transplant center.
- Approximately 1–2% of all transplants are done for HCM.

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Progression of Disease

Hypertrophic cardiomyopathy (HCM) progresses to the "end stage" in an estimated 3–15% of patients [1–5]. End-stage (ES) HCM is classically characterized by a left ventricular ejection fraction (LVEF) of <50% at rest, representing global systolic dysfunction. Recent studies have revealed several morphologically distinct patterns of remodeling in ES HCM. The most definitive remodeling includes dilation of the left ventricular (LV) cavity with regression of hypertrophy, at times progressing to distinct thinning of the walls with severe systolic dysfunction and some degree of mitral regurgitation. A second pattern includes dilated or progressively increasing LV cavity dimension with preserved hypertrophy. Yet another pattern includes a relatively normal or preserved LV cavity size with mild hypertrophy or slight regression of hypertrophy. Finally, some patients will present with continued marked hypertrophy and no dilation of LV cavity [2]. Atrial enlargement, pulmonary hypertension, and a restrictive filling pattern are common features of advanced HCM, regardless of morphology. Importantly, patients who are truly at ES typically do not have evidence of LV outflow tract obstruction.

Disease progression is variable and often unpredictable, with a range of several years to many decades from diagnosis of HCM to transition to ES disease. Once ES HCM is identified, however, it is usually a rather precipitous decline to death or heart transplant, with some studies reporting an 11% mortality rate per year [2]. A high index of suspicion is required, especially in cases where typical remodeling to a dilated phenotype is not apparent on standard transthoracic echocardiogram. High-risk clinical characteristics for progression to ES disease include younger age at diagnosis, family history of HCM and in particular family history of ES disease and/or sudden death, persistence of atrial fibrillation or ventricular tachycardia, large scar burden on MRI totaling >25% of the myocardium, greater wall thickness [1], and complex genotype with double or triple mutations of sarcomere genes [6].

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Cardiac MRI, cardiopulmonary exercise testing, and right heart catheterization can be helpful to identify high-risk features heralding the onset of ES disease. In recent years, the use of MR imaging for the identification of large, confluent, or transmural areas of delayed enhancement suggesting significant fibrosis of the LV has been associated with advanced cardiomyopathy and risk of sudden death and heart failure, especially when >25% of the myocardium. Cardiac MRI may also have an emerging role in identifying the early transition to end-stage disease, during which time the LVEF is in the 50–65% range, but significant late gadolinium enhancement can be discerned [7, 8]. In a postmortem study of explanted hearts from HCM patients who underwent transplant, more than 30% of the myocardium was replaced by fibrosis [9].

Cardiopulmonary exercise testing (CPET) objectively quantifies exercise tolerance and is useful for tracking progressive functional limitation and is often used as a threshold for referral for advanced therapies such as heart transplant. Worrisome features on CPET include a peak oxygen consumption (VO_2 max) of ≤14 mL/kg/min or less than 50% predicted for age [10]. In addition, the ratio of minute ventilation over minute carbon dioxide exhaled (VE/VCO_2) > 34 signals ventilatory insufficiency and portends a poor prognosis. Right heart catheterization is useful to define filling pressures and cardiac index in addition to the degree of pulmonary vascular disease in any patient who has symptoms of heart failure. Right heart catheterization is particularly helpful to define hemodynamics in cases where imaging has not shown typical remodeling, but signs and symptoms of heart failure are present. In these situations, significant restrictive physiology with low cardiac output and severe pulmonary hypertension can be found.

Management of End-Stage HCM

Once symptoms progress to NYHA functional class III/IV in nonobstructive HCM, especially coupled with signs of adverse remodeling by cardiac imaging and/or recurrent atrial or ventricular arrhythmias despite standard therapies, it is appropriate to reevaluate pharmacologic and device therapy and to refer the patient to a heart transplant center for further evaluation. Specifically, as outlined in both the ACCF/AHA heart failure and hypertrophic cardiomyopathy guidelines, in patients with dilated ES HCM, it is appropriate to initiate therapy with ACE inhibitors and beta-blockers and to use loop diuretics as needed to relieve congestion. In some cases, aldosterone antagonists and digoxin may be beneficial. Consideration should be given to discontinuation of negative inotropic agents such as centrally acting calcium channel blockers and disopyramide [11, 12]. Other cardiovascular conditions that may be contributing to the development of systolic dysfunction should be investigated, including coronary artery disease, valvular disease, and metabolic and infiltrative disorders. CAD must be definitively ruled out, especially in older patients with cardiovascular atherosclerotic risk factors. If onset of systolic dysfunction is abrupt or is present at the time of diagnosis, care should be taken to exclude phenocopies of HCM [13, 14]. After addressing reversible conditions, implantation of a defibrillator is reasonable for primary prevention of sudden cardiac death in patients with ES HCM who are not being referred for palliative care [12]. The role of cardiac resynchronization therapy (CRT) is less clear in this group of patients. Small single-center studies suggest that some patients with ES HCM, left bundle-branch block, and dilated LV may derive symptomatic benefit from CRT in terms of NYHA functional class and objective improvement in remodeling parameters [15, 16]. However, CRT does not appear to provide substantive improvement in systolic function [17].

Optimal medical therapy is commonly limited in this population due to hypotension with vasodilators and prerenal azotemia in response to diuretics given the steep left ventricular pressure-volume relationship present. Autonomic dysfunction, sometimes present in HCM patients, may further limit optimization of and tolerance to medications. Clinicians need to assess pulmonary hypertension including pulmonary vascular resistance and look for evidence of cardiac cirrhosis due to long-standing elevation in right-sided filling pressures as these conditions may preclude heart transplantation or necessitate dual organ transplant (heart/liver) in the case of cardiac cirrhosis.

Left Ventricular Assist Device Support in Patients with HCM

There is a very limited data reported on the use of left ventricular assist devices (LVADs) to support patients with end-stage HCM. Figure 26.1 represents a clinical case example. HCM patients were generally excluded from or not specifically mentioned in the clinical trials that have been performed to evaluate the efficacy of LVADs for destination therapy (DT) or as a bridge to transplant (BTT) [18–20]. Other than clinical experience, most data on mechanical circulatory support for patients with HCM and severe heart failure are case reports or very small single-center case series. Two case reports with the use of the HeartMate II LVAD as BTT both showed improved symptoms [21, 22]. One patient who had systolic dysfunction, pulmonary hypertension, and severe heart failure and was intolerant of medical therapy was successfully bridged to transplant. The other patient, who had had a previous myectomy and tricuspid valve repair but continued to have severe heart failure, frequent hospitalizations, and high filling pressures, was successfully

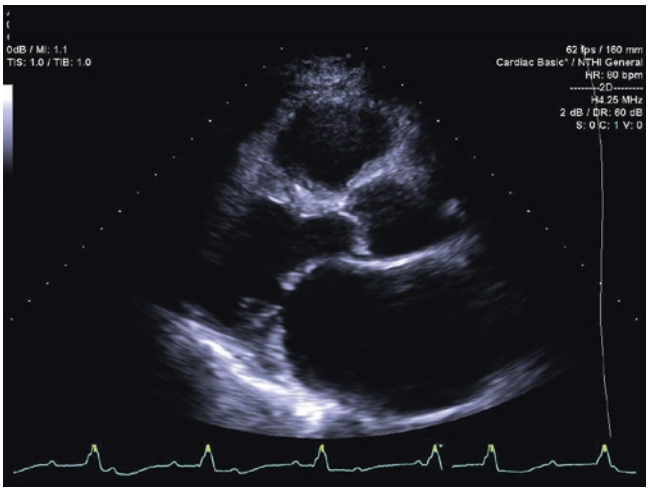

Fig. 26.1 Parasternal long axis echocardiographic view on a 55-year-old man with long-standing HCM who developed LV systolic dysfunction (LVEF 25%), LV cavity enlargement and wall thinning, and progressive heart failure symptoms. Despite all medical therapies, he progressed to class IV heart failure symptoms, underwent LVAD placement, and was successfully bridged to transplantation. LV size is mildly increased when adjusted for body surface area and larger than on previous echocardiograms. Septal thickness is at the upper limits of normal, and the left atrium is severely enlarged

supported for 10 months and was still awaiting transplant at the time of publication of the report. A case series of three patients implanted with the HeartWare left ventricular assist system (LVAS) showed similar successful support with improved hemodynamics and a similar degree of decrease in LV end-diastolic dimension when compared to those implanted with the HeartWare LVAS who had dilated cardiomyopathy [23]. One patient was successfully bridged to transplant, and one was still being supported at the time of the publication, but one patient had died during support due to thrombus formation at the device's inflow cannula at the LV apex.

A case series from the Mayo Clinic reported on the support of four patients with HCM and four patients with restrictive CM using the HeartMate II LVAD [24]. Two of the HCM patients had concomitant myectomies. On average, the LV cavities were smaller, there was more LV hypertrophy, and there was a higher incidence of right ventricular dysfunction in these patients when compared to patients with DCM and LVAD support. All of the HCM patients had very low LVEF suggesting the dilated end-stage form of HCM. After implant, pump flows were lower in the HCM patients, which were thought to be related to more RV dysfunction, but there was no difference in mortality, transfusion requirements, and overall length of stay when compared to the patients with DCM.

There are several concerns regarding the use of LVADs to support patients with severe heart failure and HCM. The smaller LV cavity size as compared to dilated cardiomyopathy may result in inadequate space for placement of the LVAD. In addition, apical hypertrophy may be present which may necessitate more extensive muscle resection at the time of implant, thereby making the procedure more complex and longer in duration. Malpositioned and hypertrophied papillary muscles may also pose a problem with LVAD cannula implantation and inflow obstruction. This may require relocation or resection of the papillary muscles in order to facilitate device implantation and allow for unobstructed flow into the inflow cannula. Lastly, once a LVAD is in place, it may be particularly important for the HCM patient to be even more diligent than other patients about maintaining adequate hydration so that the LV does not become underfilled and even smaller in size and LVAD inflow obstruction does not occur.

Bridging to Transplant

Supporting patients to a transplant can often prove to be a challenging task. Many strategies and therapies are used to bridge patients to transplantation, with the majority tailored to treating LV systolic dysfunction. Inotropic support in hospital or at home, LVADs, and intra-aortic balloon pumps (IABPs) are frequently used methods of support in the adult population. In pediatric patients extracorporeal membrane oxygenation (ECMO) plays a more frequent role than it does in adults. For the HCM patient with the end-stage dilated form of the disease, all of these treatment strategies can be and have been used with success, as the underlying anatomy in this situation is not dissimilar to patients with dilated cardiomyopathy. However, patients with end-stage restrictive HCM and smaller LV cavities are more challenging to support and bridge to transplantation. Inotropic agents are generally contraindicated and provide little or no clinical value as these patients already have normal or hyperdynamic systolic function. The small LV cavity seen in this form of HCM may not allow for LVAD (or biventricular VAD) placement or may limit the ability of the device to generate flow due to inlet obstruction. IABPs may do little to improve hemodynamics in these patients and are challenging to use long term, and ECMO only has a role in supporting those who need total circulatory support over the short term rather than for an extended period of time.

Unfortunately, the contraindication of various support strategies can place HCM patients with normal systolic function and restrictive physiology at a great disadvantage on the transplant waiting list since most listing prioritization systems throughout the world use these methods of treatment as means to justify a higher priority status. Moving HCM patients with end-stage restrictive disease to a higher status becomes more difficult, and waiting time on the list usually increases significantly. The same may also occur in those with life-threatening arrhythmias and less than severe heart

failure symptoms. In some circumstances an exception to the usual listing rules may be requested and is frequently granted.

For those patients who may not be candidates for other forms of mechanical support or who need biventricular support, the use of a total artificial heart can be considered as a means to bridge to transplant. This device provides excellent mechanical support for severe heart failure and eliminates the concern over arrhythmias since the ventricles and most atrial tissue are removed and replaced by the device. Figure 26.2 demonstrates the case of a young man with severe HCM with massive LV hypertrophy, recurrent ventricular tachycardia and fibrillation, and moderate heart failure who underwent total artificial heart implantation as a bridge to transplantation. He was deemed to not be a candidate for other therapies or other forms of mechanical support due to the extreme nature of his disease. However, the total artificial heart has the disadvantages of not being as widely available as LVAD therapy, carrying considerable morbidity and requiring longer recovery times than LVADs, and being too large for implantation into patients who are smaller than average in size or did not have significant dilatation of their native heart. There is limited data on the use of the total artificial heart, ECMO, the IABP, and BiVADs as a bridge to transplant in HCM patients. Most reports of these devices come from case reports or are briefly mentioned as being used in transplant center reports of their experience with HCM patients who are transplanted [25, 26].

Adult Heart Transplantation

Cardiac transplantation has proven to be an effective therapy for patients with end-stage heart disease from a variety of causes who have no other treatment options. Traditional indications are presented in Table 26.1. There remains no other treatment that is as effective at increasing quality and quantity of life in this select patient population. For those with end-stage heart failure, intractable arrhythmias, and severe ischemia, transplantation can transform one from a state of cardiac debilitation to essentially normal functional capacity.

Patients with HCM who undergo transplantation make up a small minority of all transplant patients, but reports from various authors have shown that heart transplantation can be an effective long-term therapy for HCM patients. A recent review of the United Network of Organ Sharing (UNOS) database found that 303 (or about 1%) of over 26,000 patients who were transplanted from 1990 to 2004 had HCM [27]. Long-term outcomes were similar to patients with dilated and restrictive cardiomyopathy and better than those with ischemic heart disease (Fig. 26.3). The 10-year survival for the HCM patients was 61%.

A single-center report by Coutu et al. has shown similar excellent long-term outcomes [28]. Thirteen of 14 patients

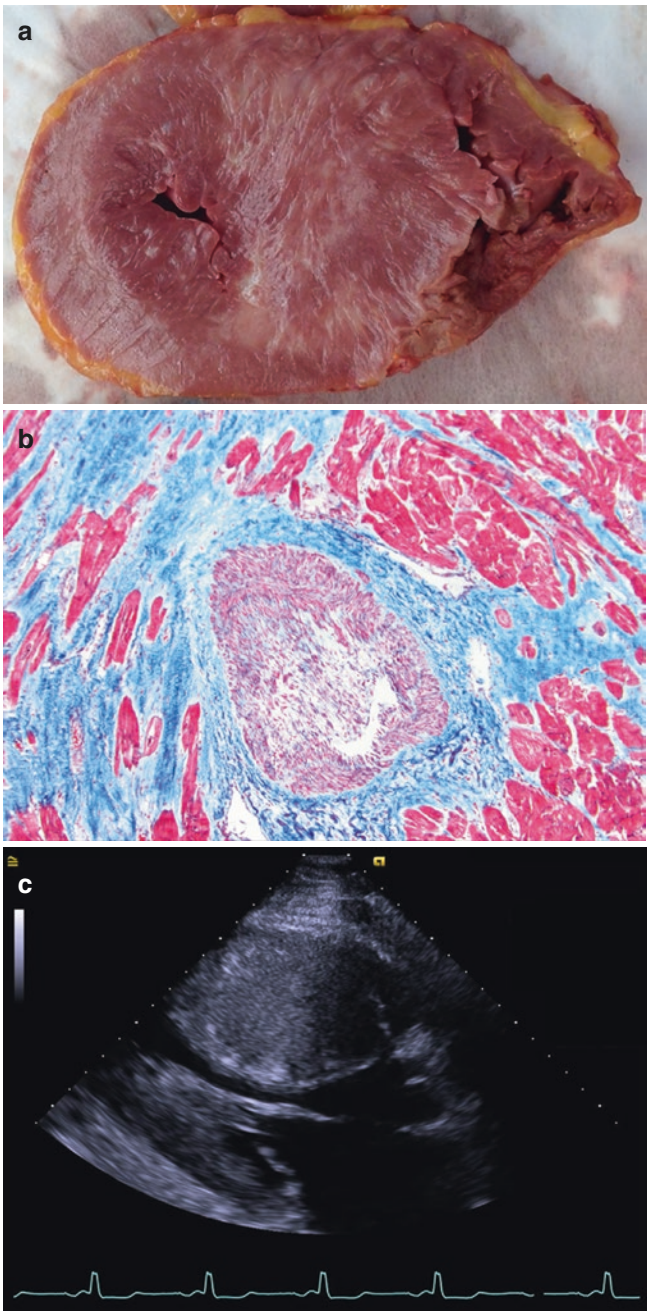

Fig. 26.2 Explanted heart from an 18-year-old man with severe HCM diagnosed at age 2 who in recent years had developed massive biventricular hypertrophy, progressive NYHA class III symptoms of heart failure, a mild resting midventricular gradient, and increasing frequency of VT/VF and ICD shocks despite antiarrhythmic therapy. Defibrillation thresholds were high, and multiple shocks at maximum device output were required to restore sinus rhythm. Due to severe nature of his disease, it was determined that transplantation was the most appropriate therapy. He was deemed ineligible for LVAD implant due to the small LV cavity, massive hypertrophy involving both ventricles, and VT/VF. A total artificial heart was successfully implanted, and he is awaiting HTx at the time of publication. Image (**a**) is a cross section at the midventricular level, showing massive hypertrophy of all walls, small LV and RV cavities, and extensive scarring. Septal dimension = 6.5 cm. Image (**b**) shows myocyte disarray, medial arteriolar hypertrophy, and extensive interstitial fibrosis on trichrome stain. Image (**c**) shows the parasternal long axis transthoracic echocardiogram image prior to implantation of the total artificial heart

(7 adults, or 2.7% of adult transplant done at this center during the period of interest, and 7 children, or 15% of their pediatric transplants) had undergone transplant for severe heart failure, while 1 had intractable ventricular tachycardia. The average age at the time of transplant was 40 years in the adult population and 13 years in the pediatric population. The median wait time on the transplant list was 9 months. Five-, 10-, and 15-year survival was 100%, 85%, and 64%, respectively, far exceeding the most recent median 11-year survival reported by the International Society for Heart and Lung Transplantation [29]. Another single-center report from Italy has reported similar excellent survival [30]. Of 21 adults with HCM listed for transplant, 18 patients (4% of their total transplants) were eventually transplanted with 5- and 7-year survival of 94%. Twenty of the 21 listed patients had end-stage dilated HCM, while 1 had hypotension and poorly tolerated atrial fibrillation. Median age was 45 years, and time on the wait list averaged 13 months. For those with the dilated end-stage form of the disease, the average time from diagnosis of HCM to development of LV dilation was 10 years, while the time from onset of dilation to transplant listing was 5 years. A small series of 9 patients reported from China has also shown good results with 8 patients having good long-term outcome with few complications [31]. In 2014, Lee and colleagues reported on their experience with transplant in HCM patients at UCLA between 1996 and 2004. Of the 462 transplants done during that time period, 11 (2.4%) were done for HCM. Two thirds were male and the mean age was 45 years. Long-term there was no difference in survival, rejection, or development of transplant vasculopathy when compared to non-HCM patients, and there was no evidence of recurrence of HCM in the donor hearts [32].

Table 26.1 Indications for heart transplantation

Severe heart failure
Refractory cardiogenic shock
Dependence on IV inotropic or LVAD support
Functional class III/IV symptoms or ACC/AHA Stage D heart failure
Peak $VO_2 \leq 10$–14 (approximately ≤50% predicted)
Severe symptoms of ischemia not amenable or responsive to other therapies
Recurrent symptomatic ventricular arrhythmias unresponsive to all other therapies

One of the largest single-center reports evaluated 41 HCM patients who underwent heart transplantation at Columbia University Medical Center from 1999 to 2010 [33]. This represented 5% of the total transplants done at Columbia during this time frame, which is higher than other reports and was attributed to referral bias since Columbia is a large transplant center. Thirty-nine of the patients had severe heart failure as their indication for transplant, while the remaining two had intractable arrhythmia. When the HCM patients were compared to other transplant patients, they were found to be younger, more frequently Caucasian, and less frequently supported with LVADs prior to heart transplantation. Interestingly, 27 of the patients had non-dilated hearts with restrictive physiology, low cardiac

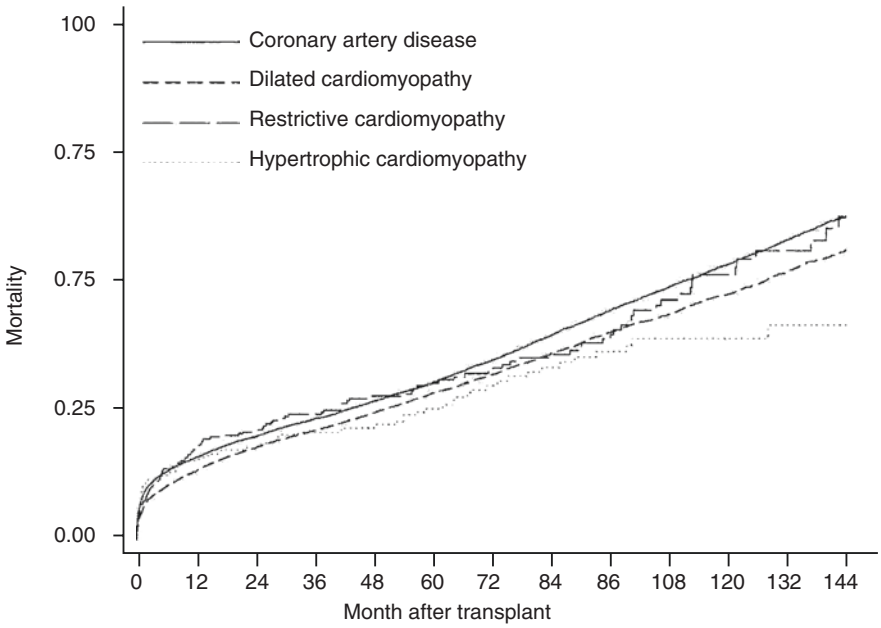

Fig. 26.3 Kaplan–Meier curves for all-cause mortality after cardiac transplantation in patients with HCM, ischemic cardiomyopathy (coronary artery disease), dilated cardiomyopathy, and restrictive cardiomyopathy. (Reprinted from Maron et al. [20], with permission)

output, and poor exercise capacity. The time spent on the waiting list for these patients with restrictive end-stage HCM was approximately twice as long as that for those with dilated end-stage HCM. This difference may be reflective of the disadvantage that severe heart failure patients with normal LVEF and non-dilated hearts have while on the transplant wait list. The 1- and 5-year survival of 90 and 86%, respectively, in HCM patients was better than those with ischemic cardiomyopathy and similar to those with other heart disease.

Two recent reports from large HCM centers in the United States and Italy have added to the description of HCM patients who have been transplanted. Rowin et al. looked at patients from two of the largest HCM centers in the United States. Of 2100 patients seen in these clinics, 46 (2.2%) either received or were listed for transplant, with 20 (1.1%) having normal LVEFs. All had severe clinical symptoms in the absence of LVOT obstruction, and nearly all had abnormal hemodynamic parameters, reduced peak oxygen consumption on stress testing, or echo findings suggestive of diastolic dysfunction. Of the 20 with normal LVEF, 9 were bridged to transplant with the use of inotropes, 1 with a LVAD, and 1 with an IABP [25]. Pasqualucci et al. reported on combined data from two large Italian HCM centers. Of 1014 patients seen between 1980 and 2012, 71 had severe symptoms in the absence of a LVOT obstruction. Of these 71 patients, 37 were evaluated for transplant, with 14 having undergone transplant (average age 43 years) at the time of the report. Of the remaining 23 patients evaluated for HT, 13 were not listed, 6 were still awaiting HT, and 4 died while waiting. Five of the evaluated patients had normal LVEFs, although the overall average LVEF in all patients was 33% [34].

It appears that HCM patients undergoing transplantation have key differences when compared to those with dilated forms of cardiomyopathy. Unfortunately most reports do not contain significant pretransplant clinical data such as LV size, wall thickness, LVEF, right ventricular function, valvular function, and hemodynamics. The data from some of the abovementioned reports and from individual clinical experience suggest that a significant portion of HCM patients who are transplanted have non-dilated ventricles with normal LVEFs but restrictive physiology, low output heart failure, and perhaps some degree of pulmonary hypertension. Some of these findings were also reported in a clinical and morphologic comparison of HCM, dilated cardiomyopathy, and ischemic cardiomyopathy patients undergoing heart transplantation [35]. The patients with HCM had a longer period of time from symptom onset to transplant (which may have been related to longer wait times), lower heart weight, and smaller LV cavity size but thicker and more scarred septums, higher LVEFs (45% vs 20% for non HCM patients), higher pulmonary artery and pulmonary capillary wedge pressures, and larger left atrial dimensions. Unfortunately, there was a significant amount of variation within the three groups, so in many cases the clinical and morphologic features were not specific enough in differentiating patients in one group from those in another.

Pediatric Heart Transplantation

HCM presenting in the first year of life is associated with increased mortality and morbidity especially when associated with symptoms of heart failure. In addition, children with end-stage dilated HCM, restrictive HCM, inborn errors of metabolism, and malformation syndromes are at increased risk of death or need for transplantation [36]. Small LV cavity size and massive LV hypertrophy are also linked to worse outcomes in the very young [37].

Heart transplantation in children is performed less frequently than in adults, and HCM as the reason for transplant represents a similarly small percentage of the total number of transplants in children as in adults. Patients with HCM appear to represent approximately 2–3% of the total patients listed for transplant according to data from the Organ Procurement and Transplantation Network (OPTN) database and the Pediatric Heart Transplant Study [38, 39]. There may be a higher mortality rate for children on the transplant waiting list, perhaps because of challenges in supporting and bridging them to transplant compared to patients with other forms of heart disease. At the time of transplant, pediatric HCM patients are more frequently on ECMO and ventilator support, and fewer have LVADs. Despite these challenges and difficulties, heart transplantation for children with HCM has been shown to be a viable therapy for children of all ages, including newborns who may have been diagnosed in utero and infants [37, 40]. Survival may be worse than that of children with other forms of heart disease and that of the average for adults, but most of this difference is driven by worse outcomes in those less than 1 year of age. Other risks for death and worse outcome include ventilator or ECMO support and UNOS status 1 at the time of transplant, all markers of a more critically ill patient whom one would expect to be at higher risk [38, 39].

Conclusions

Hypertrophic cardiomyopathy is a heterogeneous disease with variable clinical presentation, anatomical morphology, and long-term clinical course. A minority of patients with HCM may develop LV cavity dilatation and LV systolic dysfunction, a situation that should prompt aggressive medical therapy due to its ominous prognosis. Another

group of HCM patients has severe heart failure secondary to diastolic dysfunction and restrictive physiology, a clinical situation with few treatment options. Mechanical support and transplantation are two possible options for HCM patients with severe heart failure or intractable ventricular arrhythmias who have failed all other treatments. Outcomes of adult HCM patients undergoing transplantation appear to be better than the average for all transplant patients, whereas that for the pediatric HCM patient is worse than other children undergoing transplantation for other indications, primarily due to significantly worse outcomes in patients less than 1 year of age. Prompt recognition of the situation and severity of those with ES disease is essential, and referral to an HCM center and/or transplant center should be strongly considered.

Clinical Pearls

- Many HCM patients referred for transplant appear to have preserved EF but severe nonobstructive heart failure due to diastolic dysfunction/restriction.
- ES hypertrophic cardiomyopathy is a term used primarily for systolic dysfunction, reduction in EF, and wall thinning, with loss of any previous LVOT obstruction, but should also include patients with nonobstructive disease and profound heart failure.
- Patients with either form of ES disease should be referred early to heart transplantation, so that sequelae of long-standing heart failure such as cirrhosis and pulmonary hypertension do not develop or progress.
- ICDs should be considered in all patients with persistent reduction in EF, once the EF drops below 50%, given that HCM is typically marked by a hyperdynamic ventricle.

Questions

1. Which of the following is an indication for heart transplantation (HT) in a patient with hypertrophic cardiomyopathy?
   A. Severe heart failure symptoms unresponsive to medical therapy in the setting of normal systolic function
   B. Severe heart failure symptoms unresponsive to medical therapy in the setting of reduced systolic function
   C. Severe left ventricular outflow tract obstruction
   D. Massive left ventricular hypertrophy
   E. A and B

   Answer: E. Heart failure that is severe and unresponsive is an indication for OHT regardless of whether there is reduced or preserved systolic function. A LVOT obstruction should be treated with specific therapies that relieve that obstruction (such as septal reduction therapy and medications) and the symptoms it may be causing. Massive LVH by itself is not an indication for OHT; other factors (heart failure symptoms, uncontrolled ventricular tachycardia, and/or persistent symptoms of ischemia) need to be present for transplant to be considered.

2. Which statement is true regarding long-term outcomes in HT in adult patients with HCM?
   A. Median survival is less than that for those undergoing HT for ischemic cardiomyopathy.
   B. Average survival is less than 10 years.
   C. Median survival is at least as good as that for non-HCM patients who are transplanted.
   D. HCM tends to recur in the transplanted heart.
   E. There is a higher incidence of graft rejection in HCM patients after transplantation.

   Answer: C. Data from single center reports, multicenter databases, and large transplant databases suggest that survival in HCM patients after transplantation is excellent and is better than those who had ischemic CM and similar to those with nonischemic DCM. Average survival appears better than the overall 11-year average survival of all transplant patients. Although LVH may occur in the transplanted heart from a variety of factors (hypertension, rejection, ischemia, calcineurin inhibitor use), HCM does not recur in the transplanted heart. The incidence of graft rejection is not increased in HCM patients compared to other non-HCM patients who have been transplanted.

3. Transplantation in the HCM population is characterized by which of the following:
   A. HCM is a common indication for HT.
   B. Most HCM patients will need to be considered for HT.
   C. HCM patients undergoing HT are, on average, older than non-HCM patients undergoing HT.
   D. HCM patients tend to have longer wait times on the HT list.
   E. LVEFs are lower, and LV cavities are larger in HCM patients being considered for HT compared to non-HCM patients.

   Answer: D. Patients with HCM who are listed for OHT tend to have longer waiting times for transplantation. This seems to be driven primarily by patients who have

preserved LVEF who are not candidates for therapies that elevated transplant status such as inotropes and LVADs. HCM is not a common indication for OHT (<2–3% of all transplants are for HCM), and most transplant patients will not progress to need OHT (perhaps 1–2% of all HCM patients). HCM patients who are transplanted are generally younger than the average of non-HCM patients who are transplanted. This is likely influenced by the older age of patients with ischemic CM who undergo OHT.

4. HT in pediatric HCM patients differs from that in adults in which of the following ways:
   A. There is a lower overall survival in pediatric patients.
   B. There is more frequent use of LVADs in the adult HCM population.
   C. ECMO is used more often prior to HT in children.
   D. Pediatric patients more frequently have normal LVEFs and restrictive physiology.
   E. All of the above.

   Answer: E. All these statements are true. There is greater use of ECMO use and lower use of LVADs in the pediatric population due to anatomical constraints related to patient size and higher incidence of small LV cavity size, normal LVEF, and restrictive physiology in children. Survival after transplant in pediatric patients is lower, primarily due to a much higher mortality in those who are less than 1 year of age.

5. A 50-year-old man with HCM has increasing dyspnea and fatigue that do not respond to medical therapy. His LV is mildly dilated and his LVEF is 40%. He is placed on the HT waiting list but continues to clinically decline. Which of the following therapies could be considered as strategies for bridging to HT?
   A. LVAD
   B. Continuous inotrope infusion
   C. Intra-aortic balloon pump (IABP)
   D. Total artificial heart
   E. All of the above

   Answer: E. For the patient with reduced LVEF, all of these strategies can be considered. However, for the patient with preserved LVEF, the use of VADs and inotropes, and possibly IABPs, is more challenging and possibly detrimental. Total artificial heart placement may be a better approach in the HCM patient with normal LVEF in need of advanced mechanical therapies to bridge to transplant.

6. Left ventricular assist devices as a means of circulatory support are problematic in many patients with HCM due to all of the following except:
   A. Small LV cavity size
   B. Apical hypertrophy
   C. Mitral regurgitation
   D. Normal or hyperdynamic LV systolic function
   E. Hypertrophied, apically displaced papillary muscles

   Answer: C. Mitral regurgitation is not a contraindication for VAD placement. All the other factors may make VAD placement and long-term support and management difficult or impossible. LVADs should generally be avoided in those settings.

7. A 35-year-old female with HCM is listed for heart transplant. An extended wait time is anticipated due to blood group and size. LVEF is 45%, and she is being treated with beta blocker, ACE inhibitor, spironolactone, and Lasix. Which of the following is the most appropriate next therapy?
   A. Biventricular pacing
   B. Prophylactic defibrillator
   C. Continuous inotropic therapy
   D. Hemodialysis
   E. Sildenafil

   Answer: B. Prophylactic defibrillator is indicated for end-stage HCM when LVEF is <50%. Biventricular pacing has been shown in small studies to have some impact on remodeling parameters in patients with HCM, but no substantive improvement in ejection fraction or survival once listed for transplant. Continuous inotropic therapy can be utilized in selected patients with reduced cardiac output, and sildenafil may be beneficial in patients with elevated pulmonary vascular resistance. There is no need for dialysis in this patient.

8. A 65-year-old male with HCM, HTN, and hyperlipidemia reports new symptoms of breathlessness and chest pain. Transthoracic echocardiogram reveals resting left ventricular outflow tract gradient of 25 mmHg and LVEF of 50% which is decreased from 65%. What is the next best step in management?
   A. Left heart catheterization with coronary angiography
   B. Initiation of verapamil
   C. Initiation of diuretic therapy
   D. Implantation of prophylactic ICD
   E. Uptitration of beta blocker dose

   Answer: A. In patients with HCM who develop new systolic dysfunction, other cardiac disorders should be ruled out. This patient has risk factors for CAD including HTN and hyperlipidemia and is presenting with new breathlessness and chest pain. Coronary angiography with left heart catheterization to measure LVOT gradient

will provide the best hemodynamic and anatomic assessment. Stress testing may also be considered with careful attention to background medical therapy as beta blockers may interfere with assessment of ischemia in exercise testing. Changes in medical therapy should be guided by the underlying cause of systolic dysfunction. Prophylactic defibrillator may be indicated if LVEF remains <50% once reversible causes are treated.

9. Long-standing restrictive cardiac physiology can result in which of the following?
   A. Biatrial enlargement
   B. Congestive hepatopathy
   C. Cardioembolic disease
   D. Pulmonary hypertension
   E. All of the above

   Answer: E. Long-standing restrictive cardiac physiology can lead to chronically elevated biventricular filling pressures, adverse remodeling of the atria, atrial thrombus formation, and thromboembolic disease. Congestive hepatopathy and frank cirrhosis can develop if right atrial pressure is elevated chronically, with or without tricuspid regurgitation. Similarly, pulmonary vascular disease can progress with long-standing elevation of left-sided filling pressures.

10. A patient with history of obstructive HCM has progressed to end-stage disease with LVEF of 35% and fluid retention. There is no longer LVOT obstruction by echocardiogram. Peak VO_2 = 13 mL/kg/min, respiratory quotient = 1.2. Right heart catheterization reveals RA 11 mmHg, mean PA 27 mmHg, PCW 19 mmHg, CI 2.0 L/min/m^2, and pulmonary artery saturation 58%. Which of the following is appropriate medical management?
   A. Discontinue diuretic.
   B. Uptitrate disopyramide.
   C. Discontinue verapamil.
   D. Referral to transplant center.
   E. C and D.

   Answer: E. In this patient who has a reduced LVEF, marginal cardiac index, and severely reduced functional capacity as evidenced by CPET, it is appropriate to discontinue negative inotropic agents and start transplant evaluation. Diuretics should be continued for symptomatic congestion.

11. A 54-year-old female with HCM presents with worsening exercise tolerance. Exam is notable for perioral cyanosis, elevated jugular venous pressure, and palpable liver. TTE reveals no obstruction and LVEF of 60% with biatrial enlargement. BNP is elevated. Six-minute walk distance = 300 m. What is the next best step in management?
   A. Increase beta blocker dose.
   B. Order pulmonary function testing.
   C. Start ACE inhibitor.
   D. Right heart catheterization.
   E. Add digoxin.

   Answer: D. This patient is presenting with volume overload and marginal cardiac output as evidenced by elevated venous pressure, palpable liver edge, and cyanosis. Right heart catheterization should be done to evaluate hemodynamics. Normal LVEF with biatrial enlargement and elevated BNP are concerning for restrictive phenotype of end-stage disease.

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Novel Medical Therapeutics for Hypertrophic Cardiomyopathy

27

Stephen B. Heitner

Key Points

- Drugs commonly used in HCM management, with the exception of propranolol, are not formally indicated for treatment and are thus all deemed off-label in this population.
- HCM is considered a candidate for orphan drug development, which has spurred discovery of novel therapies in recent years.
- Three drugs have recently made it to clinical trial, although only mavacamten (Myokardia, Inc.) is slated for large-scale enrollment with encouraging early results in patients with obstructive HCM.

Introduction

Current first-line medical treatment for symptomatic hypertrophic cardiomyopathy (HCM) consists of use of beta-blockers, verapamil, or diltiazem. Treating physicians can consider the addition of disopyramide, where available, if not contraindicated and if tolerated. This strategy is outlined in both the 2014 European Society of Cardiology [1] and the American College of Cardiology Foundation/American Heart Association guidelines for the diagnosis and management of hypertrophic cardiomyopathy [2]. Patients with refractory symptoms are often considered for septal reduction therapies (surgical myectomy or percutaneous alcohol septal ablation), which are very often effective at reducing LVOT obstruction and improving symptoms and longevity [3].

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An important subgroup of patients includes those with refractory symptoms due to the development of systolic dysfunction and/or heart failure with preserved ejection fraction – in these patients cardiac transplantation may be the only effective option.

Importantly the last drug approved for the treatment of HCM was propranolol. This was based on a discovery published in 1964. Since then no drugs have been approved in the United States for the treatment of HCM, and unless propranolol is used, all therapies recommended within those guidelines are considered "off-label."

The unique etiopathology of HCM begs the question as to whether these agents, studied in more common forms of cardiomyopathy, will be ineffective or may expose patients to unwanted off-target effects. Despite their effectiveness in some patients with HCM, standard therapies for dilated cardiomyopathy, ischemic cardiomyopathy, and angina are often contraindicated in patients with HCM [4]. With this clear and unmet clinical need, the Working Group of the National Heart, Lung, and Blood Institute [5] has identified the need for therapies targeted at direct modification of HCM pathophysiology. Moreover, the Orphan Drug Act of January 1983 is specifically designed to encourage the pharmaceutical industry to develop drugs for rare and/or inherited conditions. Accordingly, HCM has recently been given orphan disease status for this explicit purpose.

Within the past 5 years, three drugs, each targeting different pathways within HCM pathophysiology, have come to the clinical trial arena:

- *Perhexiline* – Sodium and calcium channel blockade, as well as metabolic modulation
- *Eleclazine (GS-6615)* – Selective late sodium channel blocker
- *Mavacamten (MYK-461)* – Direct cardiac myosin modulator

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Perhexiline

The mechanism of action of perhexiline in hypertrophic cardiomyopathy is proposed to be threefold:

I. Inhibition of carnitine palmitoyltransferase I (CPT-1)
II. Inhibition of INaL
III. Effects on Ca^{2+} channels

CPT-1 is the enzyme responsible for mitochondrial uptake of long-chain fatty acids, and inhibition of this enzyme is thought to result in greater cellular dependence on carbohydrate utilization for adenosine triphosphate (ATP) production. Unlike ATP production from long-chain fatty acids (the usual metabolic pathway in cardiomyocytes), ATP production from carbohydrates is oxygen-independent and potentially more efficient. This hypothesis has been applied to cardiac ischemia and has resulted in the drug being licensed in Australia and New Zealand for many years [6–8].

Perhexiline is a late sodium current inhibitor ($I_{Na}L$) and is thought to be anti-arrhythmogenic in a similar way to amiodarone [9, 10]. HCM is associated with abnormal $I_{Na}L$ enhancement, which may contribute to the pathogenesis of both electrical and contractile dysfunction (see eleclazine) [11]. Furthermore, inhibition of $I_{Na}L$ that reduces intracellular sodium-dependent calcium overload may be cardioprotective and enhance myocardial contraction [12]. Finally, blockade of voltage-gated L-type calcium channels may further protect the cardiac myocytes from intracellular calcium overload and potentiate effects on the $I_{Na}L$ channel [13].

The known serious side effects of this agent include neuropathy, hepatitis, rash, renal failure, myositis, and hypoglycemia. These tend to be dose related and can be mitigated by therapeutic drug monitoring.

Perhexiline was evaluated in the United Kingdom at a single center, in a randomized fashion, with 46 symptomatic nonobstructive HCM (peak oxygen consumption <75% predicted) patients for a period of 3–6 months. In this study, perhexiline improved myocardial energetics, improved markers of diastolic dysfunction, improved symptoms, and improved the peak oxygen consumption (peak VO_2) compared with placebo. The primary endpoint of peak VO_2 increased by an absolute of 2.1 ml/kg/min in the perhexiline group versus a decline of 1.3 ml/kg/min in the placebo group [14].

This study provided the impetus for a phase-IIb clinical trial in the United States that began in August 2016 (NCT02431221). To date the independent data monitoring committee has not reported any specific safety concerns regarding the drug, but unfortunately, after enrolling 30 patients with nonobstructive HCM, the sponsor decided to terminate the study early.

Eleclazine (GS-6615)

Eleclazine is a potent and selective inhibitor of the cardiac $I_{Na}L$. It was being developed by Gilead Sciences, Inc., for the treatment of long-QT syndrome type 3 (LQT3) and symptomatic HCM and for the suppression of ventricular arrhythmias in other cardiomyopathies.

The impetus to evaluate this pathway stems from the fact that it has been shown that HCM, myocardial ischemia, and congestive heart failure are associated with an enzyme-induced acquired sodium-channel phosphorylation that may disrupt sodium-channel inactivation and increase $I_{Na}L$ activity. This is somewhat different to the mechanism of QT prolongation seen in hereditary long-QT III syndrome. In long -QT III, there is a mutation in the gene SCN5A that results in changes of the amino acid sequence of the sodium-channel that prolongs the inactivation phase and ultimately the QT segment on a 12-lead EKG [15]. Furthermore, in HCM it is felt that this $I_{Na}L$ secondarily favors entry of calcium into the cell via the sodium/calcium exchanger and disrupts cytosolic calcium handling. This in turn predisposes to arrhythmias as well as altered cardiomyocyte mechanics (increased contractility and diastolic dysfunction) [11].

In an in vitro study of tissue obtained from patients undergoing septal myectomy, $I_{Na}L$ activity was more than double compared with controls. Treating this tissue with ranolazine (another $I_{Na}L$ inhibitor) resulted in improvement or reversal of electrical and mechanical metrics [11]. Based on these findings, it was hypothesized that there were four potential mechanisms whereby eleclazine would be effective in HCM [16]:

- Improving diastolic dysfunction
- Decreasing microvascular ischemia (though improved diastolic function)
- Reducing the burden of ventricular arrhythmias
- Reducing LV outflow tract obstruction

In an open-label study using ranolazine with 14 nonobstructive HCM patients, investigators showed an improvement in patient-reported symptoms over the 2-month study period, primarily with the greatest impact on angina relief. There were no improvements in patient-reported physical limitation [17].

With an appreciation of the preclinical data for eleclazine in HCM, and the perceived benefit of ranolazine in these patients from the RHYME study, Gilead Science, Inc., funded the largest randomized-blinded clinical trial in HCM history – LIBERTY-HCM (NCT02291237) – with a goal enrollment of 180 patients [16]. The primary endpoint was an improvement in peak VO_2. The study began enrolling patients in February 2015, but the study was closed early,

failing to meet the target recruitment by only a few patients. Eleclazine was being evaluated simultaneously for suppression of ventricular arrhythmias in a non-HCM cohort, as well as in patients with long-QT type III syndrome. Gilead Sciences reported that they were no longer pursuing eleclazine in HCM after they noted a failure of the drug to suppress ventricular arrhythmias in the non-HCM cohort but that the data collected thus far would be analyzed and presented at a scientific meeting in the future. Many in the HCM community are anticipating that eleclazine will not be brought to clinical practice.

Mavacamten (MYK-461)

Mavacamten (MyoKardia, Inc) is a first-in-class small molecule, which acts as an allosteric modulator of beta cardiac myosin. There is selective targeting of cardiac myosin ATPase which results in reversible inhibition of the actin-myosin complex. This in turn reduces the inotropic force and may also facilitate diastolic relaxation [18]. Mavacamten is therefore predicted to improve both diastolic dysfunction and relieve left ventricular outflow tract obstruction in patients with HCM.

In a mouse model of HCM, mavacamten was shown to attenuate the development of the HCM phenotype when administered early. This was accompanied by studies that showed a reduction of cardiomyocyte disarray and interstitial fibrosis, as well as an attenuation of the profibrotic gene expression profile [18]. Clearly this is of particular interest for individuals with a known disease-causing genetic mutation, but who have not yet developed the clinical phenotype, so-called genotype-positive, phenotype-negative patients.

To date there are limited publications regarding the efficacy of this agent in humans. The PIONEER-HCM (NCT02842242) study is a phase IIa open-label clinical trial evaluating the effect of a variety of doses of mavacamten on patients with symptomatic obstructive HCM. To date, the study has enrolled to its target (20 patients), and according to a press release in August 2017 on the first 11 patients, the drug resulted in a very impressive reduction in the degree of postexercise left ventricular outflow tract obstruction (mean 125 mmHg to 19 mmHg) and an increase in the peak VO_2 by an absolute 3.5 ml/kg/min. This was mirrored by a significant improvement in overall New York Heart Association functional class and was generally well tolerated. More recently, at the Heart Failure Society of America's annual scientific meeting in September 2017, the top-line results were rounded out. In addition to the dramatic reduction in exercise LVOT obstruction, there seems to be a very rapid and complete resolution of the resting LVOT obstruction as early as 2 weeks into treatment, a reduction in serum NTproBNP levels, and a concomitant intentional reduction in left ventricular ejection fraction. Importantly, the impact on the LVEF is impermanent with the drug effect being reversible, as were the beneficial effects on symptoms and LVOT obstruction. Subjectively patients on study experienced impressive improvement in symptomatic dyspnea while on drug. There were no significant safety signals noted by the independent data safety monitoring committee, as there are now plans to move to a randomized placebo-controlled registration study.

Conclusion

While the last FDA-approved medical therapy for the treatment of hypertrophic cardiomyopathy was >50 years ago (propranolol, Harrison 1964), HCM is now considered an orphan disease, and as such there are incentives for the pharmaceutical industry to invest in drug development. This has resulted in a reduction in the inertia with drug discovery, despite fewer potential patients when compared with much more common disease states. We have already seen three recent clinical trials, and despite the fact that two have failed to produce a marketable drug, their research has helped illuminate important potential pathways and targets within HCM. No doubt, with the added interest and engagement of the medical community and patient advocacy groups, an important discovery is imminent.

Clinical Pearls

- HCM patients should be seen at designated HCM centers of excellence, or at least receive periodic consultations from these centers, as they are the ones that participate in large clinical trials in HCM and can potentially offer these in-trial medications to patients prior to FDA approval.

Questions

1. Which of the following drugs are FDA-approved for the treatment of symptomatic obstructive hypertrophic cardiomyopathy?
   A. Metoprolol
   B. Verapamil
   C. Propranolol
   D. Disopyramide
   E. Diltiazem
   F. None of the above

Answer: C. Only propranolol carries an on-label indication for HCM. All other drugs used in this space, including those medications considered and used first-line in the majority of patients, are off-label.

2. This agent has been evaluated for the treatment of hypertrophic cardiomyopathy in a phase III randomized, placebo-controlled study:
   A. Metoprolol
   B. Verapamil
   C. Disopyramide
   D. Eleclazine
   E. Mavacamten

   Answer: D. Only eleclazine has been randomized in a phase III clinical trial, although mavacamten is in the process currently of initiating the phase III trial.

3. Which of the following have been shown to have a beneficial effect on mortality in patients with symptomatic obstructive hypertrophic cardiomyopathy?
   A. Metoprolol
   B. Verapamil
   C. Disopyramide
   D. Surgical myectomy
   E. None of the above

   Answer: D. Septal reduction therapies including both alcohol septal ablation and surgical myectomy have been shown in observational experience to have ensuring mortality trajectories similar to the age- and gender-matched non-HCM population leading some to believe mortality might be improved in patients undergoing these therapies. While selection bias may also be at play here, and a randomized clinical trial of septal reduction compared to continued medical therapy has not been performed, this is the best data to date on therapies that might alter the natural history of patients with HCM who are severely symptomatic due to LVOT obstruction.

4. What was the presumed primary mechanism of action for eleclazine in treating patients with symptomatic hypertrophic cardiomyopathy?
   A. Ryanodine receptor blocker
   B. Late sodium channel blocker
   C. Inhibition of hypertrophic signaling at the cardiomyocyte level
   D. Voltage-gated L-type calcium channel blocker
   E. Inhibition of carnitine palmitoyltransferase I

   Answer: B. Eleclazine was presumed to work through the late sodium channel blocker, similar to ranolazine. Although the phase III trial neared completion, the study was terminated due to findings of a similar parallel trial in a different population of patients.

5. Which of the following is not part of the proposed therapeutic mechanisms with perhexiline?
   A. Inhibition of carnitine palmitoyltransferase I (CPT-1)
   B. Inhibition of the late sodium channel
   C. Blockade of β-adrenergic receptors
   D. Effects on L-type Ca^{2+}-channels
   E. Inhibition of actin-myosin interaction

   Answer: C. Inhibition of the late sodium channel is a target of eleclazine.

6. Mavacamten is a novel therapy that targets which of the underlying pathological pathways seen in hypertrophic cardiomyopathy?
   A. Inefficient cardiomyocyte energetics
   B. Prolongation of cardiomyocyte action potential through excessive $I_{Na}L$ activity
   C. Upregulated actin-myosin crosslinking.
   D. Inappropriate intracytosolic calcium trafficking
   E. Unchecked ischemic signaling

   Answer: C. By blocking the upregulated actin-myosin crosslinking, ejection fraction is reduced and diastolic dysfunction is improved, both potentially leading to improvements in subject and objective markers of heart failure in obstructive HCM.

7. Mavacamten, in a phase II open-label study, has recently been shown to result in all of the following except:
   A. Improvement in the left ventricular ejection fraction with therapy
   B. Rapid reduction in resting left ventricular outflow tract obstruction
   C. Average 3.5 $ml/m^2/min$ improvement in peak VO_2 on cardiopulmonary exercise testing
   D. Improvement in NYHA functional class
   E. Reduction in serum NTproBNP concentration

   Answer: A. On the contrary, there is a drop in ejection fraction with mavacamten which is partially responsible for the drop in obstructive gradients and symptoms.

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Approach to the Initial and Follow-Up Visits

28

Paolo Spirito and Camillo Autore

Key Points

- The initial approach to the evaluation of patients with HCM includes (A) reconstruction of family history of the disease focused on identification of affected relatives and sudden death events potentially related to HCM, (B) assessment of the presence and severity of HCM-related symptoms, and (C) evaluation of a recent 12-lead electrocardiogram and 24-h ambulatory (Holter) ECG recording, assessment of cardiac morphology and function by imaging techniques (echocardiography and cardiac magnetic resonance), and, in selected patients, determination of functional capacity using exercise testing.
- The distinction between obstructive and nonobstructive HCM represents a key point in the clinical evaluation of patients with HCM, because disease management is strongly influenced by the presence or absence of LV outflow obstruction and patients with the obstructive form are more likely to develop important heart failure symptoms.
- Risk stratification for sudden death is mandatory in all HCM patients and is generally quantified as high, intermediate, or low, based on the identification of a number of major HCM risk factors, as well as the evaluation of the prognostic strength of each individual risk factor and the overall patient clinical profile. The 2014 European Society of Cardiology HCM guidelines have suggested the use of a risk score, derived from a statistical model, that may help in the risk stratification for sudden death.
- Given the lifelong implications of HCM for the patients and their families, issues such as lifestyle, physical activity, family screening, and genetic counseling need to be addressed with the greatest clarity and represent an integral part of the initial clinical evaluation.
- Patient follow-up is based on serial evaluations and focused on the identification of possible signs of clinical deterioration, including progression of either symptoms and/or morphologic and functional cardiac abnormalities, development of arrhythmias, and changes in the risk profile for sudden death.

Scope of This Chapter

Hypertrophic cardiomyopathy (HCM) is a genetic cardiovascular disease characterized by a greatly diverse clinical presentation and natural history [1, 2]. This marked heterogeneity makes patient management particularly difficult. The purpose of this chapter is to offer a practical and systematic approach to the clinical evaluation and management of patients with HCM. This approach applies to patients with established HCM or a high suspicion of the disease and is based on management strategies used at HCM referral centers.

A detailed documentation of the initial patient evaluation is particularly important for subsequent follow-up visits. Therefore, the first section of this chapter will discuss the main clinical aspects that should be addressed as part of the initial patient evaluation, including confirmation of the diagnosis of

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HCM, assessment of LV morphology and function, evaluation of symptoms, risk stratification for sudden death, selection of treatment strategy, and patient education regarding lifestyle modification, family screening, and genetic testing. The second section of this chapter will discuss how to plan a follow-up program on the basis of the severity of the patient clinical presentation and revise the treatment strategy in relation to disease progression. Inevitably, many parts of the present chapter will cover issues already discussed in detail in previous sections of this book. The aim here is to condense these complex subjects into a format that summarizes the most important clinical points in a practical manner and can be used in the assessment and management of individual patients and families with HCM.

Initial Patient Evaluation

In the ACCF/AHA guidelines published in 2011, HCM is defined as "a disease state characterised by unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient" [1]. Therefore, the first step in the initial patient evaluation is to verify that the clinical presentation is consistent with the definition of the disease reported in the guidelines. Because this definition is based on cardiac morphologic features, cardiac imaging plays a major role in the initial patient evaluation.

Confirmation of the Diagnosis of HCM

The general approach to the confirmation of the diagnosis of HCM is outlined in Fig. 28.1. In the great majority of patients with HCM, the 12-lead electrocardiogram (ECG) shows QRS and/or S-T segment abnormalities [2–4]. Indeed, an abnormal ECG is often the alteration that has first raised the suspicion of HCM [5]. Therefore, it is important to begin the initial patient evaluation by examining the ECG. Electrocardiographic abnormalities such as deep Q waves (>0.3 mV) with a short duration and/or deep negative

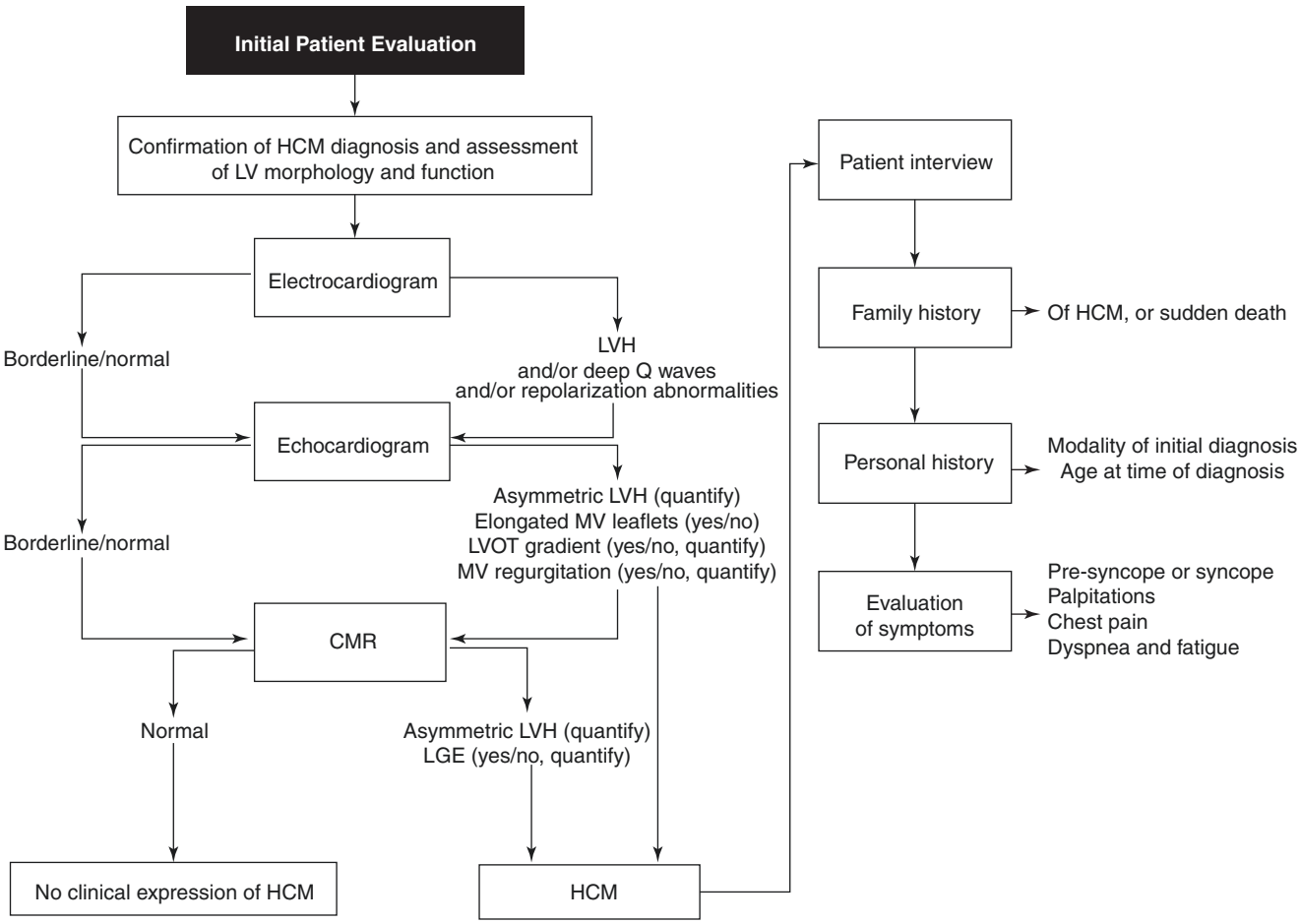

Fig. 28.1 Schematic representation of the general approach to the initial evaluation of patients with hypertrophic cardiomyopathy (HCM). CMR cardiovascular magnetic resonance, LGE late gadolinium enhancement, LV left ventricular, LVH left ventricular hypertrophy, LVOT left ventricular outflow tract, MV mitral valve

T waves in the inferolateral or precordial leads strongly support a diagnosis of primary cardiomyopathy and exclude ventricular hypertrophy secondary to systemic arterial hypertension or valvular heart disease. On the other hand, absence of ECG abnormalities does not exclude HCM, because some patients have mild and localized ventricular hypertrophy involving a small portion of the left ventricle that can be detected only by cardiac imaging [6, 7].

Clinical evaluation proceeds with a two-dimensional and Doppler echocardiographic study. The two-dimensional echocardiogram must be performed with great care to assess the magnitude and distribution of LV hypertrophy, presence and severity of anterior systolic movement (SAM) of the mitral valve, and left atrial dimension [1, 2, 8]. In many patients with HCM, LV remodeling due to ventricular wall and papillary muscle hypertrophy may lead to alterations of the mitral valve apparatus, with progressive fibrosis and retraction of secondary mitral valve chordae and elongation of valve leaflets. These abnormalities usually contribute to displacement of the valve apparatus in the LV outflow tract and outflow obstruction [9–11]. Identification of elongated and anteriorly displaced mitral valve leaflets with marked SAM and LV outflow obstruction strongly supports the diagnosis of HCM, because these morphologic and functional alterations are absent in patients with secondary ventricular hypertrophy and uncommon in patients with ventricular hypertrophy associated with genetic diseases such as storage cardiomyopathies and Fabry disease [12–14].

Doppler echocardiography allows the assessment of the presence and severity of the LV outflow gradient, mitral or aortic valve regurgitation, and LV diastolic filling abnormalities [1, 2]. Of note, LV outflow obstruction in patients with HCM is quantified in terms of maximum peak instantaneous gradient rather than mean gradient [15]. The Valsalva maneuver should be performed in each patient to measure the increase in the resting gradient or to elicit an outflow gradient that may be absent under basal conditions [16]. In patients with heart failure symptoms during routine physical activities and without a significant LV outflow gradient under basal conditions or during the Valsalva maneuver, Doppler echocardiography in combination with exercise testing may help to document an exercise-induced gradient. Indeed, exercise testing is the most accurate method to identify an outflow gradient that is absent at rest but is generated by physical activities [16]. Identification of an inducible LV outflow gradient may have important clinical implications because, in many HCM patients without a gradient under basal conditions, dyspnea and fatigue during physical activities or after an abundant meal may be explained by the development of an outflow gradient which is absent in resting conditions [1, 2, 16].

In recent years, the high resolution of cardiovascular magnetic resonance (CMR) has proved superior to echocardiography in the assessment of the morphologic features of HCM [17, 18]. This technique has also shown that morphologic alterations associated with HCM may not be identified by echocardiography when hypertrophy is confined to some areas of the left ventricle such as the anterolateral free wall or apex [17–20]. Therefore, CMR is routinely performed as an integral part of the initial patient evaluation to assess LV morphology and magnitude and distribution of LV hypertrophy. In addition, contrast-enhanced CMR with late gadolinium enhancement (LGE) permits the identification of areas of myocardial fibrosis in patients with HCM [21–24]. Several studies have documented that patients with LGE tend to have a more unfavorable prognosis, including a higher risk of sudden death, than those without LGE [25–28].

Patient Interview

Family and Patient History of HCM In most patients, HCM is a genetically transmitted familial disease [1, 2, 29, 30]. Therefore, the patient interview begins with the family history (Fig. 28.1). A history of sudden and unexpected death in young relatives (generally defined as <50 years of age) may have important implications in patient management. Because sudden deaths that occurred decades earlier are often not mentioned by the patient, family history must be investigated meticulously. When a history of one or more sudden and unexpected deaths is identified in the family, detailed information needs to be gathered regarding age and circumstances at the time of the events in order to assess the likelihood that these deaths may have been HCM-related.

As part of the patient personal history, it is important to ascertain the modality of the initial diagnosis of HCM, as a diagnosis during clinical evaluation for development of symptoms is usually associated with a less favorable long-term clinical course than identification of the disease during routine checkup or family screening. Age at the time of diagnosis is also important and may offer prognostic information, because patients diagnosed with HCM at a young age appear to have a less favorable long-term clinical course and prognosis than those diagnosed later in life [31, 32].

Evaluation of Symptoms Many patients with HCM have no or only mild symptoms [33–36]. However, when present, symptoms are typically variable and may include presyncope or syncope, palpitations, chest pain, and dyspnea. Therefore, it is useful to follow a systematic approach when inquiring for the presence of HCM-related symptoms. Below, symptoms are addressed beginning with the least common and ending with dyspnea and fatigue, which are the most common symptoms and have an important impact on patient clinical course and quality of life.

Syncope and pre-syncope are relatively infrequent in patients with HCM but may have important prognostic implications depending on the characteristics of the event. Recent and unexplained syncopal episodes that have occurred in circumstances not clearly consistent with a neurally mediated vasovagal event have been reported to be associated with an increased risk of sudden death [37]. Such episodes include syncope without apparent explanation at rest, or during ordinary activity, or during an intense effort. Neurally mediated vasovagal syncope has virtually no prognostic implications [37]. Pre-syncope may be reported by patients as lightheadedness/near fainting or the perception that a loss of consciousness was imminent but did not occur. No systematic data are available regarding the prognostic implications of symptoms such as lightheadedness or near fainting (pre-syncope). However, the potential clinical importance of pre-syncopal episodes should not be underestimated and needs to be interpreted within the context of the patient overall clinical presentation [38]. Palpitations are reported by the majority of patients with HCM. Therefore, the interpretation of the clinical significance of this symptom is based on a careful reconstruction of its characteristics, including incidence, duration, intensity, and possible association with symptoms such as shortness of breath, near fainting, or fainting. In the majority of patients with HCM, palpitations are of brief duration and not associated with other symptoms. However, despite a scrupulous questioning, the clinical interpretation of reported palpitations remains uncertain in the absence of Holter ECG documentation of the cardiac rhythm at the time of symptoms.

Chest pain or chest discomfort is often reported by patients with HCM. In some patients, the episodes of chest pain are intense, similar in their characteristics to angina pectoris, and develop during exertion. More commonly, chest pain symptoms are mild, prolonged, and atypical for angina pectoris. Myocardial ischemia is an established pathophysiologic feature in HCM [39–43]. However, the relationship between episodes of chest pain and myocardial ischemia has not been resolved [41, 42], and the mechanisms responsible for myocardial ischemia in HCM have not been completely clarified. Abnormal intramural coronary arterioles with thickened walls, secondary to intimal and medial hypertrophy, and associated with relatively reduced lumen, as well as abnormal compression of intramural coronary vessels during systole, appear to play a role in myocardial ischemia in HCM [40, 42, 43]. Nevertheless, in the absence of associated epicardial coronary artery disease, the prognostic implications of chest pain remain unclear.

Shortness of breath and fatigue are the symptoms that more accurately reflect the severity of the functional abnormalities in patients with HCM. Because management decisions are based on the severity of symptoms [1, 2] and there is a strong and independent relationship between New York Heart Association (NYHA) functional class and prognosis in HCM [44–46], it is particularly important to assess with great care the level of the patient's functional limitation. In selected patients, exercise testing and determination of maximum oxygen consumption may be useful to assess functional capacity more accurately [1, 2, 47, 48].

Management of Symptoms

At this point in the initial patient evaluation, the physician has confirmed the diagnosis of HCM and knows in detail the patient clinical presentation, including personal and family history, characteristics and severity of symptoms, and cardiac morphology and function. The general approach to subsequent management decisions is outlined in Fig. 28.2. Because of the major role of LV outflow obstruction in the clinical course of HCM, patient management is strongly influenced by the presence or absence of outflow obstruction.

LV Outflow Obstruction

In patients with HCM, LV outflow obstruction causes an increase in LV systolic pressure and leads to important functional abnormalities, including elevation of diastolic filling pressure, prolongation of ventricular relaxation, mitral valve regurgitation, left atrial dilatation, decrease in forward output, and myocardial ischemia [1, 2, 49–51]. Of the patients with HCM evaluated at referral centers, 20–25% have LV outflow obstruction under basal conditions (defined as a maximum peak instantaneous gradient ≥30 mmHg), and another 50–60% may spontaneously generate an outflow gradient during daily activities that can usually be elicited by physiologic maneuvers (such as the Valsalva maneuver) or exercise [1, 15, 16]. Several studies have shown that LV outflow obstruction under basal conditions is a strong and independent predictor of disease progression to severe heart failure and atrial fibrillation, as well as death secondary to heart failure or stroke [1, 36, 45, 46]. No data are available regarding the prognostic implications of LV outflow gradients elicited with provocative maneuvers in patients without outflow gradients under basal conditions. However, in clinical practice, management strategies are similar in patients with important symptoms of heart failure and either resting or physiologically induced outflow gradients [1].

LV outflow obstruction and symptoms of dyspnea or fatigue In patients with LV outflow obstruction and symptoms of dyspnea or fatigue, beta-blocking drugs are the medication of choice [1, 2, 4, 52]. Administered at standard dosages, beta-blockers may alleviate symptoms through their negative inotropic and chronotropic effects. In patients

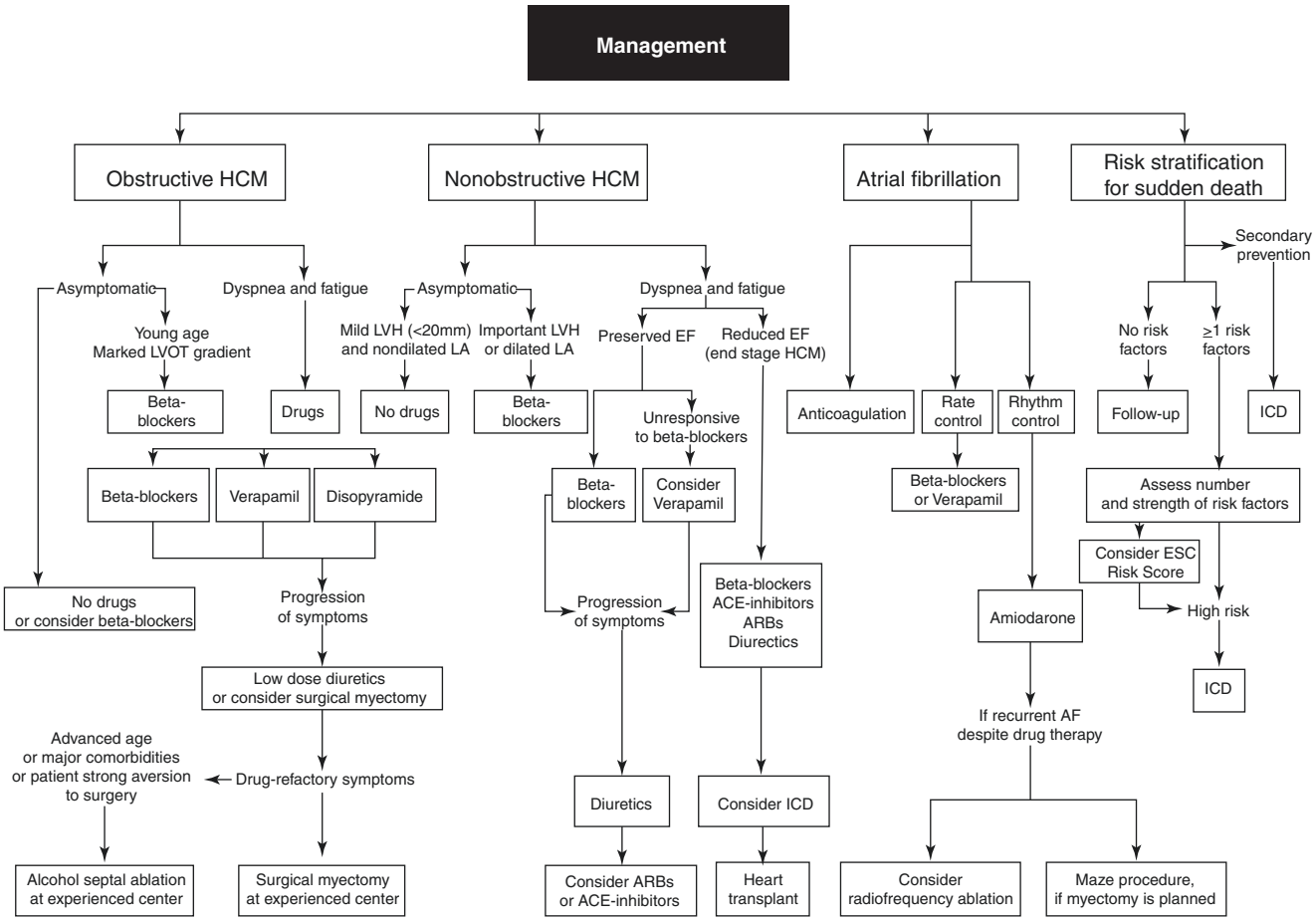

Fig. 28.2 Management of patients with hypertrophic cardiomyopathy (HCM) at the time of the initial evaluation. ARBs angiotensin receptor blockers, AF atrial fibrillation, EF ejection fraction, ESC European Society of Cardiology, ICD implantable cardioverter-defibrillator, LA left atrium, LVH left ventricular hypertrophy, LVOT left ventricular outflow tract

unable to tolerate beta-blocking drugs or unresponsive to these medications, verapamil may have favorable effects on symptoms [2, 4, 52, 53]. However, in patients with high outflow gradients, verapamil should be used with caution and started at low dosages, because the vasodilative effects of the drug may increase the gradient [1, 2, 54]. When important symptoms of heart failure persist despite treatment with beta-blockers or verapamil, diuretics at relatively low dosages may be useful [1, 2, 4]. In some patients who do not respond to beta-blockers and verapamil, disopyramide may prove effective in reducing the LV outflow gradient and improving symptoms [1]. However, because of its potential pro-arrhythmic effects, this medication should be initiated in-hospital and with cardiac monitoring [1]. High-dose diuretics and vasodilator therapy should be avoided or used with caution in patients with resting or provocable obstruction, as these medications may increase outflow obstruction by reducing LV filling, or afterload, respectively [1, 2, 4].

Patients with symptoms unresponsive to medications and marked gradients (≥50 mmHg), either at rest or with provocation, are candidates to surgical septal myectomy or percutaneous alcohol septal ablation [1, 2]. In recent years, the selection criteria for these two techniques have been a source of controversy. However, the 2011 ACCF/AHA guidelines report that "Surgical septal myectomy, when performed in experienced centers, can be beneficial and is the first consideration for the majority of eligible patients with HCM with severe drug-refractory symptoms and LV outflow obstruction" and that "When surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LV outflow obstruction and severe drug-refractory symptoms (usually NYHA classes III-IV)" [1].

Therefore, surgical myectomy is the primary treatment option and the preferred approach in most patients, while the ACCF/AHA guidelines suggest limiting alcohol septal ablation to patients of advanced age, those at an unacceptably high operative risk as a result of important comorbidities, or with a strong aversion to surgery. However, it is important to reiterate here, as stated by the HCM guidelines, that operator

and institutional experiences are key determinants of successful outcome for either surgical myectomy or alcohol septal ablation, and all potential candidates to invasive therapy for relief of outflow obstruction should be objectively informed regarding the availability, advantages, and limitations of these two techniques.

LV outflow obstruction and no or only mild symptoms There is no definitive evidence that beta-blocking drugs reduce the LV outflow gradient under basal conditions, delay disease progression, or improve prognosis in HCM patients with LV outflow obstruction and no or mild symptoms [1, 2]. However, the decision to initiate pharmacologic treatment in asymptomatic children and adults with outflow tract gradients is justified by the expectation that medications, by reducing heart rate and prolonging diastole, may have a favorable effect on diastolic function and delay the onset of symptoms [1, 2]. It is also important to educate the patients with outflow tract gradients regarding the mechanism of LV outflow obstruction and how to avoid environmental situations that may lead to a marked increase in the LV outflow gradient, as summarized in the section on "Patient Education and Counseling."

Nonobstructive HCM

The majority of patients with HCM have no or only mild symptoms, relatively mild LV hypertrophy (<20 mm), and no resting or provocable LV outflow obstruction [33–35]. Many of these patients will have a favorable clinical course with normal life expectancy and without major functional limitation [35–37, 55–58]. However, a minority of patients with the nonobstructive form of HCM and no or mild symptoms may have a less favorable clinical course [1, 2, 49, 56]. Left atrial dimension has an important role in the identification of these latter patients, because an enlarged left atrium usually reflects important diastolic dysfunction and is associated with an increased risk of developing symptoms of heart failure and/or atrial fibrillation [57–59]. Therefore, an enlarged left atrium may justify treatment with beta-blocking drugs even in asymptomatic or mildly symptomatic patients with nonobstructive HCM.

A minority of patients with nonobstructive HCM present with severe symptoms of heart failure [1, 2, 4, 51, 56]. Such patients usually have important diastolic dysfunction with marked left atrial dilatation and preserved systolic function. In these patients, therapeutic options are limited [2, 4, 49, 56] (Fig. 28.2). Beta-blocking drugs or verapamil are useful to control heart rate and prolong ventricular diastolic filling. Diuretics and ACE inhibitors or angiotensin receptor blockers are indicated for treatment of congestive heart failure symptoms [1, 2, 4, 51, 52, 56]. However, the dosage of diuretics should be increased with caution, because patients with severe diastolic dysfunction may need relatively high filling pressures to achieve adequate ventricular filling. Anticoagulation is indicated in HCM patients with documented paroxysmal or chronic AF [1, 2, 59]. Prolonged asymptomatic episodes of low-rate AF may occur in patients with a markedly dilated left atrium treated with high dosages of beta-blocking drugs or verapamil. In such patients, anticoagulant therapy for prevention of thromboembolic events may be considered, also in the absence of documented AF.

A proportion (3–5%) of patients with nonobstructive HCM and severe heart failure symptoms are in the end-stage phase of the disease, characterized by LV remodeling with progressive wall thinning, cavity enlargement, systolic dysfunction, and extensive LGE on CMR [60–62]. In patients with end-stage evolution, treatment should be changed to standard medications for heart failure associated with systolic dysfunction, including diuretics, ACE inhibitors or angiotensin receptor blockers, beta-blocking drugs, and other drugs routinely used in the management of heart failure due to systolic dysfunction [1, 2] (Fig. 28.2). Anticoagulation for prevention of thromboembolic events may be considered. Ultimately, heart transplantation may become necessary in these patients with end-stage evolution [1, 2, 4]. In general, heart transplantation is indicated in patients with end-stage evolution and advanced heart failure symptoms that are refractory to all other interventions. Long-term outcome after heart transplant in patients with HCM is favorable and does not differ from that of patients with idiopathic dilated cardiomyopathy [62–65]. Because the risk of sudden death is increased in patients with end-stage evolution, prophylactic ICD implantation may be considered [62].

Atrial Fibrillation

Atrial fibrillation is a particularly important arrhythmia in HCM. It develops in 20–25% of adult patients followed at referral centers and is a predictor of unfavorable prognosis with increased risk of heart failure, stroke, and death [59, 66, 67]. The risk of developing AF is higher in patients with LV outflow obstruction and/or a dilated left atrium, and it increases with age [59, 67]. While some patients may remain asymptomatic during episodes of AF, many develop prolonged palpitations, shortness of breath, or dizziness. However, the cause-effect relationship between paroxysmal AF and such symptoms can be proved only in those patients in whom 12-lead ECG or Holter ECG documentation of AF is available at the time of symptoms. Hence, HCM patients experiencing recurrent episodes of prolonged palpitations should be advised to go to an emergency department, without waiting for spontaneous remission of symptoms, primarily for the purpose of obtaining 12-lead ECG documentation of the underlying arrhythmia.

Amiodarone is the most effective antiarrhythmic agent for the prevention of recurrent AF in patients with HCM [1, 2].

The maze procedure may be considered during surgical myectomy in patients with a history of paroxysmal AF [1]. Radiofrequency ablation may play a role in the management of highly selected HCM patients with AF, but the medium- and long-term benefits of this procedure remain undetermined [1]. Chronic AF is often well tolerated, particularly in older patients, if the heart rate is adequately controlled. Beta-blocking drugs or non-dihydropyridine calcium channel blockers are usually efficacious in controlling the heart rate in HCM patients with chronic atrial fibrillation [1, 2].

The risk of thromboembolic events is high in patients with HCM and AF [59, 66, 67]. Therefore, paroxysmal, persistent, or chronic AF is a strong indication to anticoagulation therapy [59, 67]. Because even brief recurrent episodes of AF in HCM have been associated with an important risk of systemic embolization, the threshold for the initiation of anticoagulation should be low, and a single episode of AF may justify taking into consideration anticoagulant therapy [1, 2].

Risk Stratification and Prevention of Sudden Death

A systematic approach to risk stratification for sudden death has become mandatory in all patients with HCM in view of the documented efficacy of the ICD for sudden death prevention in this disease, as well as the inefficacy of antiarrhythmic drugs and beta-blockers in reducing the risk of sudden death [1, 2, 68–70]. Although only a minority of patients with HCM die suddenly, all are at risk for sudden and unexpected death independently of the presence or absence of symptoms, including those without sudden death risk factors [68–71]. Therefore, all patients with HCM should undergo risk stratification and be informed that no patient with this disease can be considered at zero risk for sudden death [1, 2, 68–71].

Patients with HCM and prior documented cardiac arrest, ventricular fibrillation, or sustained ventricular tachycardia are candidates to the ICD for secondary prevention of sudden death [1, 2, 69, 72]. Identification of candidates to the ICD for primary prevention of sudden death remains less certain, given the many difficulties in the investigation of risk stratification in HCM, including the relatively infrequent identification of the disease, low rate of events, diversity in disease clinical presentation, and risk factor strength in individual patients, as well as differences in the definition of risk factors in the literature. These difficulties in the selection of appropriate candidates to ICD implantation for primary prevention of sudden death have generated some controversies in the approach to risk stratification recommended by the ACC/AHA HCM guidelines and the more recent European Society of Cardiology (ESC) HCM guidelines published in 2014 [73].

In the ACC/AHA HCM guidelines, risk is stratified as high, intermediate, or low based on the prognostic strength and number of major conventional risk factors, including history of ≥1 HCM-related sudden deaths in family members <50 years of age, massive LV hypertrophy (maximal wall thickness ≥ 30 mm), recurrent or prolonged nonsustained ventricular tachycardia (VT) on ambulatory ECG monitoring, and unexplained (non-vasovagal) recent syncope [1, 2, 37, 44, 68, 70, 74–76]. A failure to increase blood pressure by at least 20 mmHg, or a blood pressure decrease of at least 20 mmHg, during exercise has also been reported to be associated with an increased risk of sudden death [77, 78]. Therefore, exercise testing may contribute to the assessment of sudden death risk in the individual patient. Patients with multiple risk markers are generally considered at high risk. Patients with a single strong risk marker, such as one or more HCM-related sudden deaths in first-degree relatives, massive LV hypertrophy (≥30 mm), or unexplained non-vasovagal syncope within the previous months, are also considered at important risk and potential candidates for prophylactic implantation of an ICD [1, 69, 70]. However, in a proportion of patients, risk assessment based on major conventional risk factors may remain uncertain. In some of these patients, presence of associated clinical features defined as "risk modifiers" in the ACC/AHA guidelines, including severe LV outflow obstruction at rest, extensive LGE identified at CMR, and LV apical aneurysm, may help to solve uncertain management decisions in favor of ICD implantation [62, 79–81]. Furthermore, recent investigations indicate that extensive LGE identified at CMR and LV apical aneurysm could be considered independent risk markers and justify ICD implantation, particularly in patients without conventional risk markers [28, 82–84].

In the ESC HCM guidelines, risk stratification is mainly based on a statistical model that calculates a risk score and provides 5-year risk estimates of sudden death risk in the individual patient. The risk score is based on a higher number of risk factors than the ACC/AHA guidelines, including patient age, LV wall thickness, LV outflow gradient, and left atrium diameter as continuous variables. This statistical model does not include LGE on CMR or LV aneurysm as indicators of increased risk. In this model, a risk <4% at 5 years is considered low and ICD implantation not recommended, a risk ≥4% and < 6% is judged intermediate and ICD implantation may be taken into consideration, and a risk ≥6% at 5 years is high and ICD implantation should be considered [73].

However, in the absence of prospective and randomized trials, which are not possible in HCM because the disease is unfrequently diagnosed and sudden death events are rare, the international HCM guidelines cannot give definitive indications to ICD implantation for primary prevention of sudden death. Furthermore, the level of risk associated with many of the risk markers cannot be evaluated exclusively in terms of

number of risk factors or presence or absence of risk factors, because the prognostic implications may differ in relation to the individual strength of the risk marker or the overall clinical profile of the individual patient. For example, a history of multiple sudden deaths in a family with a small number of affected relatives may be considered a stronger indicator of increased risk than a single sudden death in a family with many affected family members, each without risk factors other than the sudden death of their relative. Alternatively, independent of patient's age, prolonged and multiple episodes of nonsustained VT recorded on a recent Holter may carry a stronger prognostic weight than a single brief episode recorded years before patient evaluation. A recent episode of unexplained syncope may be associated with a higher risk than a similar episode that occurred many years before patient evaluation. These examples show that the final risk assessment has to rely on the judgment of the managing physician on a case-by-case basis, depending on the patient's individual clinical and risk profile. It is also important to emphasize that the attitude toward the risk of sudden death and the ICD can vary considerably in individual patients and in different countries and cultures. Therefore, the final decision should also include a thorough discussion with the patient and family regarding the risk of sudden death, advantages and potential complications of the ICD, as well as persisting limitations of risk stratification in HCM [1].

Patient Education and Counseling

Because of the complexity, clinical heterogeneity, and genetic nature of HCM, physicians should make a major effort to inform the patients and their families regarding the general features of the disease. In particular, patients should be informed of the important variability in the natural history of HCM, which includes a favorable clinical course with a normal or near-normal longevity in the majority of affected adults, development of important heart failure symptoms in a minority of patients, and sudden and unexpected death in a small minority of individuals. Proper information will make it easier to justify difficult management decisions. Given the lifelong implications of HCM for the patients and their families, considerations regarding lifestyle, physical activity, family screening, and genetic counseling should also be part of this information and are briefly summarized below.

Lifestyle Considerations

Patients with HCM should be advised not to participate in competitive sports associated with intense exertion or other strenuous physical activities, to avoid situations that may cause excessive vasodilation, maintain proper hydration, keep to a healthy weight to reduce the heart workload, and avoid excessive use of alcohol or caffeine as well as the use of drugs that increase sympathetic tone. Patients with a favorable clinical profile may participate in recreational sports associated with mild-to-moderate physical activity [1].

Pregnancy is not contraindicated in women with HCM who are asymptomatic or whose symptoms are well controlled with beta-blocking drugs [85, 86]. In such patients, spontaneous labor and vaginal delivery are common, and caesarian section is usually performed for obstetric reasons. In women with LV outflow obstruction under basal conditions, with or without symptoms, pregnancy is associated with an increased risk of morbidity and mortality [85]. In women with advanced heart failure symptoms, pregnancy is associated with high morbidity and mortality, and it should be strongly discouraged [85, 86]. A multidisciplinary team is essential for adequate management of patients throughout pregnancy. Continuous ECG monitoring is indicated during labor and delivery, as well as in the early postpartum period.

Family Screening

HCM is inherited as a Mendelian autosomal dominant trait [30]. Hence, each first-degree relative of a patient with HCM has a 50% chance of carrying the mutation (or mutations) responsible for the disease and is at risk of developing HCM. Therefore, clinical screening of first-degree relatives and other family members should be encouraged. The purpose of family screening is to identify affected relatives with undiagnosed HCM, as well as to inform relatives without clinical expression of HCM regarding the risk of developing the disease later in life and the indication to periodic clinical screening. The recommended strategies for family screening include 12-lead ECG, echocardiographic and clinical evaluation. In family members in whom a diagnosis of HCM remains uncertain, CMR should also be performed. During adolescence, HCM may develop more rapidly in association with body growth. Therefore, clinical screening is advisable every 1–2 years for young family members (12–21 years of age) [1]. Because the disease may also develop later in life, it is prudent to recommend screening every 5 years in adults who have a normal 12-lead ECG and echocardiogram at initial evaluation [1].

Genetic Testing and Counseling

The ACC/AHA HCM guidelines recommend genetic counseling as part of the evaluation of patients with HCM to address the medical, psychological, and family aspects of the disease [1]. Genetic testing may be considered in the index

patient to facilitate the identification of first-degree family members at risk for developing HCM. Genetic testing is not indicated in family members, when a definitive pathogenic mutation has not been identified in the index patient [1]. In countries in which the results of genetic testing may have consequences for health and life insurance, these issues should be discussed with the index patient and those family members who may be candidates to genetic screening.

Follow-Up Visits

Timing of Visits During Follow-Up

The timing for follow-up visits is based on the initial patient clinical profile, as outlined in Fig. 28.3. In patients with a benign clinical presentation, a routine follow-up evaluation every 1–2 years (including a 12-lead ECG, echocardiogram, and 24-h Holter ECG monitoring) is usually adequate. Clinical presentation is generally considered benign when the patient meets each of the following criteria: no or only mild symptoms, mild LV hypertrophy (<20 mm), no LV outflow obstruction under basal conditions, no HCM risk factors for sudden death, and no or mild LGE on CMR.

In patients with a more complex clinical presentation, including one or more of the following features: heart failure symptoms, LV hypertrophy ≥20 mm, LV outflow obstruction under basal conditions, paroxysmal or chronic AF, risk factors for sudden death, or extensive LGE on CMR, the timing for subsequent visits should be scheduled in relation to the severity of the individual patient clinical presentation. In some of these patients, additional tests may be included in the routine follow-up evaluation. For example, Doppler echocardiographic measurements of the LV outflow gradient during exercise may be helpful to document an exercise-induced gradient in patients without LV outflow obstruction at rest who have heart failure symptoms during physical activities. Determination of maximum oxygen consumption during exercise may be useful in patients in whom uncertainties persist regarding presence or severity of heart failure symptoms and functional limitation. At many HCM referral centers, serial CMR evaluations are becoming a standard component of the follow-up of patients with a complex clinical presentation.

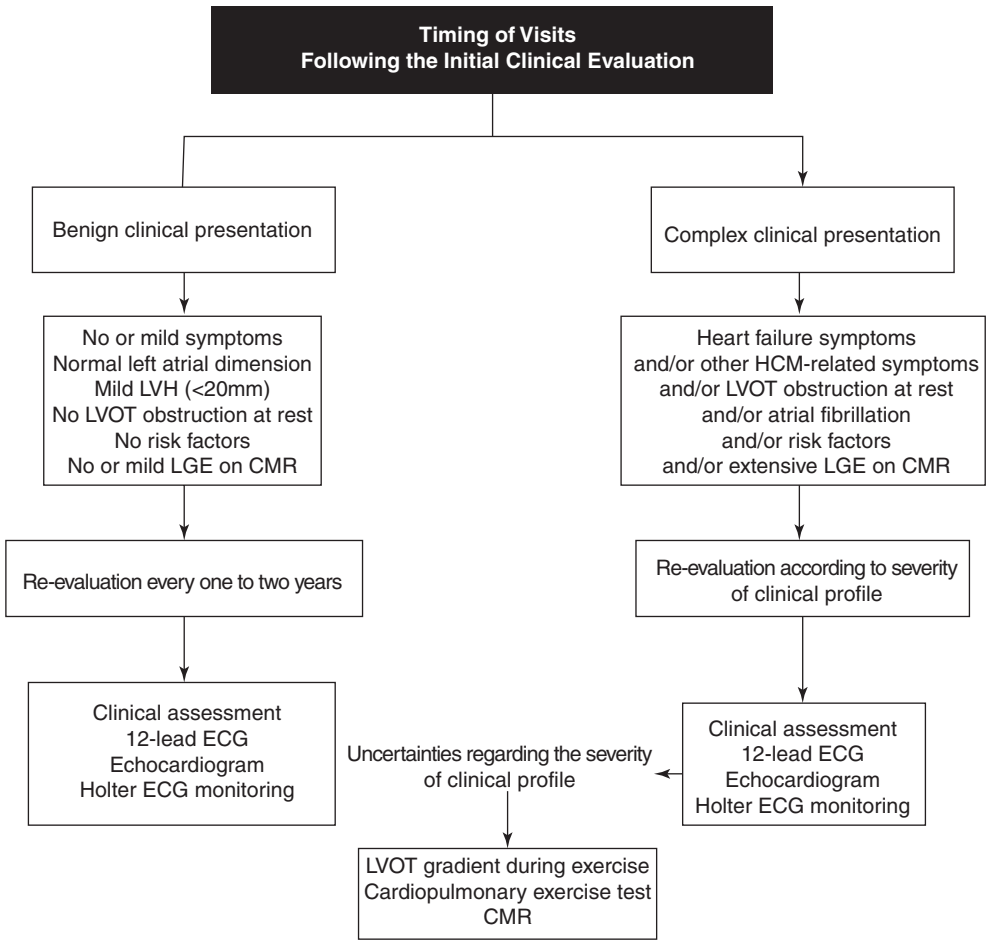

Fig. 28.3 Timing of visits following the initial clinical evaluation. CMR cardiovascular magnetic resonance, ECG electrocardiographic, HCM hypertrophic cardiomyopathy, LGE late gadolinium enhancement, LVH left ventricular hypertrophy, LVOT left ventricular outflow tract

Management of Disease Progression During Follow-Up

The management of patients with clinical deterioration during follow-up is outlined in Fig. 28.4. In patients with development or progression of heart failure symptoms, management options depend on the pathophysiologic and functional expression of the disease. In patients with LV outflow obstruction, it may be necessary to decide whether pharmacologic treatment can be sufficient to control symptoms, or invasive therapy should be taken into consideration to abolish the outflow gradient and reduce or abolish symptoms. In the large majority of patients with the nonobstructive form of HCM and clinical deterioration secondary to diastolic dysfunction, pharmacologic therapy is the only option. In a small number of highly selected patients with preserved systolic function but severe symptoms secondary to restrictive diastolic features, heart transplant may be considered. In patients with end-stage evolution and systolic dysfunction, a continuous adjustment of pharmacologic treatment is necessary. Ultimately, most patients with end-stage HCM become candidates for heart transplant. In such patients, ICD implantation should be considered as a bridge to transplant [1, 2, 62].

In patients who develop AF during follow-up, the issues of anticoagulant therapy and treatment for prevention of recurrent AF or heart rate control need to be addressed. Management of such patients is discussed in detail in the section on AF reported in the present chapter.

In patients with changes in their risk profile for sudden death, the level of risk should be reassessed to decide whether ICD implantation for primary prevention of sudden death may be justified. For example, development of one or more of the following risk factors should raise the issue of ICD implantation: progression of LV hypertrophy to ≥30 mm (or values that approach 30 mm in young patients), recent sudden cardiac death in a young first-degree relative known to be affected by HCM (or in whom HCM may be suspected as the most likely cause of the event), documentation of alarming ventricular tachyarrhythmias such as frequent, or prolonged (>10 beats), bursts of rapid nonsustained VT on Holter ECG monitoring, or recent (within months) unexplained non-vasovagal syncope in a young patient [1, 2, 37, 44, 70, 76].

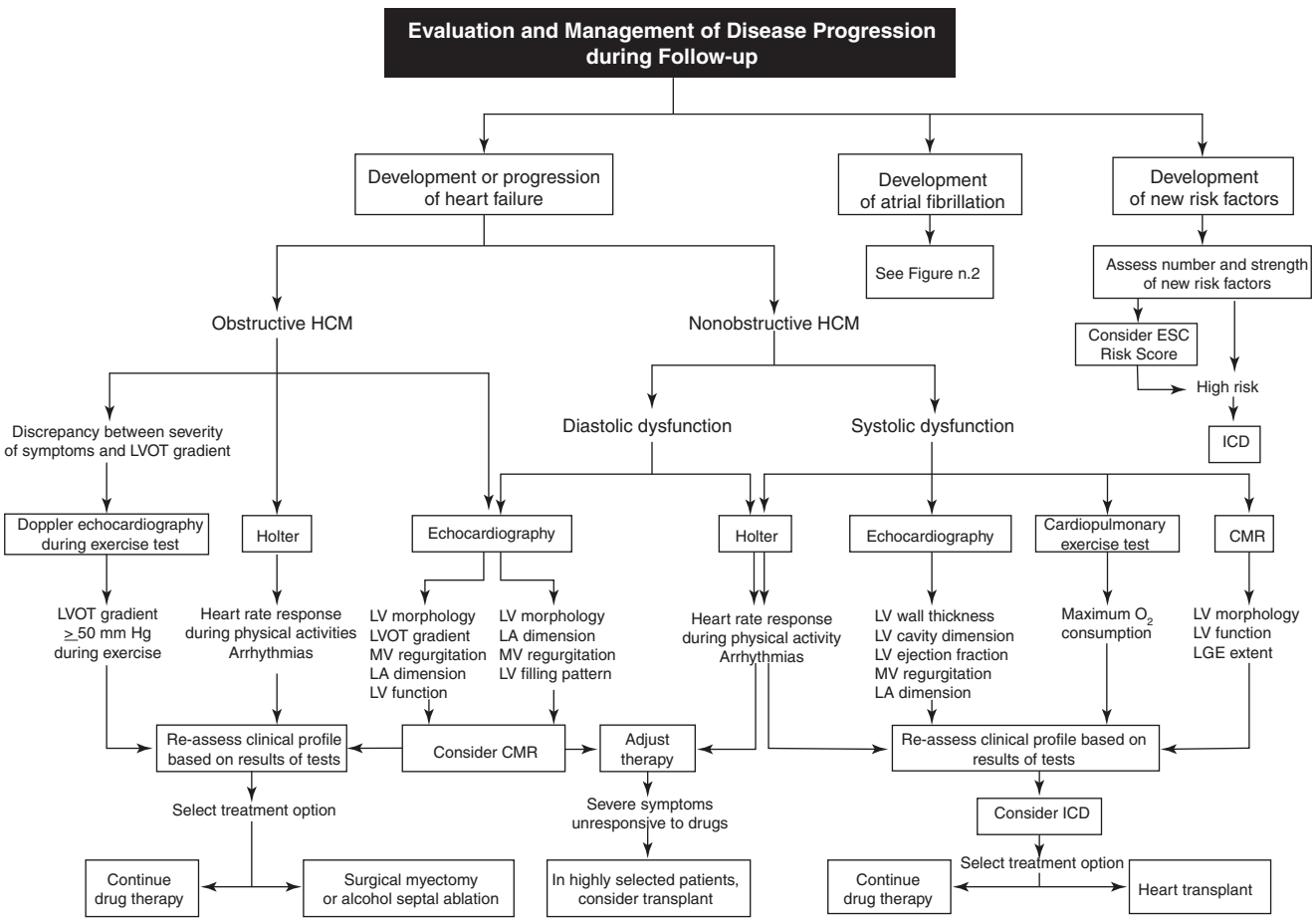

Fig. 28.4 Management of patients with hypertrophic cardiomyopathy (HCM) and progression of the disease during follow-up. CMR cardiovascular magnetic resonance, ESC European Society of Cardiology, ICD implantable cardioverter-defibrillator, LA left atrium, LGE late gadolinium enhancement, LV left ventricular, LVOT left ventricular outflow tract, MV mitral valve

Echocardiographic Assessment During Follow-Up

During follow-up, serial echocardiographic and Doppler evaluations allow the identification of changes in cardiac morphology and LV function secondary to disease progression. In children, attention is focused on a possible substantial increase in the LV wall thickness. This morphologic evolution is frequently associated with rapid body growth during adolescence and may occur within the space of 1–2 years or even a few months [87]. In adults, rapid progression of LV hypertrophy has not been reported during follow-up [88, 89]. At the opposite extreme of the morphologic evolution of the disease, LV wall thinning and/or cavity dilatation with development of systolic dysfunction and progression to end-stage HCM may occur in patients of all ages, including adolescents [60–62]. The incidence of LV wall thinning and systolic dysfunction has been reported to be 3–5% in patients followed at HCM referral centers and is more common in some HCM families [60–62]. A relation between specific genetic mutations and evolution to end-stage disease has not been identified [90].

Serial measurements of left atrial size are particularly helpful in the follow-up evaluation of patients with HCM. In most patients with the obstructive form of the disease, left atrial dimension increases progressively as a consequence of the long-term impact of LV outflow gradient on ventricular hemodynamics, including elevation of LV systolic and diastolic pressure, and mitral valve regurgitation. In patients with the nonobstructive form of HCM, left atrial dimension closely reflects the severity of LV diastolic function. Progressive left atrial enlargement indicates deterioration in the LV hemodynamics, increased risk of atrial fibrillation, and the need for reassessment of the clinical profile and treatment strategy [57–59, 71, 91].

Continuous wave Doppler echocardiography allows the identification of changes in the LV outflow gradient during follow-up. Because of the dynamic nature of LV outflow obstruction in HCM, modest changes in the magnitude of the outflow gradient have no clinical relevance. However, repeated documentation of a significant outflow gradient under basal conditions and prolonged systolic mitral-septal contact in patients previously known to have the nonobstructive form of the disease indicates a transition to obstructive HCM. This evolution is usually the consequence of a progressive increase in LV wall thickness with a decrease in outflow tract dimension, as well as development of secondary alterations in the mitral valve apparatus that contribute to outflow obstruction [10]. No data are available regarding the incidence of the evolution from nonobstructive to obstructive HCM. At the other extreme of the functional spectrum, loss of the LV outflow gradient can be an early sign of evolution toward end-stage HCM.

Doppler echocardiography is routinely used to assess mitral valve regurgitation and diastolic function in patients with HCM. In most patients, mitral valve regurgitation is secondary to LV remodeling and outflow obstruction and may have an important impact on the clinical course of the disease [1, 50, 51]. In a minority of patients, mitral regurgitation is due to primary abnormalities of the valve apparatus [92]. Impairment of diastolic filling has an important role in the pathophysiology of HCM [2, 4]. However, Doppler indexes of diastolic function have limited clinical implications in most HCM patients, as they are strongly influenced by the LV loading conditions. These diastolic indexes may be useful under certain circumstances, such as the assessment of left atrial function in patients with marked atrial enlargement or the documentation of a restrictive LV filling pattern in patients with clinical evidence of severe diastolic dysfunction.

Holter ECG Monitoring During Follow-Up

Evaluation of heart rate during 24-h Holter ECG monitoring can be useful for titration of therapy with beta-blocking drugs or verapamil. For example, a mean heart rate ≥ 70–75 beats/min may indicate the need to increase drug dosage in patients with persistent important dyspnea despite pharmacologic treatment, while a mean heart rate < 45–50 beats/min with a peak rate < 80–85 beats/min suggests excessive drug-related bradycardia and chronotropic incompetence as the possible explanation for persistent symptoms. Identification of supraventricular arrhythmias may suggest the need to modify pharmacologic treatment. Documentation of frequent, or prolonged (>10 beats), bursts of rapid nonsustained VT alters the patient risk profile and may have important management implications in terms of risk stratification and prevention of sudden death [1, 2, 70].

Exercise Testing During Follow-Up

In patients who develop heart failure symptoms during follow-up, exercise testing may be useful in the assessment of their functional limitation [1]. In particular, in those patients without a significant LV outflow gradient under basal conditions, exercise testing in combination with Doppler echocardiography may help to assess the potential role of an exercise-induced LV outflow gradient in the development of heart failure symptoms [16]. In patients who develop one or more of the main HCM risk factors during follow-up, documentation of an abnormal blood pressure response during exercise testing may contribute to the overall assessment of the sudden death risk [77, 78].

CMR During Follow-Up

Because of the high tomographic resolution of magnetic resonance, serial CMR evaluations in patients with HCM

allow a high degree of accuracy in the identification of (1) progression of LV hypertrophy, (2) LV remodeling with wall thinning and decrease in systolic function, (3) development of apical aneurysm, and (4) assessment of LV outflow tract morphology and characterization of the mitral valve and papillary muscle apparatus in candidates to surgical myectomy [93–97]. Comparison of LGE distribution in serial CMR evaluations may allow identification of an increase in the extent of myocardial fibrosis, a possible sign of disease progression and augmented risk of ventricular tachyarrhythmias [23–25, 27, 97]. Current guidelines, however, do not advocate routine CMR evaluation during follow-up.

Clinical Pearls

- The first clinical evaluation of a patient with a suspected diagnosis of HCM should always begin with the examination of the 12-lead ECG, because 90–95% of patients with HCM have ECG abnormalities, which usually include deep Q waves (>0.3 mV) with a short duration, deep negative T waves, and/or increased amplitude of the QRS complex. *Absence* of any ECG abnormalities on the 12-lead ECG makes a diagnosis of HCM unlikely in individuals without family history of HCM.
- In patients with HCM, an enlarged left atrium usually reflects augmented LV filling pressures and is associated with an increased risk of developing heart failure symptoms and/or atrial fibrillation. Therefore, left atrial dimension has an important role in the clinical evaluation of patients with HCM.
- The word "obstruction" recurs continuously in the conversation between physicians and patients with the obstructive form of HCM. Therefore, physicians should make the utmost effort to explain to the patient, in everyday language, the mechanism of LV outflow obstruction. Drawing simple sketches of the heart, hypertrophied septum and systolic anterior motion of the mitral valve may be helpful for this purpose.
- The patient's psychological attitude toward risk of sudden death and ICD implantation varies greatly and plays an important role in the final management decision. Therefore, patients judged to be at high or moderate risk should be explained, in simple words, their level of risk, the advantages and potential complications of the ICD, as well as the persisting limitations of risk stratification in HCM. Patients judged to be at low risk should be explained that their clinical profile does not justify ICD implantation, because the risk of ICD complications would be substantially higher than that of sudden death. *However*, *all patients should be informed that no individuals with HCM are at zero risk of sudden death*, *including those judged to be at low risk*.
- The physician confronted with a patient first diagnosed with HCM should include in the presentation of the disease information regarding lifestyle, the role of family screening, and possible indication to genetic testing, as well as pregnancy, when the affected individual is a young woman.

Posttest

1. Which is the prevalence of HCM in the general population?
   A. 1/50.000
   B. 1/25.000
   C. 1/10.000
   D. 1/5000
   E. 1/500

   Answer: 1/500, as HCM is the genetic familial cardiac disease with the highest prevalence, although most patients have mild clinical expressions of the disease and remain undiagnosed.

2. In which proportion of patients with HCM genetic screening identifies the mutation responsible for the disease?
   A. 50–60%
   B. 80–90%
   C. 20–30%
   D. <20%
   E. <10%

   Answer: In 50–60%, as the genetic causes of HCM are complex and not completely clarified.

3. The clinical evaluation of a patient with a suspected diagnosis of HCM should always begin with the examination of the:
   A. Echocardiogram
   B. 12-lead ECG
   C. Cardiac magnetic resonance
   D. Reconstruction of a possible family history of sudden death
   E. Reconstruction of patient's symptoms

Answer: 12-lead ECG, because the great majority of patients with HCM have an abnormal ECG, and the majority have ECG abnormalities that are typical for HCM, such as deep Q waves (>0.3 mV) with a short duration and deep negative T waves.

4. Which of the following clinical features has the most important prognostic implications?
   A. Abnormal 12-lead ECG
   B. History of brief and sporadic palpitations
   C. Marked left atrium dilatation
   D. Maximal septal hypertrophy of 15–16 mm
   E. History of sudden death in a 70-year-old second-degree relative

   Answer: Marked left atrium dilatation, as this echocardiographic feature has been shown to be independently associated with an increased risk of HCM-related death.

5. Which is the prevalence of severe symptoms of heart failure in the overall population of patients with HCM?
   A. > 90%
   B. > 80%
   C. > 50%
   D. < 40%
   E. < 30%

   Answer: < 30%, as most patients with HCM have no or mild symptoms and a favorable clinical course.

6. Left ventricular outflow obstruction in resting conditions is defined as an outflow gradient of:
   A. ≥ 20 mmHg
   B. ≥ 30 mmHg
   C. ≥ 40 mmHg
   D. ≥ 50 mmHg
   E. ≥ 70 mmHg

   Answer: ≥ 30 mm Hg.

7. Left ventricular outflow obstruction in resting conditions is identified in which proportion of patients with HCM?
   A. 20–25%
   B. 40–50%
   C. 50–60%
   D. > 60%
   E. > 90%

   Answer: 20–25%.

8. In which proportion of patients without left ventricular outflow obstruction in resting conditions is outflow obstruction provoked with physiologic maneuvers (such as the Valsalva maneuver) or exercise?
   A. 10–15%
   B. 20–25%
   C. 30–40%
   D. 50–60%
   E. None

   Answer: 50–60%. These data refer to patients evaluated at HCM referral centers.

9. Which patients with obstructive HCM have an indication to invasive treatment for relief of the outflow gradient?
   A. Patients with an outflow gradient at rest ≥30 mmHg
   B. Patients with an outflow gradient at rest ≥50 mmHg
   C. Patients with an outflow gradient at rest ≥50 mmHg and severe symptoms unresponsive to medical treatment
   D. Patients with an outflow gradient at rest or with provocation ≥50 mmHg and severe symptoms unresponsive to medical treatment
   E. All

   Answer: Patients with an outflow gradient at rest or with provocation ≥50 mmHg and severe symptoms unresponsive to medical treatment, as patients with this clinical profile have been shown to have a more favorable outcome with invasive than with medical treatment.

10. Which HCM patients are considered reasonable candidates to ICD implantation for primary prevention of sudden death by the ACC/AHA HCM guidelines?
    A. Patients with nonsustained ventricular tachycardia on 24-h Holter recording
    B. Patients with an outflow gradient at rest ≥50 mmHg
    C. Patients with maximal left ventricular hypertrophy ≥25 mm
    D. Patients with either maximal left ventricular hypertrophy ≥30 mm, recent unexplained syncope, family history of sudden death in first-degree relatives, or multiple risk factors
    E. All

    Answer: Patients with either maximal left ventricular hypertrophy ≥30 mm, recent unexplained syncope, family history of sudden death in first-degree relatives, or multiple risk factors

11. Which one of these 5 HCM patients should be considered as a candidate to ICD implantation for primary prevention of sudden death, on the basis of the ACC/AHA HCM guidelines?
    A. Patients with a run of 5 beats of nonsustained ventricular tachycardia on a 24-h Holter recording
    B. Patients with an episode of unexplained syncope 6 years before clinical examination
    C. Patients with a maximal left ventricular hypertrophy of 32 mm
    D. Patients with a history of a sudden death in his uncle
    E. A patient with an episode of unexplained syncope 6 years before clinical examination and a run of 5 beats of nonsustained ventricular tachycardia on a 24-h Holter recording.

    Answer: The patient with a maximal left ventricular hypertrophy of 32 mm.

12. Which are the clinical features associated with evolution to end-stage HCM?
    A. Progression to severe symptoms of heart failure
    B. Documentation of recurrent ventricular tachyarrhythmias on Holter recordings
    C. Progressive increase in left ventricular hypertrophy
    D. Progressive left ventricular wall thinning, left ventricular cavity dilatation, and development of systolic dysfunction
    E. All

    Answer: Progressive left ventricular wall thinning, left ventricular cavity dilatation, and development of systolic dysfunction.

13. Which is the incidence of end-stage evolution in patients with HCM?
    A. 3–5%
    B. 15–20%
    C. 30–40%
    D. >50%
    E. All

    Answer: 3–5%.

14. Which is the pharmacologic treatment of HCM patients with end-stage evolution?
    A. Beta-blocking drugs without any association with other medications
    B. Calcium antagonists
    C. Disopyramide
    D. Diuretics, ACE inhibitors or angiotensin receptor blockers, beta-blocking drugs, and other drugs routinely used in the management of heart failure due to systolic dysfunction
    E. Diuretics without any association with other medications

    Answer: Diuretics, ACE inhibitors or angiotensin receptor blockers, beta-blocking drugs, and other drugs routinely used in the management of heart failure due to systolic dysfunction.

15. Which is the incidence of atrial fibrillation in HCM patients evaluated at HCM referral centers?
    A. 1–5%
    B. 10–15%
    C. 20–25%
    D. 40–50%
    E. >50

    Answer: 20–25%.

16. In which HCM patients with recurrent or persistent atrial fibrillation and without major contraindication to anticoagulant medications is anticoagulation therapy indicated?
    A. Patients with marked left atrial dilatation
    B. Patients with moderate or marked left atrial dilatation
    C. Patients with associated left ventricular outflow obstruction
    D. Patients with associated symptoms of heart failure
    E. All

    Answer: All, as atrial fibrillation is associated with an important risk of embolic stroke in patients with HCM.

17. As HCM is a genetic familial disease inherited as a Mendelian autosomal dominant trait, which clinical screening should be advised in the patient's family?
    A. 12-lead ECG in the family members, to repeat once a year if initially negative for HCM
    B. Echocardiogram in the family members, to repeat once a year if initially negative for HCM
    C. Clinical screening, including ECG and echocardiogram, once a year in adolescent siblings and once every 5 years in adults, if initially negative
    D. 12-lead ECG and echocardiogram only once, if negative
    E. None

    Answer: Clinical screening, including ECG and echocardiogram, once a year in adolescent siblings and once every 5 years in adults, if initially negative.

18. As HCM is a genetic familial disease inherited as a Mendelian autosomal dominant trait, which genetic screening should be advised in the patient and patient's family?
    A. Genetic screening should be advised in the index patient to facilitate the identification of first-degree family members at risk for developing HCM. Genetic

testing is not indicated in family members, when a definitive pathogenic mutation has not been identified in the index patient.

B. Genetic screening should be advised only in the index patient.

C. Genetic screening should be advised in family members, independently of whether a definitive pathogenic mutation has been identified in the index patient.

D. Genetic screening should be advised to assess the risk of sudden death in the index patient, when uncertainties regarding sudden death risk persist after risk stratification based on the patient clinical profile.

E. Genetic screening is not indicated in patients with HCM and their families.

Answer: Genetic screening should be advised in the index patient to facilitate the identification of first-degree family members at risk for developing HCM. Genetic testing is not indicated in family members, when a definitive pathogenic mutation has not been identified in the index patient.

19. Which is the clinical presentation that is generally considered benign in a patient with HCM?
    A. No or mild symptoms.
    B. Mild left ventricular hypertrophy (< 20 mm).
    C. No left ventricular outflow obstruction in resting conditions.
    D. No HCM risk factors for sudden death.
    E. All the above features have to present.

    Answer: All the above features have to present.

20. Which is the correct timing for follow-up visits in HCM patients with a benign clinical presentation?
    A. 3–6 months
    B. 6 months to 1 year
    C. 1–2 years
    D. 2–3 years
    E. Every 5 years

    Answer: 1–2 years

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Evaluation and Management of Hypertrophic Cardiomyopathic Patients Through Noncardiac Surgery and Pregnancy

Nadia B. Hensley and Theodore P. Abraham

Key Points

- HCM patients are at increased risk for sudden death, stroke, congestive heart failure, and arrhythmias; therefore preoperative assessment involves a thorough history and physical exam to assess risk for noncardiac surgery or pregnancy.
- Progression and severity of HCM symptomatology (dyspnea, presyncope or syncope, palpitations, and angina), duration of symptoms, and functional status currently are most valuable in assessing risk of HCM patients perioperatively or peripartum.
- Beta-blockers; calcium channel blockers, i.e., verapamil or diltiazem; and disopyramide should be continued in the perioperative period in HCM patients undergoing noncardiac surgery, including the day of surgery.
- For patients with provocable obstruction, with or without congestive heart failure symptoms, attention must be paid to optimal volume status intraoperatively, especially in high-risk surgeries with large fluid shifts. Consideration of intraoperative placement of TEE or PA catheters may assist the anesthesiologist in determining optimal cardiac left-sided filling pressures.
- The anesthesiologist should avoid medications that dramatically decrease systemic vascular resistance. Pure alpha-agonists, such as phenylephrine, are preferred in the setting of decreased end-diastolic volumes or systemic vascular resistance.
- Physiologic changes of pregnancy can potentially worsen left ventricular outflow tract obstruction in HCM patients due to increased contractility and decreased systemic vascular resistance from the low resistance placenta.
- NYHA class prior to pregnancy is generally the best indicator of whether or not the parturient will hemodynamically tolerate the physiologic changes of pregnancy. End-stage HCM patients with NYHA Class III/IV prior to pregnancy should consider termination of pregnancy given the risk of mortality to both fetus and mother.

Introduction

Given the prevalence of hypertrophic cardiomyopathy (HCM) being relatively high (1:500 in the general population) across all races and regions, physicians will encounter these individuals preoperatively prior to noncardiac surgery as well as in the setting of pregnancy [1]. It is well known that the anesthetic and surgical perturbations in the setting of HCM pathophysiology can result in increased morbidity and mortality, yet there are few studies that have examined the risk involved. Recently, Barbara et al. reviewed 57 HCM patients for 96 noncardiac surgeries [2]. They found that HCM patients with NYHA I and II symptoms tolerated anesthesia fairly well. Patients with NYHA Class III and IV symptoms preoperatively were more likely to experience worsening heart failure symptoms postoperatively. Hreybe

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et al. examined the risk of acute myocardial infarction (MI) and in-hospital mortality after noncardiac surgery in HCM patients. The risk of in-hospital MI and death was higher in the HCM patients than in the control group (6.7% vs. 2.5% [$P < 0.001$] for death and 2.2% vs. 0.3% [$P < 0.001$] for MI) [3]. Haering et al. conducted a retrospective study of HCM patients undergoing noncardiac surgery and found 40% had one or more adverse perioperative cardiac events, most commonly congestive heart failure (CHF) (16%) [4]. Therefore, this chapter will review how to assess HCM patients for risk of postoperative or peri-pregnancy complications and how best to manage such patients, including when surgery or pregnancy may be contraindicated.

Preoperative Evaluation for Noncardiac Surgery

Most HCM patients can be managed through surgery, including high-risk operations. The baseline functional status of the patient, including symptoms and degree of heart failure, is likely the most significant discriminating factor on whether a patient with HCM will tolerate surgery. Those who are asymptomatic or mildly symptomatic, including those in NYHA Class I and II, are likely to have fewer complications than those with higher degrees of dysfunction and symptoms. Accordingly, a thorough understanding of the patient prior to surgery is required.

Preoperative Clinical Presentation and Diagnostic Imaging

Patients with HCM are at increased risk for sudden death, stroke, congestive heart failure, and arrhythmias such as atrial fibrillation, ventricular tachycardia and fibrillation, and atrial reentrant tachycardia [3], and therefore a thorough history should be conducted to help determine risk [5]. Some patients may already have a genetic diagnosis; however, due to the genetic heterogeneity [1], phenotypic expression depends not only on the mutation but also environmental factors [6], such as diet and exercise [7]. A subgroup of HCM patients has emerged with genetic mutations but without left ventricular hypertrophy, and the clinical ramifications and natural history of this subgroup are yet unknown [1]. However, since the risk of clinical symptoms increases with age, this subgroup of patients should be periodically screened with serial ECG, 2D-transthoracic echocardiography, and clinical assessments [8]. If there is a strong family history of HCM and the patient is asymptomatic with normal phenotype, genetic testing should be considered to help establish the genotype positive, phenotype negative status and help determine a treatment strategy [6]. If genetic testing is not possible, first-degree relatives and other family members of known HCM patients should be assessed by 2D-transesophageal or transthoracic echocardiography (TEE or TTE) or cardiovascular MRI [9] prior to noncardiac surgery and pregnancy [6]. However, general consensus is currently that patients with genotype-positive, phenotype-negative disease are at very low risk of perioperative or other HCM-related events and can be managed similar to the non-HCM population.

Since symptoms can occur anytime between infancy and the 9th decade, even the asymptomatic patient with HCM can be at increased risk under general anesthesia for noncardiac surgery or during the physiologic alterations that occur in pregnancy [10]. Indeed, sudden death usually occurs in asymptomatic or mildly symptomatic patients [11]. However, the more severe symptomatology can signify further progressed disease. Most HCM patients' symptomatology involves dyspnea, presyncope or syncope, palpitations, and angina [12]. Progression and duration of symptoms, as well as current functional status, should be assessed in a preoperative work-up. Those patients that have NYHA Class III or IV symptoms most likely have increased LVOT gradients (resting or provoked) of >30 mm Hg [13] and/or atrial fibrillation [14] and/or diastolic dysfunction [15], all of which increases perioperative risk, particularly of heart failure but also of arrhythmias [6]. Any history of arrhythmias, cardioversion, radiofrequency ablations, and placement of an implantable defibrillator should also be ascertained [1]. Those with angina, especially the elderly, should undergo cardiac catheterization or stress testing to rule out concomitant coronary artery disease. Current medications, such as antiarrhythmics, rate-control drugs, or anticoagulants, should be assessed as these may need to be continued or withdrawn perioperatively. Patients with uncontrolled or controlled vascular congestion are also at increased risk for worsening of congestive heart failure after noncardiac surgery.

Risk Stratification of the HCM Patient for Noncardiac Surgery

HCM patients should be risk-stratified during preoperative evaluation, including diagnostic exams such as TTE, TEE, or cardiac MRI. They should be categorized as far as their degree of obstruction: (1) nonobstructors, (2) labile obstructors with provocable LVOT peak pressure gradients of ≥30 mm Hg, and (3) obstructors with resting LVOT peak pressure gradients ≥30 mm Hg (see Figs. 29.1 and 29.2). Haering et al. found that factors associated with adverse cardiac events in this population undergoing noncardiac surgery were increasing length of surgical time and intermediate- to high-risk surgery [4]. Intermediate- to high-risk surgery was defined as major vascular, orthopedic, open peritoneal, and

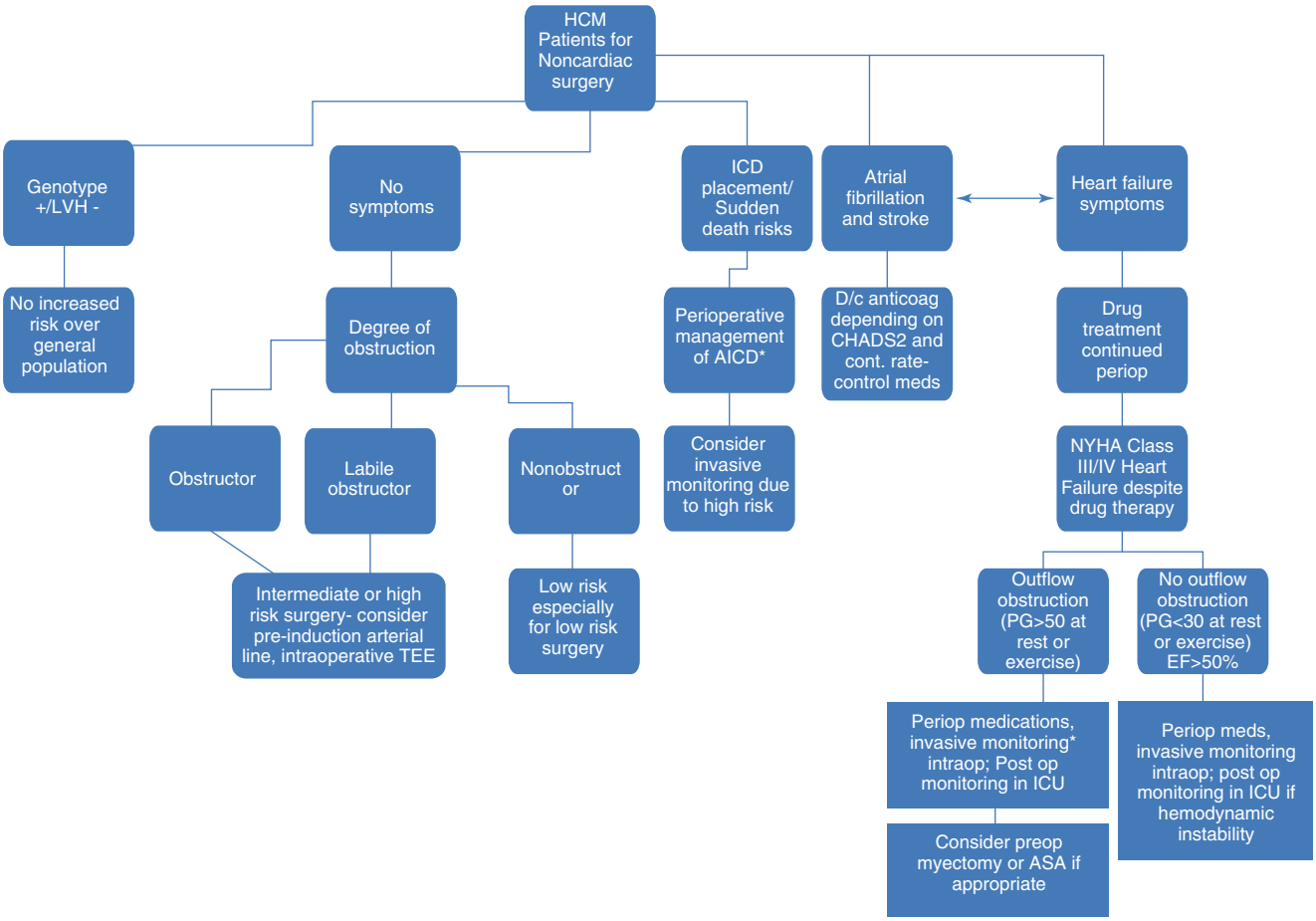

Fig. 29.1 Suggested algorithm for risk stratification and intraoperative monitoring of HCM patients going for noncardiac surgery. (Adapted from Ref. [1]). = Primary prevention markers for AICD: (1) Family history of sudden cardiac death; (2) unexplained recent syncope; (3) multiple repetitive nonsustained ventricular tachycardia; (4) hypotensive response to exercise; (5) massive LVH ≥ 30 mm; (6) extensive and diffuse late gadolinium enhancement. Invasive monitoring* = intra-arterial catheter, TEE, pulmonary artery catheter, or central venous pressure monitoring. PG pressure gradient, LVH left ventricular hypertrophy, ASA alcohol septal ablation

head and neck surgeries [16]. Risk stratifying HCM patients prior to noncardiac surgery should follow AHA/ACC guidelines for preoperative evaluation [16]. If a known HCM patient is undergoing intermediate- to high-risk surgery and has not had a recent 2D-TTE or TEE or if there is a progression in severity of symptoms or new arrhythmias, then further work-up should be completed.

2D-TTE or TEE should focus on the degree of resting and provoked LVOT obstruction, mitral regurgitation and systolic anterior motion of the mitral valve, abnormalities of the mitral valve and subvalvular apparatus, degree of diastolic dysfunction, chamber enlargement, and LV systolic function. Recent studies have examined the use of 2D strain analysis or speckle tracking to be able to better differentiate between left ventricular hypertrophy and HCM [17]. Outflow track gradients of 30 mm Hg or more under resting conditions (measured by continuous wave Doppler) are independent determinants of symptoms of progressive heart failure and death [18] and thus risk factors for increased perioperative cardiac morbidity and mortality. HCM patients may have significant or even severe angina, which may be due to microvascular dysfunction, excessive wall tension, or epicardial disease. Older patients with risk factors may require stress testing or cardiac catheterization prior to noncardiac surgery. Cardiac catheterization has the added advantage of hemodynamic assessment, including an evaluation of resting cardiac output, pulmonary pressures, and filling pressures.

For those without a clear diagnosis, murmurs that are dynamic and do not meet the criteria for a benign murmur (Table 29.1) should be referred for echocardiographic review [19]. The typical features of the murmur in HCM are a systolic murmur that is heard loudest at left sternal border, does not radiate to the neck, and increases with exercise, Valsalva, or standing [19]. A 12-lead ECG should be performed; however the changes in ECG seen with HCM patients are often nonspecific (Table 29.2). A 12-lead ECG is abnormal in 75–95% of HCM patients [20] and can help identify arrhythmias or evidence of prior myocardial infarcts.

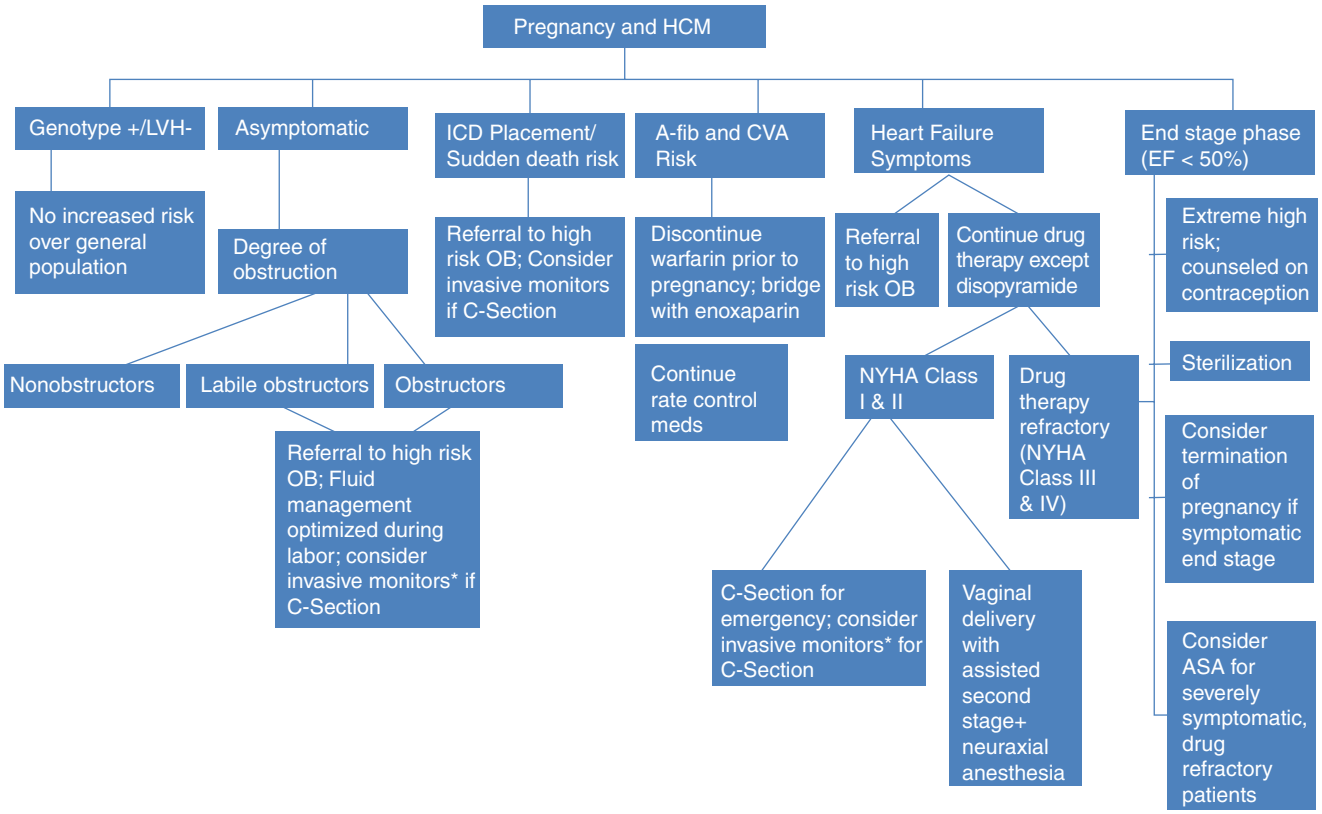

Fig. 29.2 Suggested algorithm for risk stratification and monitoring of HCM patients during pregnancy and delivery. + = assisted second stage with low forceps or vacuum-assisted delivery. C-section cesarean section, ASA alcohol septal ablation

Table 29.1 Clinical features of the functional (benign) heart murmur

Location: left sternal border and nonradiating[a]
Timing: mid or early systole[b]
Intensity: grade 2 or lower
No unexplained cardiac or pulmonary symptoms (e.g., dyspnea, chest pain, orthopnea, syncope)
No additional unexplained cardiac signs (e.g., rales, S3, significant peripheral edema)
No electrocardiographic or chest radiograph evidence of ventricular hypertrophy)

Adapted from reference [19]
[a]Murmurs radiating into the neck should be considered due to aortic stenosis or HCM and are thus not functional
[c]Diastolic murmurs are always considered pathological

Table 29.2 Nonspecific EKG changes accompanying HCM

Left ventricular hypertrophy (S wave in V1; R wave in V5 > 35 mm)
Left axis deviation
Intraventricular conduction delay (QRS > 0.12 ms)
Left atrial enlargement (broad notched P wave in lead II; deeply inverted P wave in V1)
ST segment & T wave abnormalities
Poor R wave progression in precordial leads
Supraventricular arrhythmias (most commonly atrial fibrillation)

HCM patients found to have atrial fibrillation are at increased risk of stroke and most likely will be anticoagulated with coumadin or direct Xa inhibitors (rivaroxaban) or direct thrombin inhibitors (dabigatran) [8]. Coumadin should be stopped within 5 days and direct Xa or thrombin inhibitors at least 2 days prior to high-risk elective surgery to decrease the bleeding risk [21] if they are considered low risk for perioperative stroke [22]. Although rare, HCM patients with a history of easy bruising and increased bleeding may actually have an acquired von Willebrands disorder due to dynamic LVOT obstruction-related shearing of large multimers of von Willebrand factor [23]. More information on this associated bleeding problem is found elsewhere in this textbook. This bleeding propensity may be significant depending on the type of surgery and should be kept in mind in preoperative planning.

Preoperative Management in HCM

Patients with significant LVOT obstruction (resting gradient >30 mm Hg or more) and exertional heart failure symptoms should be started on pharmacological treatment with beta-

blockers or, if contraindication, verapamil [8]. Verapamil should be used with caution in those patients with severe LVOT gradients at rest and advanced heart failure [24]. Disopyramide is another pharmacotherapy used to treat symptomatic HCM patients that has been shown to reduce outflow gradients at rest as well as on provocation [25]. Beta-blockers; calcium channel blockers, i.e., verapamil or diltiazem; and disopyramide should be continued in the perioperative period in the HCM patient undergoing noncardiac surgery, including on the day of surgery. The decrease in heart rate and inotropy and thus optimization of the myocardial supply-demand curve and minimization of LVOT obstruction that beta-blockade allows are particularly advantageous in the setting of surgery and sympathetic stimulation.

Patients with severe obstructive physiology who require high-risk surgery should be optimized from a symptom standpoint and volume standpoint prior to undertaking such surgery. This includes ideally a titration of medications and possibly a right and left heart catheterization to optimize fluid status and hemodynamics. In patients with severe resting or provocable obstruction refractory to optimal medical therapy, in whom the risks of major noncardiac surgery remain high, consideration to preoperative surgical myectomy or alcohol septal ablation should be given. The ideal timing of noncardiac surgery after surgical myectomy or alcohol septal ablation is unknown.

Intraoperative Management of the Low-Risk HCM Patient

The low-risk HCM patients presenting for noncardiac surgery are those that are asymptomatic or have very mild symptoms. The subclass of HCM that is genotype positive, phenotype negative is also a low-risk population. These patients are lower risk for hemodynamic instability perioperatively and therefore may not need any additional monitoring than an otherwise healthy patient would need for the same surgery. It should be kept in mind, however, that they have coronary microvascular dysfunction and diastolic dysfunction by the pathophysiologic mechanism of their disease, with exception of the genotype positive/LVH negative patients. In addition to congestive heart failure, the anesthesiologist should be vigilant to any ECG changes concerning for ischemia or arrhythmias perioperatively.

Intraoperative Management of the HCM Labile Obstructors or Resting Obstructors

For patients with provocable obstruction and no preexistent congestive heart failure, attention must be paid to optimal volume status, as intraoperative or postoperative volume depletion may stimulate worsening obstruction and progressive hypotension. All patients who are hypovolemic or euvolemic should be maintained on sufficient hydration to minimize the possibility of worsening LVOT obstruction. If there is a suspicion or concern or a procedure with significant fluid shifts or volume losses, then consideration to intraoperative TEE or pulmonary artery catheter during surgery should be given. This is particularly true of patients with large gradients or significant NYHA class symptoms at baseline, who are undergoing high-risk surgery. In addition, the anesthesiologist should avoid medications with pure afterload-reducing properties and should prioritize alpha-agonists over inotropes in the setting of hypovolemia or decreased systemic vascular resistance. Intra-aortic balloon pumps are contraindicated due to the possibility of promoting and exacerbating outflow tract obstruction and causing a paradoxical worsening of hypotension, in patients with resting or labile obstruction.

HCM patients that have a history of or current atrial fibrillation are also a unique subset that should be managed carefully. In a large single-center retrospective analysis, Siontis et al. found that those HCM patients with atrial fibrillation had worse symptoms, worse exercise capacity, and a significantly higher risk of death from any cause compared to those HCM patients without atrial fibrillation [26]. HCM patients with atrial fibrillation are also at increased risk of heart failure exacerbations and hospitalizations. Volume management for HCM patients in atrial fibrillation can be challenging. Due to the sudden drop in cardiac output (by approximately 40%) that occurs if a patient goes into atrial fibrillation intraoperatively, the anesthesiologist should be judicious in the amount of fluid given. These patients may also need monitored postoperative care as well.

In the above scenarious, while adequate preload is important, care must be taken to avoid hypervolemia as diastolic dysfunction may result in frank pulmonary edema. As such, patients with HCM may have a relatively narrow volume window within which to operate, where obstruction is minimized but congestive heart failure is avoided.

For patients with severe obstructive physiology, the anesthesiologist must understand that hypotension may be a consequence of preload reduction or due to profound obstruction. When there is doubt, a Swan-Ganz catheter can be helfpul in assuring appropriate filling pressures. If pressors are required, a pure arterial vasoconstrictor, such as phenylephrine, is preferable, given its ability to improve outflow tract obstruction and blood pressure. Inotropes should be avoided, including epinephrine and norepinephrine, unless patients have been documented to be nonobstructive by intra-op TEE.

Intraoperative Management of HCM Nonobstructors

Patients with nonobstructive HCM may also be at risk of perioperative complications, including exacerbation of heart failure or development of atrial fibrillation in particular. Approximately, 3% of nonobstructors have end-stage HCM with lower systolic function (usually <50%) and severe diastolic dysfunction. In fact, the only definitive treatment for end-stage HCM is heart transplant. Such patients typically require higher filling pressures due to severe diastolic dysfunction but may also be easily pushed into frank pulmonary edema if aggressively hydrated during surgery, as discussed above.

In addition, cardiac output is oftentimes normal in minimally symptomatic patients but may be severely reduced in patients with severe diastolic dysfunction. Apical HCM patients may also fit this category, due to both a small ventricular chamber size from apical obliteration and myocardial diastolic failure. In such patients, a Swan-Ganz catheter may be helpful in order to maintain optimal filling pressures, especially when high-risk surgeries with large fluid shifts are planned. Intraoperative TEE may be particularly helpful in difficult cases of hypotension, in order to understand physiology acutely and to reconfirm that no obstruction is present. Patients with nonobstructive HCM are also at risk of ischemia and arrhythmias and should be monitored for these complications as well.

Postoperative Management of HCM Patients After Noncardiac Surgery

Postoperatively, patients with preexistent severe symptoms or intraoperative hypotension or arrhythmia should be managed in an intensive care unit setting, especially after high-risk surgery with large fluid shifts or aggressive hydration. As previously discussed, arterial vasoconstrictors and hydration are the mainstays of hypotension treatment, unless the patient is already in pulmonary congestion. IABP is contraindicated in patients with outflow tract obstruction. Patients should be maintained or reinitiated on their outpatient medications, including beta-blockers, and fluid resuscitation or diuretics may be utilized as needed, keeping in mind that the optimal filling pressures in patients with HCM are typically higher than in the normal population. Pulmonary artery catheters may be helpful to document and titrate filling pressures to balance reduction in outflow tract obstruction physiology with avoidance of pulmonary vascular congestion in those with obstructive physiology but may also be helpful in nonobstructive HCM patients with severe diastolic dysfunction and reduced cardiac output.

Managing HCM Through Pregnancy

There are very few studies, most of which are more than 30 years old, that examine the cardiac risks involved in HCM patients that become pregnant [27, 28]. A recent retrospective review by Autore et al. looked at the risk of mortality and morbidity in this population [18]. They found that there was increased risk of death compared to the general population; however, the absolute maternal death rate was low [18]. In their study, two deaths occurred in particularly high-risk females, one of which had NYHA Class III symptoms with a previous pregnancy and the other had strong family history of sudden death in several close relatives [18]. For the most part, pregnancy is not absolutely contraindicated in HCM patients and those that are asymptomatic or have mild HCM typically tolerate pregnancy well [18].

Physiologic Changes in Pregnancy and HCM

The hemodynamic changes that occur during pregnancy can have either a salubrious or detrimental effect in the HCM parturient [29]. Increases in circulating blood volume (50% increase in plasma volume and 30% increase in red blood cell mass) and increased left ventricular end-diastolic diameter associated with increased stroke volume can be of benefit by reducing LVOT obstruction. However, patients with baseline congestive heart failure may see a worsening of congestion with expansion of plasma volume. In addition, worsening obstruction can occur due to increased cardiac contractility and decreased systemic vascular resistance due to the low resistance placenta [29] and high estrogen/progestin levels. Meticulous attention to hemodynamics, volume status, and clinical symptoms, and adjustment of medications, may be required particularly in the third trimester of pregnancy.

Physiologic changes during labor and delivery can exacerbate heart failure symptoms in HCM patients as well. Pain and anxiety can result in tachycardia which decreases diastolic filling time in patients with already impaired diastolic relaxation [29, 30]. Increases in preload can be dramatic due to the lack of IVC compression and redistribution of blood from the lower extremities, especially during contractions, which can cause pulmonary edema in those at the brink of the Frank-Starling curve [30]. There is an increase in cardiac output of up to 50% above pre-delivery values during the second stage of labor and as high as 80% above pre-labor within the first hour of delivery [29]. Cardiac output slowly declines over the next 2 weeks. These peripartum hemodynamic pertubations place the HCM parturient at risk of new or increased left ventricular outflow tract obstruction (LVOTO), arryhthmias, and CHF [30].

General Management Before or During Pregnancy in HCM

Ideally before pregnancy, there should be a clinical assessment of HCM-related risks, including which category of LVOTO HCM the patient falls into: (1) nonobstructor, (2) obstructor at rest, or (3) labile obstructor. Those with significant obstruction (>30 mm Hg peak gradient at rest) are at increased risk for morbidity and mortality [8, 18, 31] (see Fig. 29.3). Even though degree of obtruction can correlate with functional capacity, this may not always be the case. There are few studies and numerous case reports on pregnancy outcomes in HCM parturients. These generally show that NYHA class prior to pregnancy directly relates to maternal morbidity [18].

For patients (mother or father) with HCM, genetic counseling should be offered preconception [8]. In addition, some institutions are offering genetic testing of the fetus or preimplantation for family planning purposes. Other assessments should be made regarding current medications, current or history of arryhthmias, implantable defibrillators, and previous surgical or nonsurgical treatments such as myectomy or alcohol septal ablations. In patients who have undergone myectomy or alcohol septal ablation, in particular, an assessment should be made for the degree of any residual LVOT obstruction. Most patients with resolved obstruction, in whom diastolic dysfunction may have also improved, can tolerate pregnancy better than prior to such procedures, although confirmatory data are lacking.

Women with resting or provocable peak LVOT gradients >50 mm Hg or NYHA Class >II should be referred to a high-risk maternal fetal medicine obstetrician [8, 29]. If HCM patients are currently on beta-blockers, most can be continued during the peripartum period. Atenolol is the exception due to the higher incidence of fetal growth restriction compared with other beta-blockers [30]. Increased surveillance for fetal bradycardia and intrauterine growth restriction is prudent [8, 32]. For those parturients on verapamil, it can also be continued with the same precautions as in a nonparturient, i.e., it should be used with caution if functional status starts to deteriorate or those with severe LVOT gradients at rest [1, 30]. HCM patients on disopyramide prepregnancy

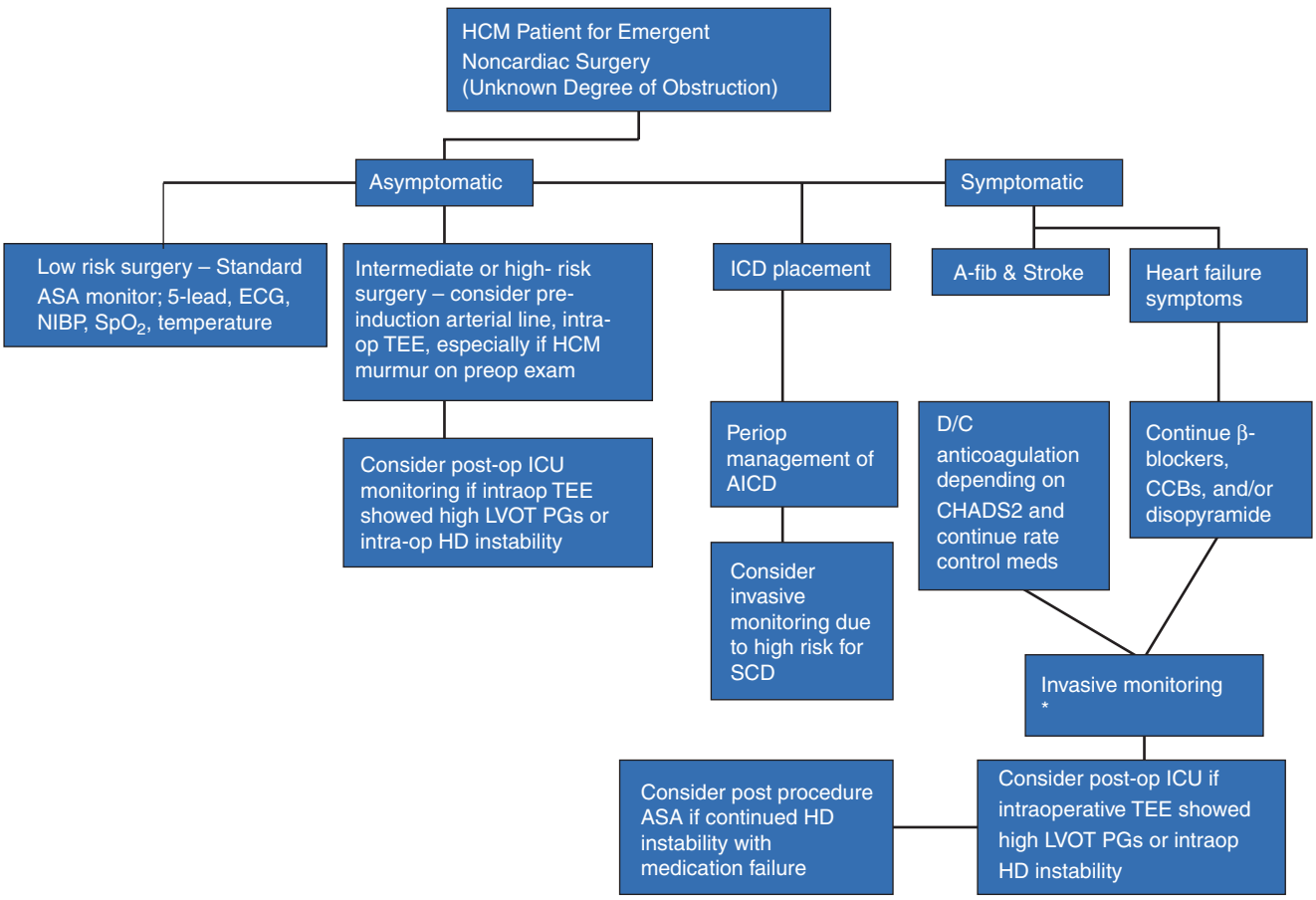

Fig. 29.3 Suggested algorithm for HCM patient requiring emergent/urgent surgery. * = intra-arterial catheter, central venous catheter, +/– TEE. LVOT left ventricular outflow tract, PG pressure gradient, HD hemodynamic, AICD automated internal cardioverter defibrillator, SCD sudden cardiac death, TEE transesophageal echocardiography, A-fib atrial fibrillation, CCD calcium channel blocker

should stop taking the medication prior to becoming pregnant due to its ability to possibly induce uterine contractions [30]. In those patients with history of atrial fibrillation and being anticoagulated, coumadin should be stopped due to its teratogenic effects [30], and they should be transitioned to therapeutic doses of enoxaparin [33].

In those patients with increased LVOT gradients (>30 mm Hg at rest) and NYHA Class III or IV symptoms, it should be impressed upon them that they are at high risk for adverse maternal and fetal outcomes. They should be educated on methods of safe contraception to avoid becoming pregnant and placing themselves and the fetus at such risk. Estrogen and progesterone contraceptives can potentiate prothrombotic risks in HCM patients. These combined hormonal contraceptives are given WHO (World Health Organization) Class 2 rating which suggests the benefit outweighs the risk in those with HCM without atrial arrythmias [29]. Other options include progestin-only formulations, intrauterine devices, barrier methods, and sterilization [29]. In patients with severe symptoms that are likely to get prohibitively worse during the second or third trimesters or postpartum, consideration to terminating an existing pregnancy should be given, in order to reduce maternal and fetal mortality.

Management During Labor and Delivery

The decision regarding the timing and mode of delivery (cesarean section vs. vaginal) should be based on the hemodynamic status of the patient. Most HCM patients that are asymptomatic or have had mild, stable symptoms can be allowed to spontaneously progress into the stages of labor [29, 30]. If there are concerns about the functional adequacy of the heart to withstand the physiological changes of pregnancy, labor can be induced in a more controlled fashion with more availability of staff and monitoring capabilities. In the decompensating patient, a discussion between the cardiologist, obstetrician, and anesthesiologist should occur that weighs the risks of continuing pregnancy to both the mother and fetus and the risk of delivery [29]. Vaginal delivery with its associated less blood loss is preferred over cesarean section unless there is fetal distress or the parturient is rapidly deteriorating hemodynamically [29].

Neuraxial anesthesia can dramatically decrease afterload, but careful titration of local anesthetics and opioids with adequate fluid administration prior to placement has been used successfully in HCM parturients [29]. In fact, the decrease in pain and sympathetic stimulation that neuraxial anesthesia allows can decrease cardiac contractility and heart rate which would benefit the HCM patient. Hemodynamic management following a spinal anesthetic may be more challenging, and slow titration using a continuous spinal, decreased dose of intrathecal local anesthetic, advanced fluid loading, and patient positioning are critical aspects of management [34].

For a mandatory cesarean section, arterial line placement is recommended. Depending on the degree of LVOTO, functional status, recent worsening of symptoms, arryhthmias, and emergent nature, it may be necessary to induce general anesthesia. If it is an emergent cesarean section, there is significant increased risk due to the cardiovascular instability that can occur with a rapid sequence induction and intubation. TEE would be of benefit in the scenario of a rapidly deteriorating or critically ill parturient undergoing general anesthesia for cesarean section. Similarly, a pulmonary artery catheter may prove beneficial to adequately monitor and manage fluid status and pressors, if needed, postoperatively. In particular, TEE could guide fluid management to maintain normovolemia, as well as assist in determining new causes of hemodynamic instability by allowing assessment of regional wall motion, degree of mitral regurgitation, or LVOT obstruction. Pulmonary artery catheters could help assess left-sided filling pressures and be useful postoperatively for several days in the critical care setting.

Postpartum HCM patients may need a higher level of monitoring, i.e., an intensive care setting, if the patient had significant hemodynamic changes during delivery or significant decline in functional status prior to delivery. Synthetic oxytocin administration after delivery to assist with uterine contractions should be administered slowly due to its side effect of decreasing systemic vascular resistance [29]. The elevated cardiac output and large fluid shifts postpartum can be especially precarious in the HCM patient, and therefore hemodynamic monitoring for 12–24 h is advised [29].

The AHA/ACC guidelines on the use of pulmonary artery catheters in cardiac patients for noncardiac surgery (cesarean section) suggest that they can be used if the patient is at risk for major hemodynamic disturbances that can be detected by a PA catheter [16]. If the patient will be going to an ICU setting and has severely compromised LV dysfunction, PA catheter insertion can be considered if the ability to measure cardiac left-sided filling pressures and SvO_2 monitoring can assist the providers in determining causation for hemodynamic instability. This is oftentimes indeed the case for patients with severe HCM with obstructive physiology, especially with resting obstruction. Intraoperatively, TEE may provide improved capabilities over PA catheters in HCM patients due to ability to assess biventricular function, new or increasing LVOT obstruction, new regional wall motion abnormalities, and degree of mitral regurgitation.

In conclusion, HCM is not an absolute contraindication to pregnancy, and the most significant predictor of the parturient to tolerate the physiologic changes peripartum is the functional status of the patient prior to becoming pregnant. Cesarean section should only be performed if absolutely needed for the well-being of the fetus and mother at the time

of delivery, i.e., rapid deterioration in mother's hemodynamic status or severe fetal bradycardia. TEE and PA catheters can be utilized in the general anesthetic cesarean section HCM patient to help guide fluid management and/or the need for pressors.

Conclusions

Most patients with HCM can be managed through noncardiac surgery and pregnancy. In general, the presence, absence, and severity of LVOT obstruction, as well as the preexisting functional status and symptomatology, are the most important determinants of perioperative or peripregnancy complications. Most decisions about the care of these patients should be made as part of a multidisciplinary team approach. Patients with severe symptoms deserve significant attention, with consideration of avoiding high-risk surgeries and prenancies for those at extreme risk. When unavoidable, however, most patients can be managed through most surgeries and pregnancy.

Clinical Pearls

- HCM patients with atrial fibrillation are more progressed in their disease process due to impaired diastolic relaxation causing increasing left atrial pressure and left atrial enlargement, leading to atrial fibrillation. Perioperatively, these patients may need judicious fluid management since they may be at increased risk for intravascular volume overload and pulmonary edema.
- Intra-aortic balloon pump is absolutely contraindicated in the HCM patient with left ventricular outflow tract obstruction (LVOTO) (resting or latent) due to its ability to promote and potentially worsen obstruction and consequent hypotension.
- Myectomy and alcohol septal ablation could be considered in patients with peak LVOT gradients ≥30 mm Hg at rest or ≥50 mm Hg provoked prior to high-risk noncardiac surgery or patients contemplating pregnancy, especially if drug-refractory.
- Neuraxial anesthesia for the HCM parturient can be beneficial due to its ability to diminish the sympathetic response to pain (tachycardia and inotropy) and therefore decrease the risk of causing LVOTO. Slow titration of local anesthetic with intra-arterial pressure monitoring is warranted due to their side effect of decreasing afterload.
- Forceps-assisted or vacuum-assisted delivery of the fetus may be considered in the second stage of labor due to decreasing the amount of valsalva/pushing required of the HCM parturient, which would otherwise potentially worsen the LVOTO.

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Conflict of Interest None of the authors have any conflicts.

Questions

1. Which pressure gradient across the left ventricular outflow tract (LVOT) is considered significant for septal reduction therapy if a HCM patient is still symptomatic despite maximal medical therapy?
   A. Mean pressure gradient ≥30 mm Hg
   B. Mean pressure gradient ≥50 mm Hg
   C. Peak pressure gradient ≥20 mm Hg
   D. Peak pressure gradient ≥30 mm Hg
   E. Peak pressure gradient ≥50 mm Hg

   Answer: E. HCM patients with significant LVOT obstruction, peak pressure gradient ≥50 mm Hg, and symptomatic despite maximal medical therapy should be evaluated to be a candidate for septal reductoin therapies. Surgical myectomy, the gold standard for intervention by the American Heart Association and American College of Cardiology consensus guidelines, is a first option, although many patients may elect for alcohol septal ablation if available and indicated given the need for a second surgery. Due to the nature of late-systolic obstruction in HCM patients, only the *peak* pressure gradient is evaluated to determine candidacy.

2. How does atrial fibrillation affect the perioperative risk of HCM patients?
   A. It is the same degree of risk for all atrial fibrillation patients, regardless of whether they have HCM or not.
   B. Since all HCM patients are very preload sensitive, those in atrial fibrillation need increased preload during their perioperative period.
   C. HCM patients rarely have atrial fibrillation since the more prominent arrhythmias are lethal ventricular arrhythmias.
   D. Due to the reduction in cardiac output by approximately 40%, HCM patients that go into atrial fibrillation during the perioperative period are at increased risk of intravascular volume overload.
   E. They are only at an increased risk for perioperative stroke.

   Answer: D. Atrial fibrillation is a strong predictor of mortality, even after adjustment for established risk factors in a recent study [26]. HCM patients with atrial fibrillation (AF) are at increased perioperative risk due to HCM-

related factors and atrial fibrillation-related factors. This is due to the loss of atrial kick in those with diastolic dysfunction and hypertrophied left ventricles, which may cause a loss of 40% of their cardiac output. This places HCM with AF at increased risk for intravascular volume overload and perioperative heart failure exacerbations.

3. An HCM patient presents in the preoperative area for an atrial fibrillation ablation and pulmonary vein isolation. He is noted in cardiology reports to have a peak pressure gradient across the LVOT of 102 mm Hg 2 years ago. No recent TEE has been done. The patient has become increasingly symptomatic with dypsnea on exertion despite maximal medical therapy and now has increasing periods of paroxysmal atrial fibrillation. What is the best management for this patient?
   A. Proceed with ablation procedure, explaining to patient that due to their last LVOT gradients, they are at much higher perioperative risk.
   B. Explain to patient that since they have significant LVOT pressure gradients and are failing maximal medical therapy, they would be a candidate for either surgical myectomy (gold standard) and may have a modified MAZE procedure during the time of their surgery. In the meantime, ensure patient is started on rate and rhythm control medication.
   C. Cancel the EP procedure due to no recent TEE and patient's symptomatology.
   D. Proceed with cardioversion, despite no TEE, and reschedule EP ablation.
   E. B and C are correct.

   Answer: E. Ideally, this patient would have a recent TEE given a history of significant LVOT gradients to 102 mm Hg 2 years ago and a recent change in symptomatology. Due to the continued increased LV intraventricular pressure across the LVOT, resulting in a higher LVEDP and left atrial pressure, the ablation has a higher risk of failure. The patient should be initiated on rhythm control medications and referred to a high-volume surgical center for myectomy. The patient may be a candidate for a modified MAZE or MAZE procedure with left atrial appendage ligation at the time of myectomy [8].

4. An HCM parturient G3P2 presents in labor and delivery after spontaneous rupture of membranes. She is having regular contraction 2 min apart that lasts 1 min, and she rates her pain as 9/10. She is interested in having an epidural. What are the next best steps?
   A. The anesthesiologist proceeds to place a lumbar epidural giving normal doses of local anesthetic since the patient is in 9/10 pain.
   B. The anesthesiologist explains to the patient that since she has HCM, she cannot labor and must go to the OR for urgent cesarean section.
   C. After obtaining a thorough history, including her most recent TEE report, that shows a peak pressure gradient of 50 mm Hg, and her functional status – NYHA Class II (the patient has continued on beta-blockade throughout pregnancy), the anesthesiologist discusses the patient's increased risk and need to place an intra-arterial monitor prior to placement of the epidural catheter. Careful titration of local anesthetic occurs to obtain an appropriate anesthetic level.
   D. Multidisciplinary discussion with anesthesiology and obstetrics regarding the patient's attempt at trial of labor and if there is hemodynamic instability with continued Valsalva during stage 2 of labor, then it may necessitate vacuum-assisted or forceps delivery.
   E. Both C and D are correct.

   Answer: E. HCM parturients can do well during pregnancy and peripartum. Studies have shown this is highly correlated with the degree of heart failure or NYHA class that the patient experienced prepregnancy [29, 30]. HCM is not an indication for cesarean section. Cesarean sections should only be performed in those patients that present in heart failure and are too hemodynamically unstable to undergo vaginal delivery. In HCM parturients, especially those with significant gradients, it is prudent to place intra-arterial pressure monitors prior to placing epidural catheters. Judicious fluid therapy may be given prior to dosing the epidural with local anesthetic to ensure optimal left ventricular filling pressures. Slow titration of local anesthetic is recommended. Second-stage vacuum-assisted or forceps delivery may be considered to prevent increasing LVOT obstruction if there is hemodynamic instability with continued Valsalva maneuvers.

5. What is the most significant predictor of how well HCM patients can tolerate noncardiac surgery?
   A. No significant LVOT obstruction
   B. Less than moderate mitral regurgitation due to systolic anterior motion of the mitral valve
   C. No history of previous ventricular arrhythmias
   D. NYHA classification
   E. Left atrial indexed diameter < 3.0 cm^2

   Answer: D. According to a recent retrospective review of HCM patients undergoing noncardiac surgeries at a high-volume center, the most significant predictor of how well patients will do is their NYHA classification preoperatively [2]. Those with NYHA I–II classification safely underwent noncardiac surgery, even though the majority of patients

received vasoactive medications intraoperatively. Those that had noncardiac surgery *emergently* had a significantly higher associated risk of death ($p = 0.0002$) [2].

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Building a Hypertrophic Cardiomyopathy Center of Excellence

30

B. Robinson Williams III and Lisa Salberg

Abbreviations

HCM	Hypertrophic cardiomyopathy
HCMA	Hypertrophic Cardiomyopathy Association
ICD	Implantable cardioverter defibrillator
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
SCD	Sudden cardiac death
TEE	Transesophageal echocardiography
VUS	Variants of unknown significance

Key Points

- A national network of referral centers has been established for patients with hypertrophic cardiomyopathy (HCM), both adult and pediatric, and continues to grow.
- The goal of these centers is to improve clinical care for patients with HCM by concentrating expertise and patient volume and to facilitate both investigator-initiated and large-scale randomized controlled trial research.
- Key components of an HCM center include HCM specialists in adult and pediatric cardiology, electrophysiology, cardiac imaging, cardiac surgery, interventional cardiology, advanced heart failure therapy, genetic counseling, and an administrative HCM coordinator. Administrative support for marketing and programmatic development is similarly important.
- An HCM center offers expertise in advanced therapies for HCM patients such as surgical myectomy and alcohol septal ablation (or appropriate referral arrangements for these services), meeting national standards for competency and clinical outcomes for both procedures.

Introduction

In the 2011 ACCF/AHA guidelines for the diagnosis and treatment of hypertrophic cardiomyopathy (HCM), the following paragraph is devoted to the concept of the HCM center:

> The writing committee considers it important to emphasize that HCM is a complex disease entity with a broad (and increasing) clinical and genetic spectrum. Although HCM is one of the most common forms of genetic heart disease and relatively common in the general population, this disease entity is infrequent in general clinical practice, with most cardiologists responsible for the care of only a few patients with HCM. This principle has led to an impetus for establishing clinical programs of excellence—usually within established centers—in which cardiovascular care is focused on the management of HCM (i.e., "HCM centers"). Such programs are staffed by cardiologists and cardiac surgeons familiar with the contemporary management of HCM and offer all diagnostic and treatment options, including genetic testing and counseling, comprehensive transthoracic echocardiogram (TTE), CMR imaging, both surgical septal myectomy and alcohol ablation, and the management of atrial fibrillation (AF)/atrial flutter, and ICDs. Another advantage is the potential to perform outcomes research on large groups of patients. [1]

In this paragraph, the guidelines writing committee emphasizes the importance of regional referral centers dedicated to the care of patients with HCM. The "HCM Centers of Excellence" serve to provide comprehensive medical care

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for patients and their families as well as facilitate the formation of a national network of centers that can collaborate in multicenter research studies. In this chapter, we will discuss the evolution of the concept of "Centers of Excellence" and discuss the components of an HCM center.

The concept of Regional Centers of Excellence in healthcare in the United States can be traced back to the National Cancer Institute (NCI), a division of the National Institutes of Health (NIH). During the first half of the twentieth century, the public and the medical community began to focus more of their attention on cancer, a disease that seemed to be rapidly increasing in prevalence and appeared to have no cure. In 1960, the NCI recommended the formation of government-sponsored cancer centers. The goal was to unify the research being done at various academic centers around the country. In 1971, the National Cancer Act was signed, which established 15 NCI-designated cancer centers. These centers were distributed throughout the United States at various institutions based on population, geography, and medical science expertise. Their mandate was to conduct "clinical research, training and demonstration of advanced diagnostic and treatment methods relating to cancer." [2]

Today, there are more than 60 NCI-designated cancer centers across the country. In order to obtain this designation, a center must meet various criteria set forth by the NCI both in terms of clinical expertise and research capabilities. Regional Centers of Excellence not only allow for collaboration between institutions but also allow patients to have access to world-class clinical care within driving distance. In the decades that have followed, other national organizations have followed the highly successful "center" model adopted by the NCI.

The HCMA was founded in 1996 with the stated goal of providing "support, advocacy and education to patients and their family members, the medical community and the public about hypertrophic cardiomyopathy." [3] One of the goals of the HCMA was to establish a national network of HCM centers. They have been very successful in this regard. Prior to the founding of the HCMA, there were only a handful of institutions with multidisciplinary expertise in the diagnosis and treatment of HCM. Currently, there are 31 HCMA-recognized Centers of Excellence programs in 20 states, and the creation of certified programs is growing at a rate of approximately 4 new programs per year (Fig. 30.1).

Much like the NCI-designated cancer centers, HCM centers allow patients to have access to state-of-the-art care closer to home. The HCMA has established criteria that an institution must meet in order to qualify. In addition, many HCM centers have collaborated to form a powerful research network. The remainder of this chapter will be spent discussing the components that comprise an HCM center as well as the role of an HCM center in community and national education and research.

Another organization specifically for the pediatric population is the Children's Cardiomyopathy Foundation (CCF) covering all forms of cardiomyopathy. The goal, similar to the HCMA, is to foster a network of centers that can address HCM in the pediatric population, including advanced therapies. The CCF has identified institutions with particular expertise in cardiomyopathy care, especially as it relates to the pediatric population (Fig. 30.2).

Of course, the centers recognized by the HCMA and CCF are not the only centers caring for patients with HCM. Both the HCMA and CCF are private organizations with predomi-

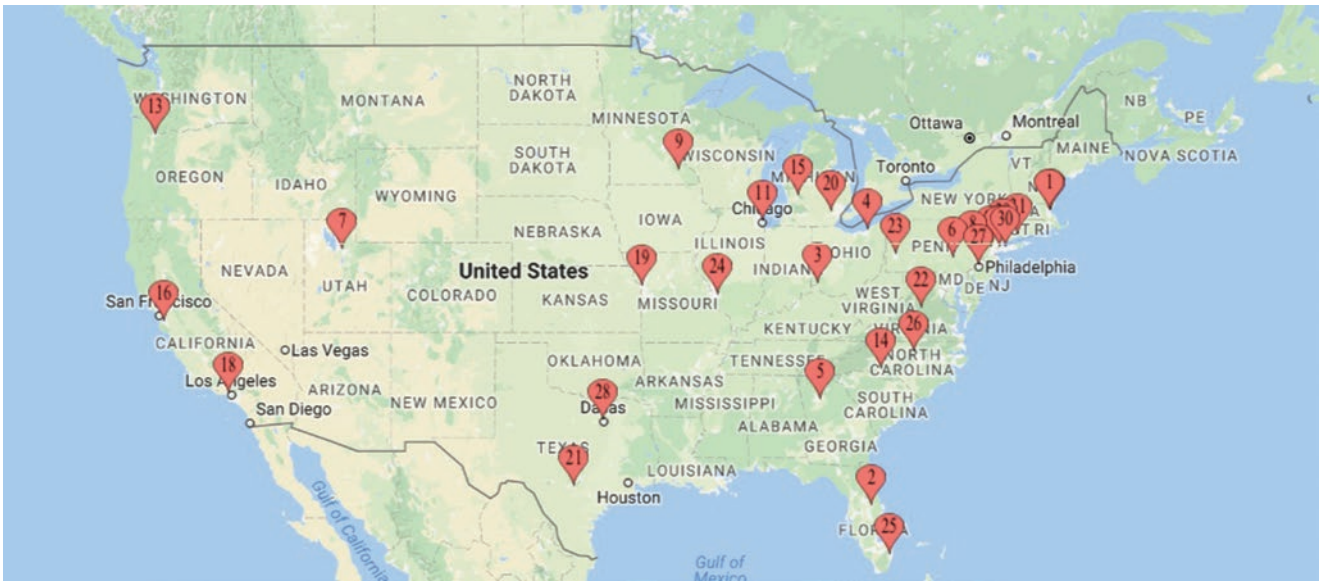

Fig. 30.1 Map of Hypertrophic Cardiomyopathy Association (HCMA)-recognized Centers of Excellence

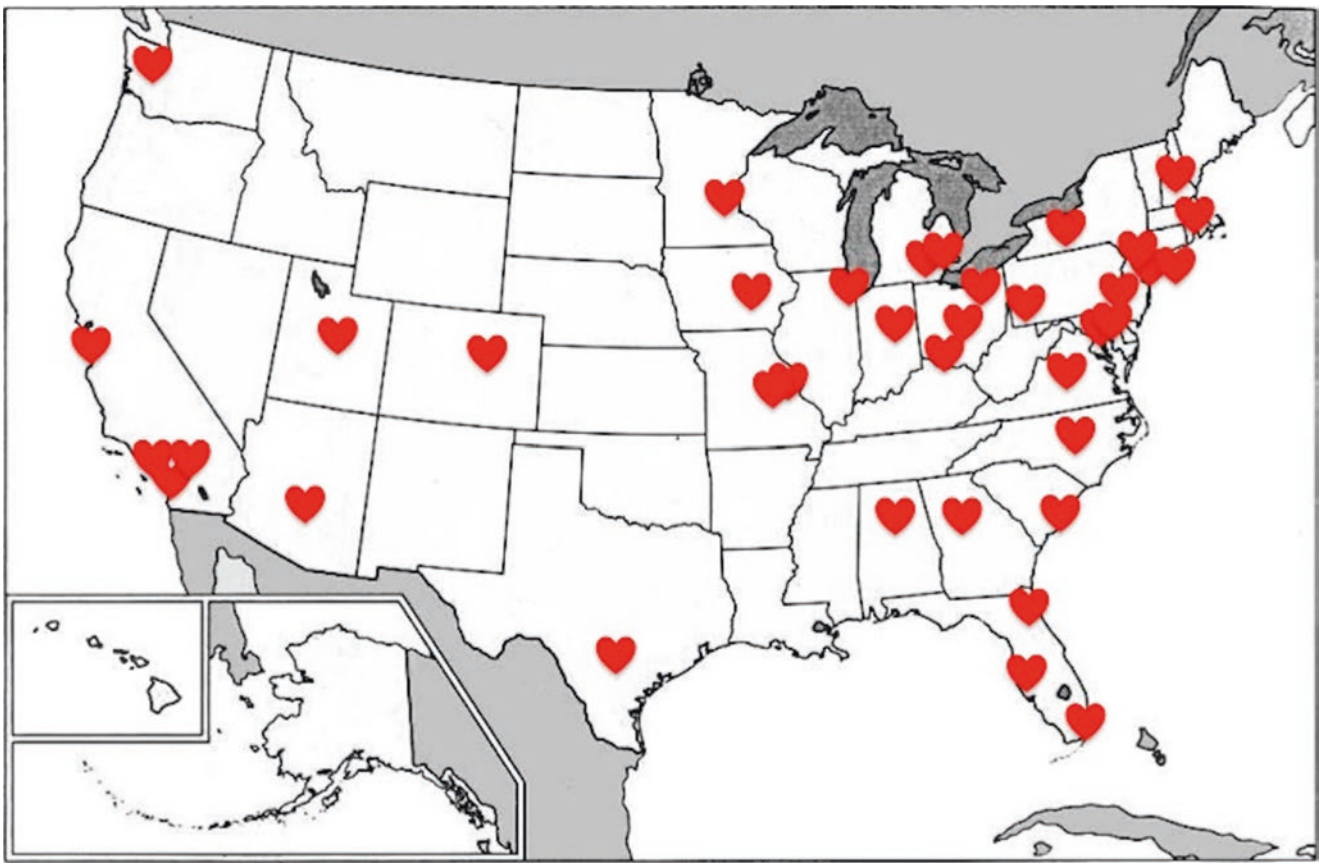

Fig. 30.2 Map of Children's Cardiomyopathy Foundation (CCF)-recognized Centers of Excellence

nantly patient advocacy missions and thus not subject to audit or other metrics that would assure objective criteria in the selection of Centers of Excellence. Accordingly, several well-known Centers of Excellence for HCM have either not participated, or not been selected, or are in process of applying for recognition but remain active and well-respected both clinically and through research, with large patient volumes and long-standing experience. Thus, the listed centers by each organization are not meant to be a comprehensive listing but rather two examples of networks for HCM. Indeed, there is excellent and comprehensive care being provided to HCM patients at centers throughout the United States and countries throughout the world not on these lists for a variety of reasons, but all follow the concepts outlined herein in terms of the components and goals of such centers.

Components of an HCM Center

HCM is a heterogeneous and unpredictable disease that is encountered relatively infrequently in a general cardiology practice. Having regional centers allows for cardiologists (both noninvasive and interventional) and surgeons to gain necessary expertise by caring for large volumes of patients. Furthermore, caring for patients and families with HCM requires a multidisciplinary team approach. Ideally, an HCM center should include a medical director, adult and pediatric cardiology, cardiac imaging (echocardiography and cardiac magnetic resonance imaging), electrophysiology, cardiac surgery, interventional cardiology, cardiac transplant, and genetic counseling (Table 30.1). A clinical coordinator that helps patients navigate the system and enhances communication with referring physicians is also important. Comprehensive programs

Table 30.1 Components of a basic HCM center

HCM coordinator
HCM specialist (director)
Pediatric cardiology
Cardiac imaging (echocardiography and cardiac MRI)
Cardiac electrophysiology
Cardiac surgery
Interventional cardiology
Advanced heart failure/transplant
Genetic counseling and geneticist
Additional HCM center components
Psychological services
Dietitian and weight loss
Obstetrics and gynecology
Complementary services

should include services for the entire continuum of healthcare including obstetrical care, diet/weight loss, psychological, and family services. Scheduling should also be equipped to handle patients and families traveling from a distance by providing appointment slots for full evaluations within a day or two and resources or guidance on travel logistics.

HCM Specialist

The medical director of an HCM center is the individual with primary expertise in the diagnosis and management of patients with HCM. This individual typically devotes a significant percentage of his/her clinical time to the care of patients with this complex disease and is involved in the vision and direction of the program and the accumulation and maintenance of knowledge regarding HCM. He or she is also responsible for coordinating the clinical care of patients at their institution and often has a dedicated clinic day or days for HCM patients. A large medical center will often already have most or all of the components needed for an HCM center, although significant time will need to be devoted to growing and maintaining the HCM expertise of each of these individuals. The medical director will also ensure that these components work in concert and continue to accrue specific knowledge and experience regarding HCM treatment. This may include promoting attendance at national HCM meetings or other off-site training dedicated to each subspecialty.

Traditionally, the medical director is a general cardiologist, often with expertise in cardiac imaging or advanced heart failure. However, a cardiology subspecialist such as an electrophysiologist or interventional cardiologist could certainly serve in this role. The medical director is often the first physician that the patient will encounter at the HCM center. The medical director will then refer the patient to other members of the team as he or she sees fit clinically. In addition, the medical director is responsible for keeping the lines of communication open among the team members, often with multidisciplinary conferences at regularly scheduled intervals. The medical director often supervises the HCM-related clinical research being performed at the center and is typically the director of the HCM-related educational efforts. She or he is also responsible for making sure the center is prioritized within the institution, including administrative and financial support to maintain and grow the program. The HCM director is oftentimes the face of the program, interacting externally from marketing and development standpoints, including raising awareness of HCM throughout the community.

Pediatric Cardiology

Pediatric cardiology is another integral part of any HCM center. Hypertrophic cardiomyopathy is a genetic disease that can affect multiple members of the same family, including children. It is also the leading cause of sudden cardiac death in children and young people under the age of 35. While the HCM phenotype most commonly manifests itself during the second or third decade of life, the disease can present at any age. Infants diagnosed with HCM at a very young age (<1 year) tend to have more severe disease and higher mortality rates [4]. Children and adolescents with HCM may develop symptoms, and/or need advanced care, such as implantable defibrillators or surgery. The pediatric cardiologist is responsible for managing these patients, and coordinating care, sometimes with outside institutions.

In addition to caring for affected children, pediatric cardiologists play a pivotal role in screening the adolescent first-degree relatives of HCM patients. For patients less than 12 years of age (or prior to the onset of puberty) with a first-degree relative with HCM, screening is optional unless there is clinical suspicion for early onset (e.g., murmur or syncope) or a malignant family history of premature death from HCM or the child is involved in high-risk competitive athletics [1]. It is recommended that adolescents undergo screening every 12–18 months. Screening typically involves history and physical examination, electrocardiography, and echocardiography. Lifestyle factors and social implications are particularly important in children; therefore, the pediatric cardiologist must have access to social and/or psychology services and work closely with the parents of the children to address any and all concerns, including sports participation, social isolation, and other psychological issues. The pediatric cardiologist may also take the lead in any discussions with local schools regarding HCM and awareness.

The introduction of genetic testing of families with HCM has resulted in the creation of a group of patients that are genotype-positive for HCM but phenotype-negative. The majority of these genotype-positive, phenotype-negative individuals will be children or adolescents and will need rigorous monitoring by a pediatric cardiologist for the development of the HCM phenotype.

Cardiac Imaging

Expertise in cardiac imaging is another important component of an HCM center. Although multiple imaging modalities are utilized, echocardiography is the predominant imaging modality for diagnosis and management of patients with HCM. As mentioned in the previous section, echocardiography is the test of choice when screening first-degree relatives of HCM patients. Echocardiography is also important in assessing those with known HCM as well. Echocardiography is used to determine if left ventricular outflow tract (LVOT) obstruction is present and accurately measure gradients, determine maximum wall thickness, assess diastolic and systolic left ventricular function and left atrial

size, and assess response to therapy. Newer echocardiographic techniques such as strain-rate imaging, three-dimensional echocardiography, and left atrial volume index are also useful in the assessment of HCM patients.

Echocardiography is also used frequently during alcohol septal ablation to help guide the interventional cardiologist. Intraoperative transesophageal echocardiography (TEE) is frequently utilized to guide surgeons during septal myectomy. A sonographer or interpreting physician at a high-volume HCM center is more likely to have a full grasp of the subtleties of diagnosing and assessing HCM with echocardiography, including abnormalities of the mitral valve and associated apparatus including the papillary muscles. Sonographers should use a consistent protocol when imaging an HCM patient, including Doppler assessment from multiple views with and without provocation and the use of myocardial contrast agents when indicated to assist in defining endocardial borders, determining wall thickness and ruling out associated apical aneurysms. In addition, sonographers at a high-volume HCM center should be familiar with the use of exercise echocardiography and optimal Valsalva maneuvers to provoke LVOT obstruction.

In addition to echocardiography, cardiac magnetic resonance imaging (MRI) plays a crucial role in the assessment of patients with HCM. Over the past decade, cardiac MRI has become an increasingly important study not only for establishing the diagnosis of HCM but also in risk stratification for sudden cardiac death. Cardiac MRI has higher special resolution than echocardiography and the ability to image the heart in a tomographic fashion. It can be useful in establishing the diagnosis in patients who are undergoing screening for HCM and have difficult echo images and in patients with focal hypertrophy in areas that are often not well visualized with echo (anterolateral wall or apex). Cardiac MRI is useful in risk stratification in HCM by being able to accurately measure maximum wall thickness and assess the extent of left ventricular delayed enhancement. Late gadolinium enhancement, representing intramyocardial scar, is associated with adverse clinical outcomes, including all-cause mortality [5].

Cardiac MRI can also be used to establish the diagnosis of HCM in patients that have equivocal echocardiograms or to provide a more accurate measurement of wall thickness in those with severe hypertrophy by echocardiogram. It is also helpful in identifying alternate etiologies of hypertrophy, such as storage diseases and infiltrative disease. In HCM, a wall thickness of $\geq$3.0 cm has been associated with an increased risk of sudden cardiac death (SCD) and may be an indication for implantation of an implantable cardioverter defibrillator (ICD); therefore patients with borderline high maximal thickness of 2.5 or higher may benefit from more accurate assessment with MRI. Altogether, cardiac MRI is emerging as an essential component of the evaluation of HCM patients, and a center should have expertise in this imaging modality.

Cardiac Electrophysiology

Cardiac electrophysiology is a subspecialty available in most cardiology practices and cardiac centers. It is also a critical component of an HCM center. As discussed elsewhere in this textbook, HCM patients are at increased risk of SCD when compared to the general population, with an average incidence of 1% annually. Many HCM patients will be deemed to be at high risk for SCD and require an ICD. Often, HCM patients who require an ICD are younger and more active than the typical adult cardiology patient, and this must be taken into consideration by the electrophysiologist. By virtue of their age, HCM patients are more likely to need multiple generator exchanges over their lifetime. Lead failure is also more common in HCM patients. This is likely a result of the patients' higher activity levels and possibly due to the hyperdynamic contraction of the hypertrophic heart. Being exposed to multiple procedures over their lifetime increases the cumulative risk for HCM patients. In addition, patients with HCM often have extensive trabeculations, making positioning difficult at times; moreover, positioning of ventricular leads for optimal hemodynamics requires precise placement. Having an experienced electrophysiologist will mitigate inherent risk and improve the likelihood of proper placement.

In addition to an increased risk for ventricular tachyarrhythmias and SCD, patients with HCM are at high risk for atrial arrhythmias such as atrial fibrillation and flutter. An electrophysiologist may be needed to help guide antiarrhythmic therapy or perform ablation procedures to treat the atrial or ventricular arrhythmias. In contrast to patients with other underlying heart diseases, ablation procedures in HCM patients may have unique challenges due to very large atria or extreme hypertrophy of the left ventricle. Thus, specialized expertise in the care of HCM patients is also needed in this regard.

Finally, pacemakers are also sometimes required in patients with HCM. Elderly patients may benefit from pacemakers to reduce outflow tract obstruction or allow higher doses of atrioventricular nodal blocking drugs (i.e., beta-blockers or calcium-channel blockers). In addition, patients following both alcohol septal ablation and surgical myectomy may require pacemakers for heart block or severe conduction disease. A team approach with electrophysiology may in particular improve the safety of alcohol septal ablation, given the relatively higher risk of post-procedural complete heart block.

Cardiac Surgery

Cardiac surgery, with specific expertise in the septal myectomy procedure, is another important component of an HCM center. The isolated septal myectomy procedure is considered the gold standard in the United States for treating symptomatic patients with LVOT obstruction that is resistant to medical therapy. Like any surgical procedure, operator experience

is critical to obtaining good clinical results and low complication rates. However, given the relative scarcity of HCM in most cardiac centers, it is difficult for surgeons to obtain the surgical volumes necessary to become proficient except in the setting of a high-volume HCM center. The 2011 ACCF/AHA guidelines recommend operator volume of at least 20 cases, and the center should achieve a mortality rate of <1% and a major complication rate of <3% [1]. The HCMA does not require the presence of an on-site septal myectomy surgeon at an HCM center. A center may have an established referral pathway to an established high-volume surgical center. Surgeons should be experienced in complex mitral valve repair, including modifications to papillary muscles and chords, in order to avoid the need for mechanical mitral valve replacement. In many instances, formal on-site proctoring by an established HCM surgeon may be required.

Interventional Cardiology

In addition to surgical septal myectomy, the other invasive treatment for symptomatic HCM patients with LVOT obstruction is alcohol septal ablation. This procedure, covered in depth elsewhere in this textbook, is a catheter-based procedure performed by an interventional cardiologist. An HCM center should offer this as an option for their patients with LVOT obstruction that fail medical therapy. This procedure should be considered in those patients whose surgical risk may be unacceptably high due to comorbidities or as a less-invasive option for those patients who refuse surgical therapy. Like surgical myectomy, high operator volumes are associated with better clinical outcomes and fewer complications. Similar to surgical myectomy, the 2011 ACCF/AHA guidelines also recommend an operator volume of at least 20 cases for those that perform alcohol septal ablations [1]. These high volumes are most easily attained in the setting of a high-volume HCM center. Similar to surgical myectomy, a center may have an established referral pathway to an established high-volume interventional cardiologist with expertise in alcohol septal ablation. Also as with surgery, formal proctoring in the performance of alcohol septal ablation, either on-site or by way of national courses, may be required. A national course, run by Editor Srihari S. Naidu and colleague Dr. George Hanzel at Beaumont Medical Center, occurs annually.

In addition to performing alcohol septal ablation, the interventional cardiologist should be adept at advanced hemodynamic assessment techniques, including a comprehensive hemodynamic evaluation to determine and isolate HCM physiology in the symptomatic patient. As alcohol septal ablation or surgery is only a viable option in those in whom severe obstructive physiology is the rate-limiting step in the patient's clinical symptoms, this assessment is absolutely vital to understanding how to manipulate medications, devices, and other invasive therapies in order to improve patient outcome.

Interventional cardiology specialists are also needed for patients undergoing surgical myectomy, performing diagnostic coronary angiography to evaluate for coexisting coronary artery disease. In those patients who are being evaluated for transplant, right heart catheterization will be required. In addition, patients with concomitant epicardial coronary artery disease may require stent placement to minimize ischemia.

Advanced Heart Failure and Transplant

Each year, 1–2% of HCM patients will progress to "end-stage" HCM. This is defined as the development of systolic dysfunction (left ventricular ejection fraction of ≤50%) and is thought to be due to progressive myocardial fibrosis resulting in wall thinning and LV dilation. An additional 1–2% will progress to end-stage heart failure (stage D) with preserved ejection fraction due to advanced diastolic dysfunction and/or low cardiac output. End-stage HCM is discussed in detail elsewhere in this textbook. The mortality rate for this patient population is high (11% per year) [6]. Many of the end-stage patients will develop progressive heart failure despite optimal medical therapy, and some will undergo cardiac transplantation. For these reasons, an established advanced heart failure program with transplant capability is an asset for an HCM center. With advances in management of arrhythmias and careful management of HCM-related heart failure, including successful septal reduction therapies, the number of HCM patients moving eventually to transplant is expected to increase in coming years.

The advanced heart failure specialist is vital in comprehensive assessment of these patients with end-stage diastolic or systolic heart failure, performance and tracking of cardiopulmonary exercise testing results, titration of advanced medications and therapies, and the timing of listing for heart transplantation, if required. For such patients, the heart failure specialist often becomes the primary treating physician. In many cases, the HCM heart failure and transplant specialist is at a different but nearby institution but works in close collaboration with both the regional HCM specialist and the local cardiologist. However, ideally, the transplant program should be at the same institution as they may also be helpful in facilitating diagnoses and ruling out infiltrative diseases as a cause of unexplained hypertrophy, through the performance of endomyocardial biopsies.

Genetic Counseling

Genetic testing and genetic counseling are an important service offered by an HCM center. HCM is a genetic disease

caused by a mutation in one of several genes encoding for sarcomere proteins. The disease is transmitted in an autosomal dominant fashion. Therefore, when an individual is diagnosed with HCM, all first-degree family members should be screened for the disease. Family screening is discussed in detail elsewhere in this textbook. A genetic counselor can determine when to utilize genetic testing and aid in interpreting the results. He or she can help explain the ramifications of a positive test, negative test, or variants of unknown significance (VUS) to patients and family members, including implications on life expectancy, complications, life and health insurance, as well as future transmission of disease.

Advances in preimplantation genetic diagnostics (PGD) and breaking research in Crispr CAS 9 technology may have significant impact on family planning in HCM families. Knowing the underlying genetic mutation is required to consider either of these options.

Genetic counselors are greatly aided by the presence of a geneticist physician, who can move the discussion to a higher level as needed in select families. As such, HCM centers should have a relationship with a geneticist for more advanced clinical discussions and evaluation, including consideration of whole exome sequencing for some patients.

HCM Nurse or Nurse Practitioner

A dedicated nurse practitioner helps to maintain high-quality patient management and decreases the workload on the HCM program director. Nurse practitioners help to manage patient care in coordination with the program director. This may include both outpatient and inpatient care. Titration of medications, ordering of testing, and acting in the capacity of daily contact when patients may be experiencing a change in symptoms help to ensure a high level of management compliance and improve overall outcomes and patient satisfaction with the center.

HCM Coordinator

An HCM center benefits tremendously from a dedicated HCM coordinator. Such an individual accepts all calls from HCM patients and referring physicians, triages and schedules patients for clinical visits, and helps coordinate testing. In particular, patients from distant locations may require multiple tests or office visits on a single day or may require complex insurance authorizations. A coordinator experienced in these aspects assures a smooth running center and enhances both the patient and referring physician experience. HCM coordinators are also helpful in the research and educational missions of the center, organizing conferences, and facilitating the work of all members of the HCM team.

Research at HCM Centers

We have discussed the advantages of the multidisciplinary approach of a high-volume HCM center and how this improves clinical care. Another advantage of regional HCM centers is that it facilitates research. HCM centers have the ability to establish large clinical databases that allow for longitudinal outcomes research. Furthermore, centers can combine their databases to form even more powerful observational or randomized prospective studies. Much of what we know today about HCM is a result of these observational studies. The rate of SCD in HCM, the effectiveness of ICD therapy in HCM patients, and outcomes from surgical myectomy and alcohol septal ablation have all been demonstrated by registries from HCM centers in the United States and elsewhere.

Over the past 30 years or so, the effectiveness of therapies for other cardiac diseases like coronary artery disease and congestive heart failure has been demonstrated in large, prospective randomized clinical trials. These diseases are very prevalent and therefore easier to study in this manner. Due to a relative paucity of patients, prospective randomized trials for HCM are uncommon. One of the benefits of a national network of HCM centers is the ability to pool patients for randomized clinical trials.

In addition to large-scale research across centers, individual centers with particular expertise (such as with surgical myectomy, alcohol septal ablation, or pediatrics) may be able to perform individual investigator-initiated research to advance the field. Such findings can then be extrapolated to other regions of the country for the benefit of all patients with HCM.

Education at HCM Centers

In addition to providing quality clinical care and conducting research, an HCM center also should be engaged in educating fellow healthcare professionals and patients about HCM. Education can come in many forms, including a local conference devoted to HCM, speaking at local hospitals and medical centers and information sessions for patients and their families. Certain centers with particular excellence can also be national leaders, educating others at national cardiovascular, surgical, heart failure or interventional meetings. Accordingly, education includes participating in national cardiology meetings such as the American College of Cardiology and the American Heart Association as well as meetings devoted specifically to HCM like the International Summit of Hypertrophic Cardiomyopathy and the HCMA Annual Meeting.

Education serves two main purposes. Naturally, it raises the awareness of HCM among local physicians and other healthcare providers and likely improves care of HCM patients. Second, it provides exposure for the HCM center

and makes other healthcare professionals aware that this national network of referral centers exists. In this regard, certain advertising such as radio commercials or website development can serve an educational function.

Conclusions

Over the past two decades, a national network of HCM Centers of Excellence has been established. The goal of the centers is to improve clinical care for HCM patients, encourage HCM research, and improve HCM-related awareness and education. A successful HCM center utilizes a multidisciplinary team with a wide array of expertise, including HCM specialists in adult and pediatric cardiology, electrophysiology, cardiac imaging, cardiac surgery, interventional cardiology, advanced heart failure therapy, and genetic counseling, all of it managed by the HCM director and a dedicated HCM coordinator. Importantly, as not all HCM centers can offer the full complement of services, nor should they. In particular, relationships are often necessary for most programs to offer high-volume alcohol septal ablation, surgical myectomy, heart transplantation, and advanced pediatric care.

The multidisciplinary HCM team brings their broad skill set together to care for patients with a complex and unpredictable disease. The existence of HCM centers also facilitates collaboration between institutions. High-volume centers have established databases and can collaborate with other centers to form even larger databases. This results in meaningful outcomes research and randomized clinical trials. The type of collaboration that occurs within *and* between HCM centers will undoubtedly advance our understanding of the disease and help HCM patients live longer, better lives.

The intent of the HCM centers is not to replace the local cardiologist in caring for HCM patients. Instead, the centers are meant to be a resource for referring providers and patients. They can offer a second opinion on patients that have symptoms that are difficult to manage or assist in assessing risk for SCD. An HCM center will likely offer services such as genetic counseling or expertise in septal myectomy or alcohol septal ablation that are not readily available in most cardiology practices. An HCM center is also available to assume care of patients or families with more severe forms of the disease. However, many patients will continue to be followed by their local cardiologist after visiting an HCM center. This may be the preferred strategy in patients who do not live in close proximity to an established center or in patients with a variety of comorbidities. Effective communication between the center and local cardiologist is imperative to ensure the HCM patient continues to receive high-quality care.

Clinical Pearls

- Although there are multiple requirements for an HCM center, some services will necessarily need to be outsourced to other HCM centers with higher volume and expertise in certain services. This is most common for alcohol septal ablation, surgical myectomy, advanced heart failure and transplantation, and advanced pediatric care (both devices and surgical).
- A dedicated HCM coordinator is a necessary first step in developing a Center of Excellence, and the institution must understand the value of dedicating resources such as this to the growth of the program.
- A dedicated office day for HCM patients will allow for streamlined yet specific HCM-related care and goes a long way toward solidifying the Center of Excellence.
- While not all HCM centers are certified by the HCM association, doing so allows the center to participate in a larger network of referrals and allows increased participation in HCMA-sponsored research and educational events.

Questions

1. Components of an HCM center include which of the following?
   A. HCM specialist/director and HCM coordinator
   B. Genetic counselor
   C. Invasive specialists (surgery, interventional cardiology, electrophysiology)
   D. Imaging specialists
   E. Pediatric cardiologist
   F. All of the above

   Answer: F. An HCM center requires the above expertise, in addition to other services such as advanced imaging (MRI) and heart transplantation. Not all HCM centers will have all services in their institution, and relationships must exist with other institutions capable of performing anything the primary institution cannot offer. In this manner, HCM patients can avail themselves of all options.

2. The role of the HCM director is to:
   A. Serve as the face of the program externally and internally
   B. Coordinate patient visits for those traveling from far away

C. Coordinate multidisciplinary team meetings and comprehensive care of individual patients
D. Both A and B
E. Both A and C

Answer: E. The HCM director or specialist is both the external and internal face of the program and serves as the primary clinical expert in HCM. He or she manages the coordinator and works with marketing and community outreach to increase awareness of the program and HCM in general. The HCM director creates the HCM team of experts and overseas the multidisciplinary team meetings that are patient-centered, to effect optimal and individualized care of the HCM patient.

3. Benefits of Center of Excellence certification include which of the following?
   A. External validation that the necessary components of a Center of Excellence have been coordinated and established
   B. Ability to network with other centers of excellence, including for select services not offered at the primary institution and additionally for research collaboration
   C. Aid in justification to the institution that dedicated resources are necessary, including resources for a dedicated HCM coordinator, marketing, and educational aspects
   D. All of the above
   E. A and B only

Answer: D. All of the above are reasonably expected benefits of maintaining Center of Excellence certification.

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Longitudinal Case-Based Presentations in HCM

31

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Abbreviations

ACCF	American College of Cardiology Foundation
AHA	American Heart Association
CMRI	Cardiac magnetic resonance imaging
CPR	Cardiopulmonary resuscitation
DCCV	Direct current cardioversion
ESC	European Society of Cardiology
ETT	Exercise treadmill test
HCM	Hypertrophic cardiomyopathy
HOCM	Hypertrophic obstructive cardiomyopathy
ICD	Implantable cardioverter defibrillator
INR	International normalized ratio
LBBB	Left bundle branch block
LGE	Late gadolinium enhancement
LVOT	Left ventricular outflow tract
NSVT	Non-sustained ventricular tachycardia
NYHA	New York Heart Association
RBBB	Right bundle branch block
SAM	Systolic anterior motion of mitral valve
SCD	Sudden cardiac death
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
VT	Ventricular tachycardia

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Introduction

Hypertrophic cardiomyopathy (HCM) has been well recognized since the 1950s. However, only recently has the frequent prevalence of this condition been recognized, affecting roughly 1 in 500 people. The complex pathophysiology continues to be delineated but includes diastolic dysfunction, outflow tract obstruction, mitral regurgitation, congestive heart failure, and pulmonary hypertension, as well as other sequelae including atrial fibrillation and stroke. Nonetheless, significant advances have been made in understanding this disease, including its genetic basis. Indeed, various mutations have been identified that help screen individuals and their families, to both help identify affected individuals and determine who is safe to exclude from further testing.

Numerous anatomic, physiologic, and clinical variables are now known to exist that can lead to a variety of presentations, ranging from no phenotypic expression of the disease in a gene-positive individual to sudden cardiac death in a massively hypertrophied individual. Alternatively, more chronic presentations including refractory heart failure requiring heart transplant are also noted. The complex interplay of various factors like diastolic dysfunction, dynamic left ventricular outflow tract obstruction, mitral valve apparatus abnormalities, pulmonary hypertension, and arrhythmias leads to a fascinating range of presentations which, if not properly managed, may progress through the life of the patient causing increased morbidity or mortality. Severely symptomatic patients present with exertional dyspnea, lower extremity swelling, orthopnea, syncope, or more crippling conditions such as cardioembolic stroke, advanced heart failure, and/or life-threatening arrhythmias. Coexistent medical conditions like obesity,

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hypertension, and lung pathologies may sometimes even further confuse the picture by causing similar and overlapping symptoms. In many cases, symptoms are ascribed to these alternate diagnoses for years prior to a firm diagnosis of HCM. The problem is compounded by the fact that many cardiologists and echocardiographers are not exposed to HCM patients in their routine clinical practice, and hence this condition is oftentimes picked up only after referral to a second or third specialist, by which time the symptoms, morphology, and function may have become even more debilitating and thus limiting potential treatments and expected quality of life or survival benefits. Indeed, methods aimed at increased awareness and early diagnosis and treatment are needed in this field.

Management of certain select populations like younger patients who participate in competitive sports, who have prospects of a long productive life ahead of them, as well as pregnant women, may be more challenging. Fortunately, after HCM is recognized in a patient, they can be referred to a high-volume HCM center, and most of the time symptoms may be abated by various noninvasive and/or invasive approaches, including appropriate pharmacotherapy and lifestyle modification, as outlined elsewhere in this book and within the current HCM guidelines.

A challenge in the dissemination of information regarding the treatment of HCM patients is the wide variability in clinical presentations, anatomy, cardiac function, and individual responses to therapies in a population that is overall relatively rare and oftentimes misunderstood. Accordingly, much of the treatment expertise resides in a few individuals at even fewer HCM Centers of Excellence. Since the management of this disease is learned through one patient at a time, the purpose of this chapter is to simulate clinical experience by case presentations. Accordingly, this chapter lays out eight cases with their initial presentations and longitudinal follow-up over several years and depicts the range of presentations of these patients and how they were managed. It is anticipated that this approach will be complementary to the didactic descriptions of diagnosis and management found elsewhere in this textbook. Importantly, as this is predominantly experienced from a few centers, some of the decisions will be based on local experience and outcomes; therefore, the point of the chapter is not to suggest the perfect course for a group of patients but to document one such course for the given patient.

Each case is organized starting with their initial encounter, including any relevant historical information, and following the patient through to the most recent office visit. Through the presentations, we will pause for clinical decision-making discussions, as well as clinical pearls, so the reader gets a firm understanding of the reasoning behind each of the clinical decisions and some of the nuanced care.

Case 1: A 58-Year-Old Man with Refractory HCM Symptoms

A 58-year-old Caucasian male with past medical history of hypertension presented after being recently diagnosed with hypertrophic obstructive cardiomyopathy. He reported previously being very physically active with good exercise tolerance. However, over the past 1 year, he had increasing shortness of breath and dyspnea on exertion that had progressed to recurrent presyncopal episodes associated with exertion for the last 6 months. There were no reports of syncope or chest discomfort, but palpitations had been frequent. During his initial evaluation, the patient expressed dyspnea on exertion after climbing one flight of stairs consistent with NYHA Class III symptoms. A 12-lead electrocardiogram showed sinus rhythm with a left bundle branch block (Fig. 31.1). An echocardiogram revealed moderate mitral regurgitation, preserved left ventricular systolic function with a 2.1 cm basal septum, a normal posterior wall, and a left ventricular outflow tract obstruction at 40 mmHg that augmented to 130 mmHg with Valsalva maneuver, consistent with HCM obstructive physiology. Subsequently, a 24-hour ambulatory electrocardiographic monitor was recommended.

Clinical Decision-Making: When to Recommend 24-hour Ambulatory (Holter) Electrocardiographic Monitoring in HCM Patients?

Ambulatory electrocardiographic monitoring should routinely be included in the initial evaluation of patients with HCM [1]. Ambulatory electrocardiography monitoring for detection of ventricular tachyarrhythmias is important for risk stratification of asymptomatic and symptomatic patients with HCM. This is because episodes of NSVT on ambulatory EKG monitoring, besides identifying patients at elevated risk of subsequent SCD events, can also help identify candidates for ICD therapy [1]. However, on its own, NSVT is a Class IIb indication for ICD implantation and usually requires other modifiers of risk to justify ICD placement. Alternatively, a relatively long and fast run of NSVT may be sufficient to prompt ICD implantation, especially in the patient with symptoms or outflow tract obstruction. Holter monitoring may also identify atrial fibrillation, which is a common etiology of stroke and clinical decompensation in HCM patients, especially those with palpitations as in this patient. Holter monitoring for subsequent annual evaluations in an asymptomatic patient is less useful but may be considered. More often, subsequent Holter, event, or loop monitors are indicated for the symptomatic patient to elucidate etiology of symptoms.

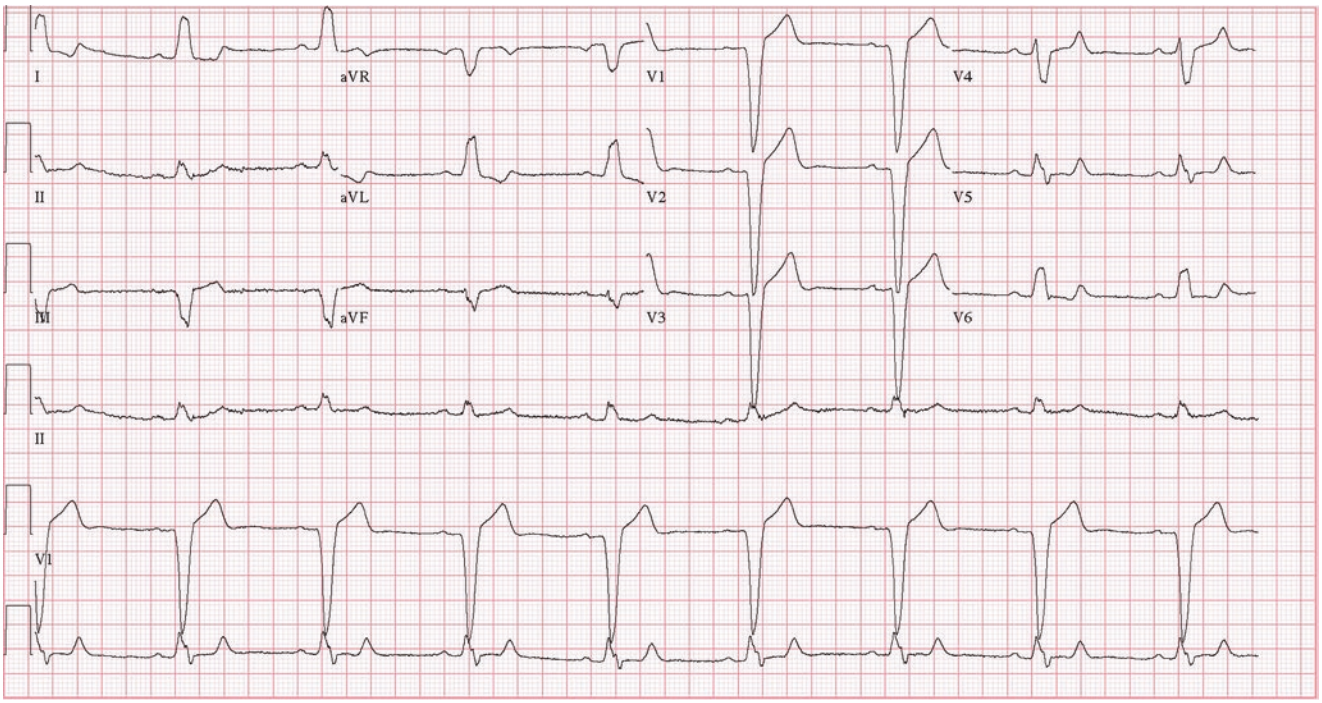

Fig. 31.1 Case 1: Electrocardiogram with left bundle branch block

Following normal Holter monitoring, the patient underwent diagnostic cardiac catheterization. Right heart catheterization revealed normal right and left heart filling pressures with borderline elevated pulmonary pressures. There was evidence of HCM obstructive physiology with no resting gradient but a provocable gradient of 90 mmHg after combined Brockenbrough and Valsalva maneuvers. Cardiac output was preserved, and coronary angiography demonstrated nonobstructive mid-LAD disease with a <30% stenosis lesion. The patient was continued on combination therapy with aggressive beta-blockade and disopyramide. In addition, a cardiac MRI (CMR) confirmed a discrete septal bulge measuring 2.2 cm with no evidence of late gadolinium enhancement.

Clinical Decision-Making: When to Recommend CMRI in HCM Patients?

Accurate characterization of the HCM phenotype by CMRI may be useful in management decisions for invasive therapies (septal myectomy or alcohol septal ablation) by more precisely defining the location and magnitude of hypertrophy. Presence of severe septal scarring may make septal alcohol ablation less effective [2]. CMRI is valuable also in providing accurate information on ventricular function especially in patients with technically difficult transthoracic echocardiographic imaging studies due to poor acoustic windows or when there is failure to visualize certain regions of the left or the right ventricle [3, 4]. Areas poorly visualized by echocardiographic imaging such as the apex and lateral wall are easier to discern on CMRI, as are associated structures such as papillary muscles or membranes. Additionally, in selected patients, when SCD risk stratification is inconclusive and high-risk status for SCD remains uncertain, CMRI with assessment of late gadolinium enhancement (LGE) may be considered in resolving clinical decision-making. Several studies have shown that approximately 50% of HCM patients have LGE suggestive of areas of fibrosis that in some patients may occupy on average 10% of the left ventricular myocardium [5, 6]. Importantly, patients with HCM with evidence of LGE on CMRI tend to have more markers of risk of SCD, such as NSVT on ambulatory EKG monitoring than patients without LGE. Accordingly, the presence and extent of LGE may aid in determination of ICD implantation, as a risk modifier. CMRI is also useful in confirming the diagnosis of HCM, or discerning HCM from athlete's heart, by its ability to image the entirety of the heart and obtain fine measurements of thickness. Finally, as maximal thickness >3.0 cm is an indication of sufficient risk to warrant an ICD, patients with borderline high maximal thickness (between 2.5 and 2.9 cm) may benefit from CMRI to determine whether areas >3.0 are present. Some HCM centers perform CMRI routinely on all patients with HCM, while others have a more selective approach.

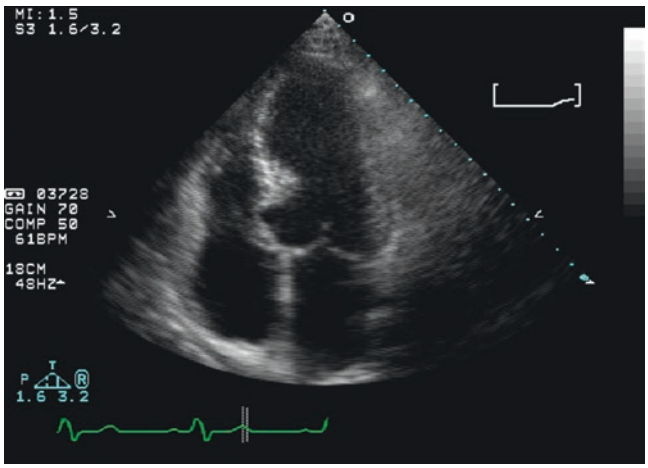

Fig. 31.2 Case 1: Postop TTE depicting septal reduction

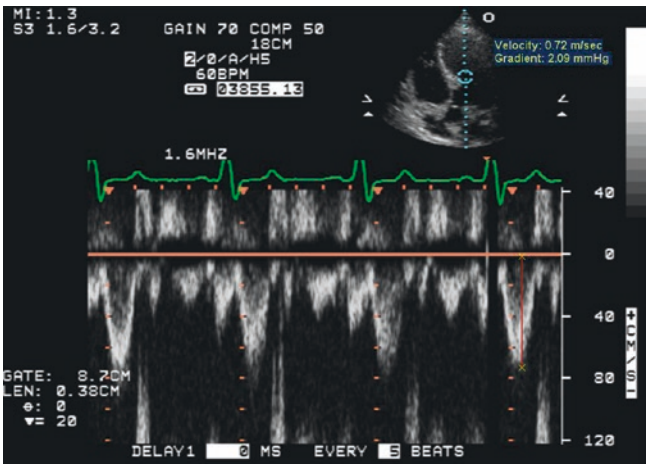

Fig. 31.3 Case 1: Post-op TTE four-chamber view showing no LVOT gradient

As a result of severe drug-refractory symptoms and dynamic LVOT obstruction, the patient was considered for septal reduction therapy. Ultimately, a decision was made to proceed with septal myectomy based on the patient's age, HCM phenotype, and underlying left bundle branch block, which would make the patient extremely at high risk for complete heart block and pacemaker requirement if a RBBB developed after alcohol septal ablation. A generous resection of the asymmetric hypertrophy was performed with intraoperative transesophageal confirming relief of the left ventricular outflow tract obstruction. Postoperatively (postoperative TTE in Figs. 31.2, 31.3, and 31.4), the patient did well, and beta-blockade was continued upon discharge from the hospital.

However, approximately 2 weeks after undergoing septal myectomy, the patient began to experience multiple syncopal episodes. He empirically underwent ICD implantation for primary prevention of SCD, which had not been preceded by an electrophysiology study. Over the next few months, the patient continued to experience repeated syncopal episodes, and subsequent device interrogation yielded no evidence for an arrhythmogenic etiology. Echocardiography also failed to reveal resting or provoked outflow obstruction (Figs. 31.2, 31.3, and 31.4).

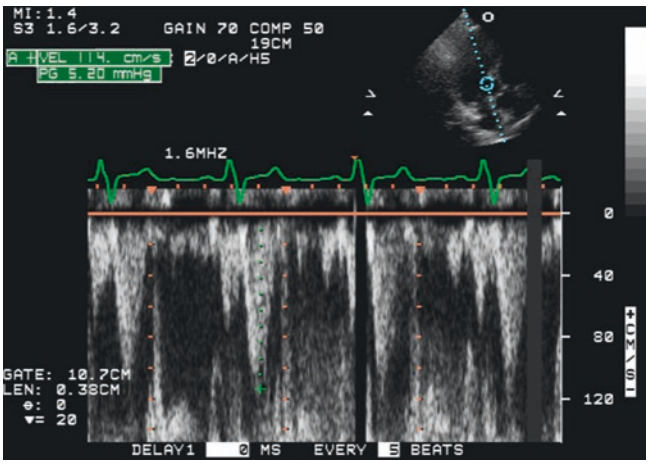

Fig. 31.4 Case 1: Post-op TTE three-chamber view showing no significant LVOT gradient

Clinical Pearl: Do Atrioventricular Conduction Patterns Affect the Choice of Invasive Therapy?

In patients with a left bundle branch block at baseline, surgical myectomy may be the preferred approach to septal reduction therapy as opposed to alcohol septal ablation as the latter would severely increase the risk of permanent pacemaker placement, due to the development of concomitant right bundle branch block and resultant complete heart block. In one small study [7] ($n = 52$) comparing effects of alcohol septal ablation vs. surgical septal myectomy on the atrioventricular conduction patterns, out of four patients with preexisting LBBB, three developed complete heart block (CHB) post-alcohol septal ablation, while out of ten patients with preexisting LBBB, none developed CHB post-surgery. This was in contrast to patients with no underlying AV conduction abnormalities in both groups where 40% developed RBBB in the alcohol septal ablation group and 46% developed LBBB in surgical myectomy group; there was no significant difference in normal conduction patterns after either procedure between the two groups (53% and 54%, respectively) [7]. Further three out of five patients (60%) with preexisting RBBB in the surgical group developed CHB in contrast to none in the alcohol septal ablation group ($n = 2$) [7]. Therefore, patients with preexistent RBBB should be referred for alcohol septal ablation, while those with preexistent LBBB should be referred for surgery, if all other considerations are equal.

Clinical Decision-Making: What Is the Indication for an ICD in HCM?

At the initial evaluation of a patient with known or suspected HCM, an evaluation of SCD risk should always take place. All patients, especially the younger ones, should be counseled about risk of inappropriate shocks and a lifetime risk of device/lead failures and other device complications as well as need for device upgrades/generator changes. As per the ACCF/AHA guidelines [1], high risk is composed of one or more of the following criteria: (1) a personal history for ventricular fibrillation, sustained VT, or SCD events, including appropriate ICD therapy for ventricular tachyarrhythmias, (2) a family history for SCD events in a first-degree relative with HCM below the age of 50, (3) unexplained recurrent syncope, (4) documented NSVT defined as 3 or more beats at greater than or equal to 120 bpm on ambulatory ECG, and (5) maximal LV wall thickness greater than or equal to 30 mm. During follow-up evaluations, ambulatory EKG monitoring, exercise treadmill tests (for hypotension or arrhythmia), and echocardiograms are usually performed, together with repeat family and personal history, to determine whether any of the high-risk markers, or confluence of high- and lower-risk markers, exist that would warrant consideration of ICD implantation. In contrast, EPS is not indicated as a risk stratification tool for patients with HCM. In the current case, the "unexplained syncope" was utilized to place the ICD. However, this patient had recent surgery, and the etiology of the syncope was not adequately determined prior to placement of the ICD. The ICD interrogation and echo ruled out arrhythmogenic and obstructive etiologies, leaving autonomic instability as the remaining culprit.

Clinical Pearl

"Unexplained" and "recurrent" syncope is a marker for SCD [1] in patients with HCM. Due to its multifactorial and complex etiology in HCM patients, a careful clinical history should be elicited to thoroughly assess patients with unexplained and recurrent syncope who are at high risk for SCD before placing an ICD. Possible etiologies of syncope in HCM patients include (1) arrhythmogenic, ventricular and supraventricular tachyarrhythmias; (2) mechanical, dynamic LVOT obstruction causing a sudden sharp reduction in systolic blood pressure (e.g., provoked by exertion); (3) neurally mediated; and (4) iatrogenic causes, e.g., medications that interfere with AV conduction as well as treatments that affect loading conditions. Another iatrogenic etiology is unrecognized heart block after surgery or alcohol septal ablation. In one study, syncope that was unexplained or thought to be consistent with arrhythmia demonstrated a significant independent association with SCD only when the events occurred in the recent past (<6 months) but not if they occurred >5 years before the clinical visit [8].

Clinical Pearl: What Are the Practical Things to Consider for ICD Implantation in HCM Patients?

To minimize inappropriate shocks, the ventricular fibrillation zone should be set high enough (>220/min), and anti-tachycardia pacing should be utilized. Single LV ICD leads may be appropriate in some patients; in fact, subcutaneous ICDs may be a great option in young patients. However, in patients with LVOTO being considered for pacing or patients with refractory symptoms thought to be due to LV dyssynchrony in whom cardiac resynchronization therapy is being considered, additional leads will be necessary. In addition, those with a high likelihood of atrial fibrillation or sinus node dysfunction, such as older patients, would benefit from dual-chamber leads, especially as this would also allow for monitoring for arrhythmias and sequential pacing.

The patient's syncope resolved with discontinuation of his beta-blocker, implicating a neurogenic cause (autonomic instability) for his syncope. Echocardiogram continued to reveal no evidence for obstruction, and no arrhythmias were noted on ICD interrogation. Over the next several months, there was no recurrence of syncope or presyncope, and the patient attained NYHA functional Class I. The patient was complaining of chest wall discomfort at the ICD insertion site requiring prolonged use of narcotics.

Given a paucity of indications for continuing ICD therapy for primary prevention in this now asymptomatic patient, coupled with an exercise treadmill test yielding excellent exercise tolerance, a decision was made to refer the patient to an electrophysiologist for ICD extraction (per the patient's wishes). He was also advised that since the device is already implanted, it may be wise to keep it. Importantly, however, the patient was told to wait at least 6 months to make sure that no arrhythmias were found and symptoms did not recur. Following a lengthy discussion evaluating the risks and benefits of ICD removal, the patient ultimately underwent system explantation without further complications. One year after this, the patient remains asymptomatic.

Case 2: Alcohol Septal Ablation in a 38-Year-Old Woman with History of Peripartum SCD

Patient A. B. presented to the hypertrophic cardiomyopathy center in June of 2010 at the age of 38, after a recent pregnancy. She was an uninsured Caucasian female with a history of hypertension and tobacco use, though she had quit 6 months prior (25 pack-years). She was taking metoprolol succinate 100 mg q.d. after a recent diagnosis of HCM. She had two pregnancies and had a 12-year-old and a 2-month-old child. Neither child had yet been tested for HCM at this time. Her medical history is divided below in two phases; first phase describes events prior to presentation to our hypertrophic cardiomyopathy center, and the second phase describes decisions taken after she presented to us in 2010.

Her first cardiac encounter was in 2004 when her family doctor noted that she had a systolic ejection murmur. The murmur appropriately prompted an echocardiogram, which was interpreted as having borderline left ventricular hypertrophy. Shortly afterward, the patient developed chest pain and dyspnea that became worse on exertion. She was found to have New York Heart Association Class II heart failure symptoms and was started on a small-dose metoprolol and aspirin. It is unclear what the physician's primary diagnosis was at the time; however, no further testing was performed.

In 2006, she underwent her first cardiac catheterization for persistent chest pain on exertion. The patient reported that the results were "unremarkable," and no explanation was found for her chest pain; she continued to have chest pain post catheterization. Two years later she complained of angina at rest in the substernal region associated with shortness of breath. Her symptoms worsened after she became pregnant in 2009, even though reportedly she had sought medical attention prior to getting pregnant and had been advised that pregnancy would be safe for her. Due to a lack of health insurance coverage, she did not seek medical care until she was 31-week pregnant. At this point she was experiencing syncope episodes daily and persistent shortness of breath. This prompted further workup during a hospital stay, where she was finally diagnosed with severe hypertrophic obstructive cardiomyopathy after an echocardiogram revealed a septal thickness of 2.4 cm, with obstructive physiology. The cardiology and obstetrics teams taking care of her debated over the merits of an earlier cesarean section and if the heart could withstand the remaining duration of pregnancy or C-section. This period was marked by repeated hospitalizations until delivery was finally scheduled by C-section at 36 weeks of pregnancy. She was not referred to a high-risk obstetrics program. It is unclear whether there was evidence for congestion or volume overload at this time. Unfortunately, the C-section was complicated by sudden cardiac arrest intraoperatively. She was successfully resuscitated after CPR and defibrillation. An implantable cardioverter defibrillator was inserted, she was started on metoprolol, and the remaining post-pregnancy course was relatively unremarkable. After discharge from the hospital, the dose of metoprolol was increased gradually to 100 mg q.d.

Clinical Decision-Making: Was Implantation of the Cardioverter Defibrillator (ICD) Appropriate for This Patient?

HCM may account for as much as 48% of SCD in patients aged <35 years [9]. In fact, SCD may be the initial presentation. ICDs provide a mortality benefit in patients at high risk of sudden cardiac death (SCD). All HCM patients should therefore be screened for risk of SCD and possible need for ICD. At this time, clinical factors rather than genetic factors are used in risk stratification for SCD in HCM patients, although a family history of SCD in first-degree patients with HCM can be associated with a fivefold increased risk of SCD [10]. In one series, patients with a range of genotypes were phenotypically indistinguishable, thus making prognostication on basis of genotype unreliable [11, 12]. The Class I ACCF/AHA indications for an ICD include a positive component in any of the following elements in history: personal history of ventricular fibrillation arrest, sustained ventricular tachycardia, sudden cardiac death, family history of sudden cardiac deaths (especially in first-degree relatives <50), recent unexplained syncope (<6 months), or maximal left ventricular thickness of greater than 30 mm [1]. Although one could argue that the ventricular arrhythmia and cardiac arrest were precipitated by anesthesia and the stress of delivery in this patient who would otherwise have been contraindicated for pregnancy, any patient who sustains SCA with a diagnosis of HCM typically warrants ICD placement. Of note, while NSVT was considered a major risk factor at one time, it alone is a Class IIb for ICD implantation; the same goes for abnormal blood pressure response by exercise treadmill testing.

Clinical Decision-Making: What Is the Risk Involved in Patients Seeking to Get Pregnant Who Are Known to Have HCM?

Women with HCM can safely experience pregnancy if asymptomatic or symptoms are mild or moderate, while NYHA Class III or IV predicts maternal mortality and morbidity [13]. 10–30% of mothers with moderate to severe symptoms worsen clinically during the pregnancy, especially if LVOT obstruction is present, while gradients >100 mmHg carry the highest risk of deterioration [14, 15]. Cesarean section delivery and special medical care (high-risk obstetrics) are not necessary for patients with preexistent mild to moderate symptoms, unless active heart failure or significant obstructive physiology develops during the course of pregnancy, but should be the mainstay for anyone with higher degrees of symptoms who become pregnant. Maternal mortality is limited to patients with advanced disease, including progressive heart failure, severe systolic or diastolic dysfunction, ventricular tachycardia, supraventricular tachycardia, or marked LVOT obstruction. These women require care of a high-risk maternal/fetal medical team with close involvement of a cardiologist preferably specialized in HCM. Beta-blockers or disopyramide should not be stopped during pregnancy if needed to control symptoms, and close monitoring should be done for fetal bradycardia. Pregnant patients with atrial fibrillation may be cardioverted with close fetal monitoring (with contingency plans for emergency cesarean section) [16] and anticoagulation administered with low-molecular-weight heparin [2, 17]. ACCF/AHA guidelines stress genetic testing and counseling for any women of childbearing age with HCM as well as counseling of parents (mother or father) with HCM regarding risks of pregnancy prior to conception [1]. Patients with NYHA Class III symptoms should be discouraged from pregnancy, while NYHA Class IV is an absolute contraindication. Spinal blocks that drop afterload are also contraindicated, and anesthesia should be well versed on medications that precipitate obstruction and medications that can be used to improve outflow tract obstruction acutely. Swan-Ganz catheters are helpful in symptomatic patients with obstruction or congestion, in order to guide pressors and fluid status.

The patient was referred to the Hypertrophic Cardiomyopathy Center in 2010. Exam revealed her blood pressure to be 112/60 mmHg, heart rate was regular at 60 beats per minute, and she weighed 230 pounds and was morbidly obese. She did not have any jugular venous distension, bruits, or masses in her neck. She had a 3/6 systolic murmur at the left sternal border that increased with Valsalva maneuver. There was trace edema in both of her legs. She had NYHA Class III symptoms of dyspnea. Review of systems revealed absence of syncope, but she did have dizziness and palpitations on exertion, in addition to one flight of stairs exertional dyspnea. A 12-lead electrocardiogram revealed that she was AV paced at 60 beats per minute.

At this consultation, an echocardiogram was recommended to evaluate for asymmetric septal hypertrophy, the degree of hypertrophy, systolic anterior motion of mitral valve leaflet, mitral regurgitation, and the extent of outflow tract obstruction at rest and during provocation. Besides this, metoprolol succinate was increased to 100 mg AM and 50 mg PM due to significant symptoms and presumed obstruction, with consideration to add disopyramide in the future for better control of symptoms. There was also discussion of possible invasive therapy (alcohol septal ablation or septal reduction surgery) should severe symptoms persist. Based on ACC/AHA guidelines and her young age (38 years), surgical septal myomectomy would be recommended over alcohol septal ablation and was discussed specifically.

At her 2-week follow-up, the echocardiogram (Fig. 31.5) was discussed; it revealed an ejection fraction 65–70%, grade 2 diastolic dysfunction, and isolated basal septal hypertrophy (2.4 cm). There was systolic anterior motion of the mitral valve with left ventricular outflow tract obstruction, peak resting gradient across the left ventricular outflow tract of 80 mmHg, right ventricular systolic pressure of 40–45 mm Hg, mild to moderate mitral regurgitation, and a severely dilated left atrium. The patient remained in NYHA Class III symptoms, and thus disopyramide CR 150 b.i.d. was initiated to further reduce outflow tract obstruction.

Despite this, the patient continued to have NYHA Class III symptoms of dyspnea, episodic lightheadedness, and Class II angina 1 month later. Therefore, a cardiac catheterization was performed (Fig. 31.6) which revealed normal coronary anatomy, mildly elevated right and left heart filling pressures, mild pulmonary hypertension with normal pulmonary vascular resistance, and normal cardiac output. She was noted to have obstructive physiology with 0–20 mmHg resting gradient provocable to approximately 80 mmHg despite her medical regimen. Following these results, a decision was made to discuss invasive options.

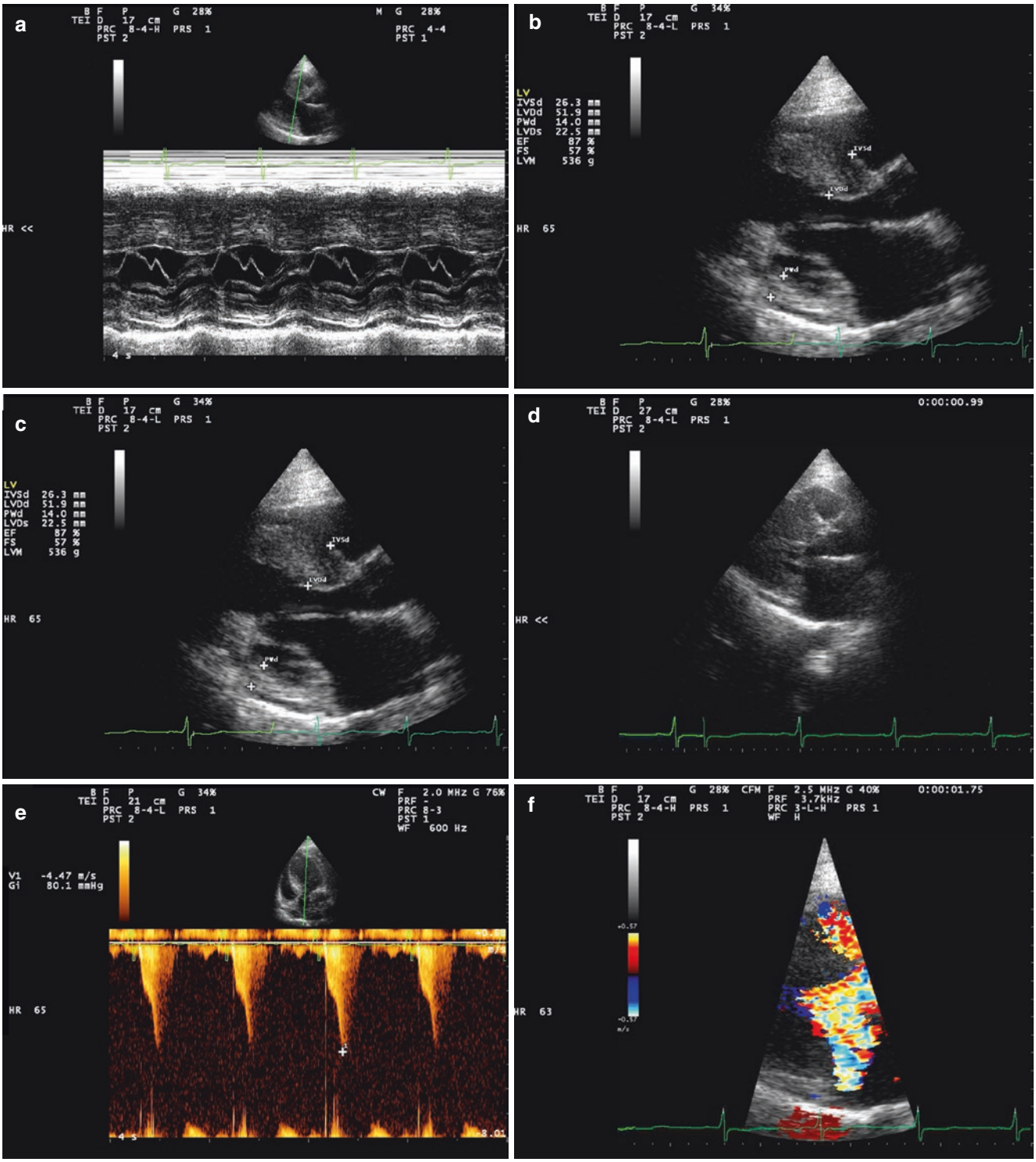

Fig. 31.5 Case 2: (**a**) TTE M-mode depicting systolic anterior motion, (**b**) TTE parasternal long-axis view measurements with asymmetric septal hypertrophy, (**c**) TTE early systole-no systolic anterior motion, (**d**) TTE mid-systole-systolic anterior motion plus LVOT obstruction, (**e**) resting gradient of 80 mmHg across the LVOT depicted by spectral Doppler, (**f**) moderate mitral regurgitation secondary to systolic anterior motion of mitral valve

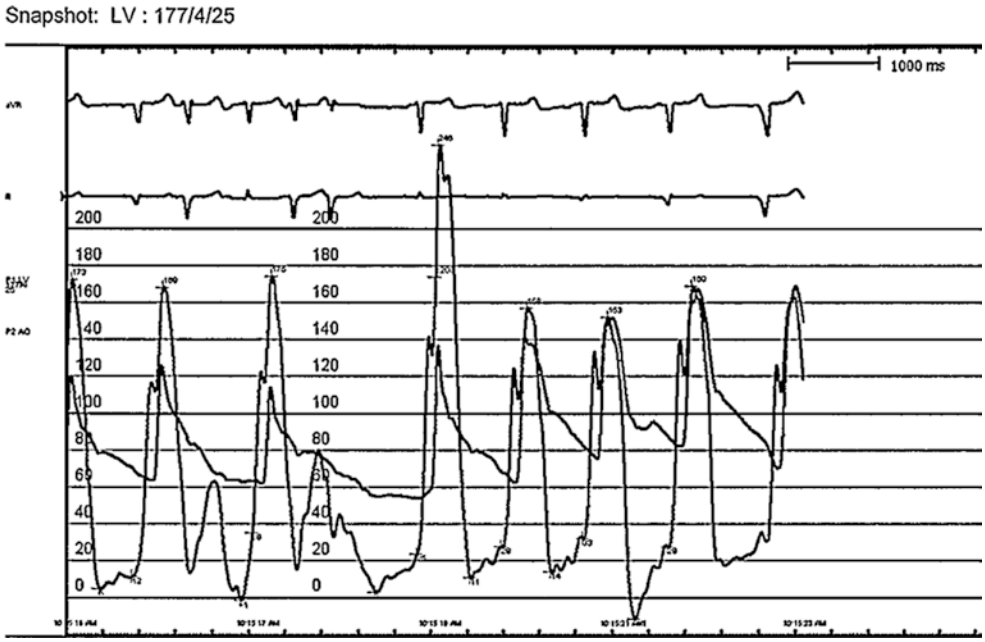

Fig. 31.6 Case 2: Cardiac catheterization depicting provocable LVOT gradient

Clinical Decision-Making: Patient Selection for Myectomy vs. Alcohol Ablation

In order to refer a patient to either invasive strategy, as reflected in the ACCF/AHA guidelines [1], it is recommended that a core set of prerequisites should be fulfilled: (1) Symptoms attributable to LVOT obstruction should be refractory to optimal pharmacologic therapy, which typically means two classes of medications titrated to side effects (2). It must be demonstrated that the obstruction is caused by apposition of the mitral valve with the hypertrophied septum (and not attributable to systolic cavity obliteration or severe diastolic dysfunction) (3). A maximal instantaneous gradient of at least 50 mmHg at rest or with physiologic provocation is necessary. When these criteria are met, invasive options can be considered. Surgical myectomy is preferred in patients of younger age, greater septal thickness, esp. >30 mm, and concomitant anatomic cardiac disease independently requiring surgical correction (e.g., intrinsic mitral valve disease) or coronary artery disease requiring coronary artery bypass grafting. Mid-ventricular obstruction, or obstruction due to abnormal papillary muscles or membranes, should also be treated surgically. Thus besides septal myectomy, other structures may also need to be treated—mitral valve surgery in 11–20% cases [18], mitral valve replacement, posterior-superior realignment of the papillary muscles, partial excision or mobilization of papillary muscles, and anterior mitral leaflet plication or extension [19–22]. Factors predicting favorable surgical outcomes include age <50 years, left atrial size <46 mm, absence of atrial fibrillation, and the male gender [2, 23]. Success in resolving LVOTO is >90% [2], while mortality for myectomy with mitral valve surgery is estimated at 3–4% [22, 24, 25]. Patients more appropriate for alcohol septal ablation include those who are older or at advanced age or with significant comorbidities that selectively increase surgical risk. In addition, patients with a preexistent pacemaker or ICD may elect to proceed with alcohol septal ablation. Importantly, while every anatomy is potentially treatable by surgery, only select anatomy is ideal for alcohol septal ablation. This includes basal septal hypertrophy, lack of intrinsic mitral pathology, and an adequate septal perforator to the target myocardium. In addition, patients with preexistent LBBB may best be served by myectomy, whereas those with preexistent RBBB may be best served by alcohol septal ablation; this approach reduces the risk of complete heart block and pacemaker requirement post-procedure. Finally, when both procedures seem equally safe and efficacious in a given patient, the principle of patient autonomy dictates that a patient may decide in favor of one or the other procedure after a balanced and thorough discussion, including appropriate consultations. It is recommended, however, that surgeons and interventionalists should have performed at least 20 such procedures to be deemed experienced.

The patient was strongly recommended to undergo surgical myectomy and received surgical consultation for the procedure. However, the patient chose alcohol septal ablation. Though myectomy is typically preferred in patients of this age, there were several reasons the patient was a reasonable candidate for alcohol ablation. The patient did not have familial support or a record of compliance that would indicate she would tolerate open-heart surgery, besides airway management issues due to morbid obesity. She was a single mother of two children, without insurance, who did not want to take the risk of prolonged recovery, including the inability to carry her children post-surgery. Ultimately after a thorough discussion, the patient opted for an alcohol ablation. A month later, alcohol septal ablation was performed using standard technique.

On outpatient follow-up 1 month later, the two-dimensional echocardiogram (Fig. 31.7) revealed improved septal wall hypertrophy (basal septum = 2 cm) with mild systolic anterior motion of the mitral valve causing minimal left ventricular outflow tract obstruction with a peak gradient of 12 mmHg and mild mitral regurgitation. There was no pulmonary hypertension. At this time, the patient's symptoms were New York Heart Association Class II, and her medical regimen, which included beta-blocker and disopyramide, was continued. She was also advised to seek genetic screening for herself and the rest of her family. On subsequent visits the disopyramide sustained release was increased to 200 mg b.i.d. due to persistent New York Heart Association Class II symptoms, and a year after her ablation, her symptoms significantly resolved to Class I. The physician and patient discussed genetic testing. At this point, 18 months post ablation, an echocardiogram (Fig. 31.8) revealed excellent remodeling of her left ventricular septum with a thickness of 1.4 cm at the base, resolution of the systolic anterior motion of the mitral valve, and a left ventricular outflow tract gradient of 15 mmHg which did not increase on provocation with the Valsalva maneuver. Her left ventricular ejection fraction was 55%, with grade 1 diastolic dysfunction. Given her favorable outcome and improvement in symptoms, the disopyramide extended release was reduced in half with consideration to terminate it in the future.

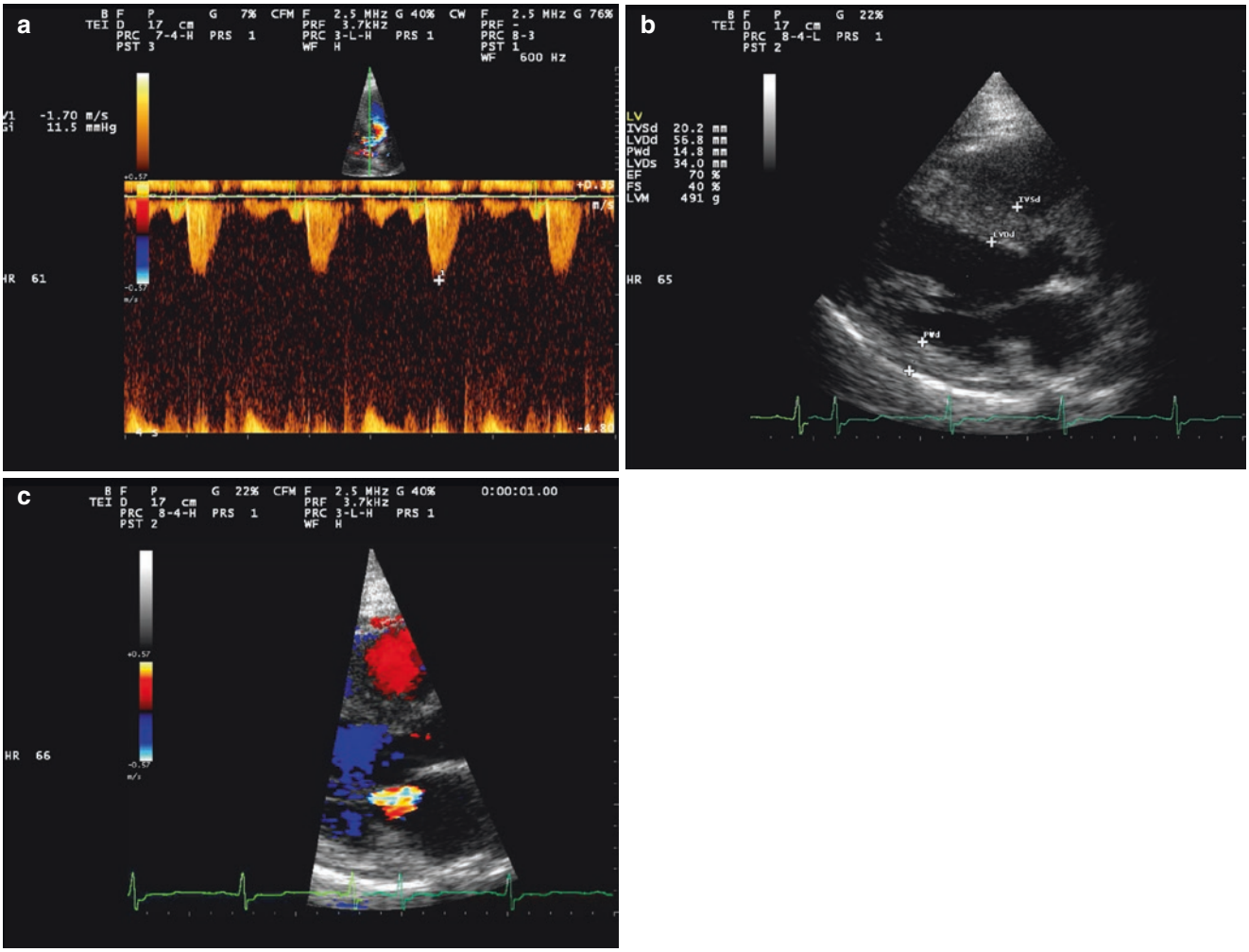

Fig. 31.7 Case 2: TTE 1-month post alcohol septal ablation. (**a**) Reduced LVOT outflow gradient on spectral Doppler; (**b**) parasternal long-axis view, basal septum reduced in size compared with baseline measurements pre-procedure; (**c**) reduction in mitral regurgitation

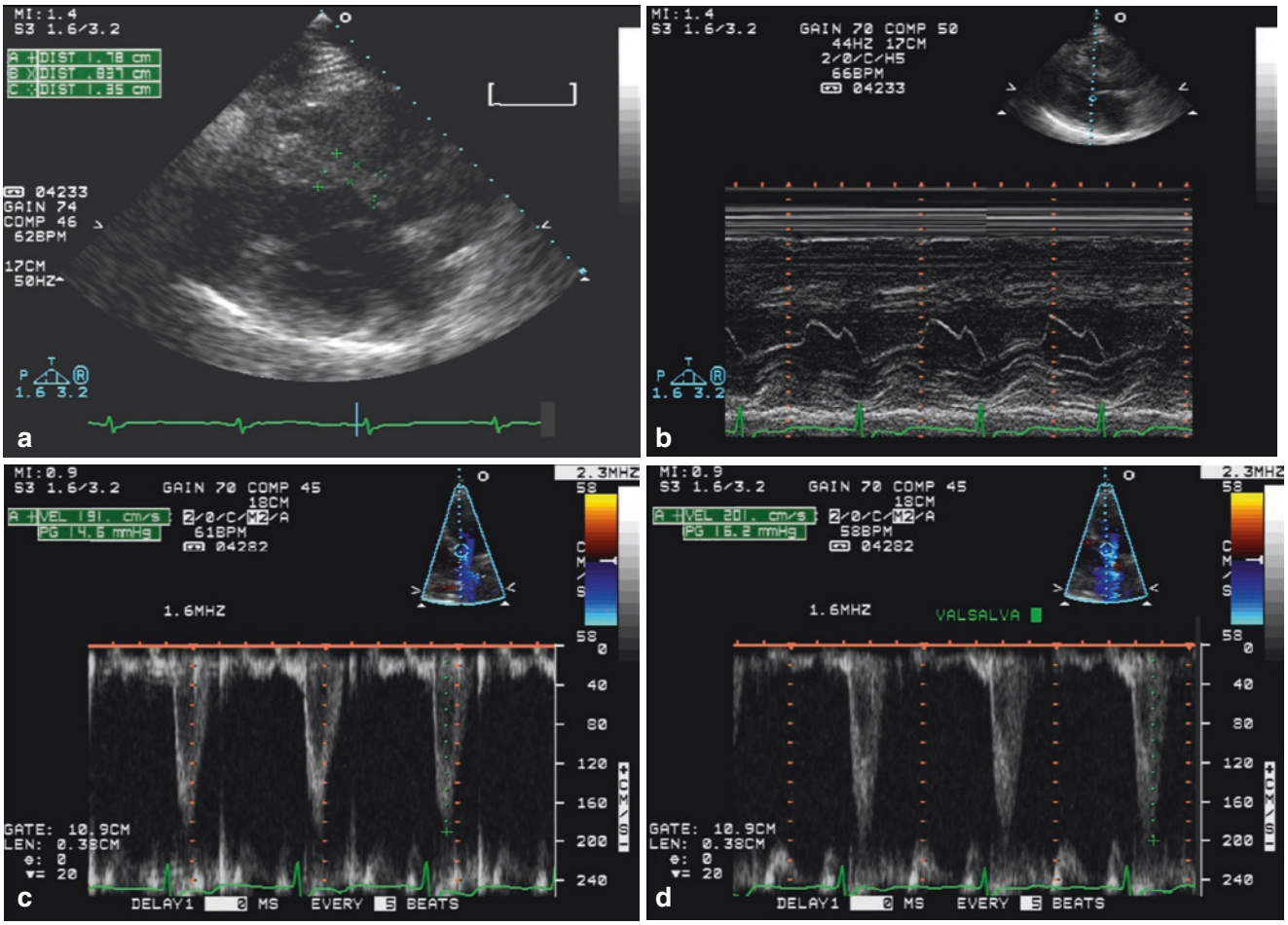

Fig. 31.8 Case 2: TTE 18-month post-procedure. (**a**) Remodeling of LV septum 18-month post alcohol septal ablation, (**b**) absence of systolic anterior motion on M-mode echocardiogram (compare with Fig. 31.5a), (**c**) 14 mmHg peak LVOT gradient on spectral Doppler with no significant change on Valsalva maneuver (16 mmHg) in (**d**)

Clinical Pearl: What Is the Response of the Left Ventricle to Invasive Therapy?

The time course to improvement differs between alcohol septal ablation and surgical myectomy. After myectomy, obstruction is removed immediately, and over the ensuing months, remodeling occurs that improves diastolic function. However, due to the recovery period from open-heart surgery, the patient may not feel significant benefit for several months. After alcohol septal ablation, in contrast, there is little recovery needed for the body as a whole. However, the initial alcohol infusion creates a localized infarction that reduces outflow obstruction. Over time, this area scars and thins, further widening the outflow tract diameter and simulating surgical myectomy. This results in similar improvements in diastolic dysfunction and remodeling of the hypertrophy and septal and distant sites. Consequently, the full effect of alcohol septal ablation may take 6–10 months, with continued remodeling after both procedures noted over several years. In both instances, there is a mild decrease in ejection fraction, although systolic function remains normal. Accordingly, patience is necessary, and waiting at least 6 months is required to make a determination of success or failure.

Family screening by two-dimensional echocardiograms revealed that one of her children had a muscular ventricular septal defect, which was conservatively managed, while her 14-year-old sibling was found to have left ventricular hypertrophy thought to be secondary to hypertrophic cardiomyopathy and was advised to avoid competitive athletics.

Clinical Pearl: When to Screen Relatives, Including children, For HCM?

It is the responsibility of the patient and the physician to make sure immediate family members are screened by genetic testing and/or imaging (e.g., transthoracic echocardiogram). Adults should be screened by echocardiogram every 5 years, while children should be screened every 12–18 months. If found, HCM should be managed at an HCM center, and careful counseling regarding symptoms, risk of sudden death, and other lifestyle discussions should take place. Issues concerning children and young adults (sex, drugs, sports) need to be discussed in detail, so that they and the parent understand the risks of their disease. Importantly, many families may be screened outside of an HCM center. In such instances, it is wise to tell the patient and family members that their physician should specifically look for any signs or symptoms of HCM. If any doubt, the images can be transferred to an HCM center for further evaluation.

Clinical Pearl: Estimating SCD Risk

Besides the traditionally accepted risk factors for SCD in HCM patients—NSVT, maximal LV wall thickness ≥30 mm, family history of SCD, unexplained syncope, and abnormal blood pressure response to exercise—a new risk prediction model has been incorporated in the 2014 ESC guidelines [2]. This model is based on the HCM risk-SCD multicenter study [26] that aimed to provide an individualized 5-year risk estimate:

$$\text{Probability}_{\text{SCD at 5 years}} = 1 - 0.998^{\exp(\text{Prognostic index})}$$

where prognostic index = [0.15939858 × maximal wall thickness (mm)] – [0.00294271 × maximal wall thickness^2 (mm^2)] + [0.0259082 × left atrial diameter (mm)] + [0.00446131 × maximal (rest/Valsalva) left ventricular outflow tract gradient (mm Hg)] + [0.4583082 × family history SCD] + [0.82639195 × NSVT] + [0.71650361 × unexplained syncope] – [0.01799934 × age at clinical evaluation (years)].

Two years after ablation, the patient returned with an episode of chest pain and left arm and shoulder pain and reported lightheadedness similar to previous episodes. The electrocardiogram revealed no changes, while an echocardiogram now showed complete resolution of gradient, both at rest and with provocation. At this time, the AV delay of the ICD was increased to allow for her native AV nodal conduction, in case this was contributing to symptoms. She also reported continued weight gain and breast discharge and subsequently was found to have prolactin level derangements and visual disturbances referable to pituitary adenoma. The patient is undergoing endocrine treatment and is now asymptomatic.

Clinical Decision-Making: When to Consider Other Diseases?

Patients with HCM may develop other diseases or may have accompanying morbidities, such as obesity, that may partly explain symptoms. In the current patient, she had symptoms from severe outflow tract obstruction and HCM early on, including cardiac arrest, followed by symptoms related to worsening obesity, and development of endocrine derangements later on after obstructive physiology was resolved, medications withdrawn, and hypertrophy reduced. Accordingly, treatment of her HCM initially improved symptoms, with objective improvements by serial echocardiograms. Recurrence or worsening of symptoms in such patients may be due to new diseases or alternate etiologies, including coronary or valve disease, lung disease, or obesity and endocrine derangements, as in our patient, and must not be ignored. The clue in this patient was that her anatomy and physiology did not support a recurrence of symptoms; therefore, an alternate etiology had to be found.

Case 3: A 43-Year-Old Woman with Long-Standing Nonobstructive HCM and Advanced Heart Failure

Ms. L.L. is a 43-year-old female with history of hypertrophic cardiomyopathy (HCM), obesity, and sleep apnea. Her history with HCM began at age 18 when a first cousin died suddenly and was found to have HCM by autopsy. Subsequently her family was screened, and she and two of her brothers were found to have the HCM phenotype with asymmetric septal hypertrophy but no outflow tract obstruction, though she was asymptomatic at the time. Over the next several years, her two brothers died, both at relatively early age, 41 and 38, from sudden cardiac death. Her 200-member family was studied at the NIH [27], and the V95A alpha-tropomyosin mutation was identified in all 15 affected members.

Clinical Pearl

As described by the study of Mrs. L's family [27], the V95A mutation is associated with low penetrance (53%), mild hypertrophy, but poor prognosis. The mean maximum LV wall thickness was 16.66 mm in the 15 affected members of her family, with wide distribution and electrocardiograms that did not fit the classic criteria for hypertrophy. Cardiomyopathy as well as symptomatic bradycardia and cardiac arrest have been noted in a large number of patients with this mutation. The most common cause of death is sudden cardiac death and may occur at rest and with mild or no LVH. Genetic counseling and preventative measures are essential when treating a patient with V95A mutation, as the phenotype is quite mild, and poor outcomes can occur in patients with little or no signs or symptoms of the disease.

By the time she was 27 years old, she began to experience symptoms of progressive decline in exercise tolerance, as well as orthopnea and occasional paroxysmal nocturnal dyspnea. She was enrolled in several investigational studies at the NIH including studies of losartan and terfenadine, though she reported minimal improvement in her functional status with either agent.

Clinical Decision-Making: What Is Pharmacologic Management in Nonobstructive HCM?

Symptoms of dyspnea and angina should be managed with beta-blockers and/or verapamil. Some experts recommend calcium channel blockers as first-line agents in such patients. While disopyramide is advocated by some in obstructive HCM, there is a paucity of data in nonobstructive patients, and thus it is generally avoided. When used, caution is advised with concomitant use of QTc-prolonging drugs and in patients with atrial fibrillation in whom drug-induced enhanced atrioventricular node conduction can mediate tachycardia [2]. Congestion is often a factor in nonobstructive disease, due to diastolic dysfunction and chronically reduced cardiac output. Patients with edema should be initiated on diuretics, starting with low-potency agents and progressing to loop diuretics without and then with additional agents. Patients should be monitored for symptomatic bradycardia and hypotension when titrating medications, and potassium should be supplemented. The usefulness of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is not well established, and these drugs should be used with extreme caution in patients with outflow tract obstruction. Ongoing research is evaluating spironolactone and novel sodium channel blockers, although results are pending. As above, diuretics may be added to patients with symptomatic volume overload, though should also be titrated cautiously to avoid hypovolemia [1]. Care must be taken to avoid significant iatrogenic chronotropic incompetence in these patients, as their ability to increase cardiac output with exertion resides mainly in their ability to increase heart rate. Therefore, while beta-blockers and calcium channel blockers are first-line, high doses should be avoided.

At age 36, after being symptomatic for several years, she underwent ICD implantation following an episode of syncope.

Clinical Decision-Making: What Are Indications for ICD in This Patient?

Patients with HCM have an increased risk of sudden cardiac death. However, some patients have low risk, while others are at high risk; SCD risk stratification aims at identifying those at high risk in whom the benefits of ICD outweigh the lifetime risks. In addition, younger patients, presumably with more dangerous genetic mutations and more severe hypertrophy, have higher rates of SCD, whereas older patients generally have a more benign course. Based on the current guidelines, this patient should undergo risk stratification at initial consultation and then yearly or as signs and symptoms change for (a) personal history of ventricular arrhythmias or SCD, (b) family history of sudden cardiac death in a person <50 with known HCM, (c) unexplained recurrent syncope, (d) NSVT, and (e) LV wall thickness greater than 30 mm. Given Mrs. L's strong family history of sudden cardiac death (11 out of 13 deceased family members), and her episode of unexplained syncope, an ICD is appropriate. Indeed, based on recent guidelines, it would have been appropriate for her to have had an ICD placed after the first episode of SCD in a first-degree family member. Accordingly, the syncope, while prompting further discussion and eventual placement of the ICD, was not the first indication for ICD placement.

The patient subsequently initiated care at the HCM center (Figs. 31.9 and 31.10 depict the initial echocardiographic findings). Over the next few years, the patient started to decompensate, with progressive symptoms including palpitations and fatigue. She had a catheterization at age 39 which revealed a mean right atrial pressure of 11 mmHg, right ventricular pressure of 45/16 mmHg, pulmonary capillary wedge pressure of 22, and aortic pressure of 109/62 mmHg with left ventricular pressure of 110/35 (no outflow tract gradient). Fick cardiac output was 4.05 L/min, and Fick cardiac index was 2.05 L/min/m^2.

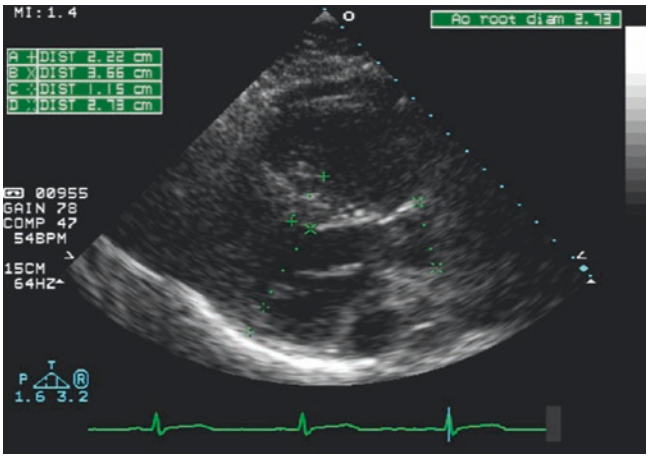

Fig. 31.9 Case 3: TTE on initial evaluation depicting basal septal hypertrophy in parasternal long-axis view

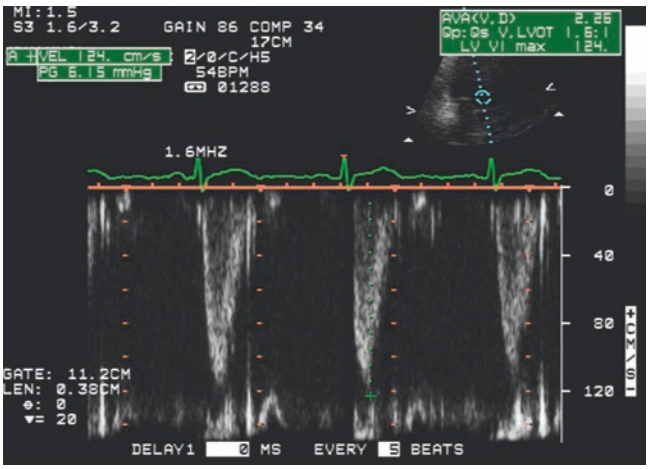

Fig. 31.10 Case 3: TTE on initial evaluation depicting lack of significant LVOT gradient in three-chamber view

Clinical Pearl: Assessment of Hemodynamics

Based on the patient's right heart catheterization, she had elevated RA filling pressure, with mildly elevated pulmonary pressures and elevated left-sided filling pressures, indicating impaired LV function. There was no transpulmonary gradient and thus no overt intrinsic lung disease. Her LV to aorta systolic pressure gradient was minimal, indicating no obstruction to LV outflow either at rest or on provocation. Based on the lack of obstruction and the elevated LV diastolic pressure, LV diastolic dysfunction was the etiology of her symptoms. Patients with severe diastolic dysfunction will typically show reduced cardiac output and index both at baseline and on exertion. Exercise hemodynamics can be helpful in elucidating diastolic dysfunction, reduced output and index, and any effects of cardiac disease on the pulmonary vasculature, which may compound symptoms. Most patients with significant diastolic dysfunction present as severe fatigue followed by worsening congestion.

Numerous studies have found that while patients with HCM may have preserved or even hypercontractile LV function, they develop diastolic dysfunction early in the disease process. Diastolic dysfunction is most likely the cause of exercise intolerance and angina in this subset of patients. Due to the massive asymmetric hypertrophy in HCM, the LV completely empties by end-systole, and in some cases, near cavity obliteration occurs, resulting in impaired suction to promote LV filling. Prolonged relaxation, myocardial fibrosis, and impaired LV filling due to diminished suction and cavity size all play a role in diastolic dysfunction [28]. In some patients, progressive LV dilation may result. Initial LV chamber enlargement occurs to allow initiation and further progression of diastolic filling and may depend directly and indirectly on active forces [29]. Also, as progressive fibrin deposition ensues, the LV walls become stiffer and, in turn, require higher pressures for diastolic filling. In such instances, diuretics typically improve symptoms.

She was enrolled in a clinical trial looking at spironolactone versus placebo in the HCM population. An echocardiogram during this time showed an ejection fraction of 70% with no obstruction and asymmetric septal hypertrophy with an interventricular septal thickness of 23 mm. Stress testing was also performed using the modified Naughton protocol, with a resting blood pressure of 100/65 and resting heart rate of 61 bpm. She exercised for 10 min and 34 s, reaching a maximum heart rate of 135 bpm and peak METs 5.6, and had no hypotension or arrhythmia with exercise. The exercise study was terminated due to chest pain. Cardiopulmonary exercise testing was also performed with a peak VO2 of 17.6 ml/kg/min and VE/VCO2 30, and anaerobic threshold was reached at VO2 of 17 ml/kg/min, which is 53% of her age-predicted maximum and is inconsistent with her advanced symptoms of heart failure.

Clinical Decision-Making: When to Perform Exercise Testing, Including VO2?

In patients without gradients greater than or equal to 50 mmHg, exercise stress testing is reasonable (IIb indication) to determine functional status as well as for SCD risk stratification [1, 30]. Concomitant echocardiogram may be used to document obstructive or nonobstructive physiology. When a patient has significant exercise impairment, such as this patient, cardiopulmonary exercise testing is also useful to determine the patient's true exercise capacity and help differentiate cardiac from pulmonary components. The peak VO2, which is the peak oxygen consumption, in conjunction with the respiratory exchange ratio helps discern whether the patient's disease process correlates with the level of impairment or whether there is a noncardiac reason for impairment, such as deconditioning. The peak VO2 is also used to determine if the patient is impaired enough to require advanced therapies. These include apical myectomy with cavity enlargement in patients with cavity obliteration and cardiac replacement therapy, such as heart transplantation [31].

Following termination of the clinical trial of spironolactone, her symptoms had persisted despite no outflow tract obstruction (Figs. 31.11 and 31.12 depict follow-up echocardiographic findings), and she was advised to seek evaluation for cardiac replacement therapy. At the time that she was referred for advanced therapies, she was on a medication regimen of verapamil 240 mg daily and furosemide 40 mg daily and had NYHA Class III–IIIb symptoms, including one-block exercise tolerance and inability to climb a flight of stairs. Her blood pressure was 124/76 mmHg, and resting heart rate was 62 bpm and regular, and she had no murmur on cardiac auscultation. Over the next several months, the patient had progressive symptoms of exertional dizziness and dyspnea on exertion. The patient was restarted on spironolactone (outside of the trial) with little change to her functional status. A repeat cardiopulmonary exercise test was performed which showed decline in her functional status with a peak VO2 of 11 ml/kg/min, which was more consistent with her class IIIB symptoms. Due to worsening symptoms, a right heart catheterization was repeated which revealed right atrial pressure of 11 mmHg, right ventricular pressure of 39/12 mmHg, pulmonary artery pressure of 36/18 (mean = 24) mmHg, mean pulmonary capillary wedge pressure of 20 mmHg, and a pulmonary artery saturation of 70.3%, resulting in a Fick cardiac output of 4.59 L/min, transpulmonary gradient of 4 mmHg, and a pulmonary vascular resistance of 0.87 Wood units. After arm exercise, her transpulmonary gradient increased to 10 mmHg, with a drop in cardiac output to 3.9 L/min, cardiac index of 1.8 L/min/m^2, and a pulmonary vascular resistance of 2.6 Wood units. These results indicate severe diastolic dysfunction and a secondary minor lung component.

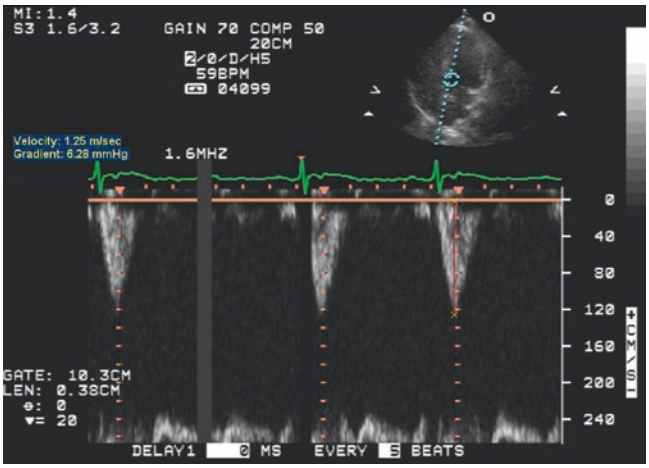

Fig. 31.11 Case 3: Follow-up TTE depicting lack of any significant resting LVOT gradients despite severe HCM-related symptoms

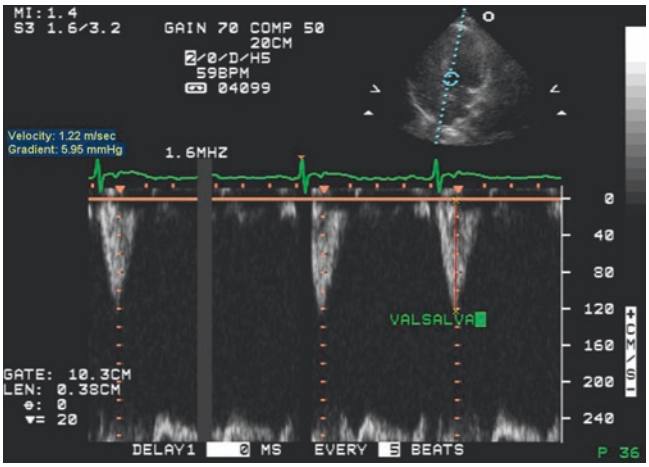

Fig. 31.12 Case 3: Follow-up TTE revealing lack of any significant LVOT gradient with Valsalva maneuver despite severe HCM-related symptoms

Clinical Decision-Making: When to Consider Orthotopic Heart Transplant?

In patients with advanced heart failure symptoms with nonobstructive HCM or restrictive physiology who are refractory to medical therapy, heart transplantation should be considered—Class IIb indication per the ESC 2014 guidelines, while as in patients with drug-refractory NYHA Class III–IV symptoms and LVEF <50%, orthotopic heart transplant is Class IIa recom-

mendation [2]. Orthotopic heart transplant may also be an option in burnt-out systolic heart failure patients with HCM, which is the more common indication. Accordingly, heart transplantation referral is not contingent on a reduced ejection fraction, though patients with preserved ejection fraction rarely are impaired enough to require transplantation. Once a patient is deemed eligible for heart transplantation, it becomes imperative that the patient's hemodynamics be maintained to ensure preservation of end-organ function. Thus it is important that the patient has timely referral to a heart transplantation cardiologist. In addition to symptoms and hemodynamic criteria, cardiopulmonary exercise testing can be used to determine the extent that the patient's functional status is impaired and is an important factor in determining if a patient is a candidate for heart transplantation. Traditionally a VO2 of less than 12 ml/kg/min is accepted for patients receiving beta-blocker therapy, and a VO2 of less than 14 ml/kg/min is used for patients who are beta-blocker intolerant [31].

The patient was listed for heart transplantation and continued to have symptoms of dyspnea and dizziness on exertion leaving her primarily homebound. Her ICD failed to reveal any significant arrhythmia, and her resting blood pressure ranged from 96/60 mmHg sitting to 85/60 mmHg standing. Her diuretics required titration due to delicate fluid balance. In addition to diuresis, the patient was able to lose 50 pounds, which resulted in improved exercise tolerance, though she continued to be limited by dyspnea. Physical exam now revealed a short systolic murmur 2/6 at the left sternal border that did not increase with Valsalva. Repeat cardiopulmonary exercise testing showed a peak VO2 of 14.2 ml/kg/min and respiratory exchange ratio (RER) of 0.97, which represents 67% of her age-predicted maximum.

Clinical Pearls: How to Manage Patients on the Heart Transplant List?

Following patients with HCM prior to transplantation can be challenging, particularly as their cardiac output begins to drop. In this patient, weight loss was a key to symptom management, as the decreased weight resulted in an improved exercise tolerance and down-titration of diuretics. In addition, it increased her chances of obtaining a donor heart. However, despite improved exercise capacity, her peak VO2 remained 14, which is still an indication for heart transplantation, and thus the patient continued to wait. In such cases, the options for advanced therapies remain quite limited, given the small ventricular size and ventricular stiffness that contributes to the overall low-output clinical state.

Inotropes have a limited benefit and may actually cause harm in patients with a restrictive cardiomyopathy. The low cardiac output in these cases is due to the non-distensible, stiff ventricle that is unable to stretch to increase stroke volume [32, 33]. As a result, inotropes may exacerbate heart failure and may also result in ventricular arrhythmias. Mechanical support, such as a ventricular assist device, would also not be suitable due to the small ventricular cavity size and preserved ejection fraction.

In most cases, patients are able to wait for heart transplant with close monitoring by a cardiologist and frequent titrations of their oral medication regimen and careful diuresis. However, in cases where the patient's functional capacity becomes extremely limited, the patient may require hospitalization with day-by-day medical optimization. In these cases, the transplant committee may provide an exception for upgrading the patient's transplant status, since the traditional criteria of intractable arrhythmias or inotrope dependence may not be met. In the extreme cases, patients may ultimately develop "burnt-out" HCM, in which cases, their ventricle dilates and therapy is then modified to treat the dilated cardiomyopathy with inotropes and mechanical support.

Finally, at age 43, almost 2 years after being listed for heart transplantation, the patient underwent successful orthotopic heart transplantation and was ultimately discharged home. Although she has had some of the typical posttransplantation complications, she has not had significant rejection episodes and is currently noting improved symptom status.

Clinical Pearl: Management of Patients with Diastolic Dysfunction.

Most patients with nonobstructive HCM have minimal to no symptoms. This is because the lack of obstruction also makes progressive hypertrophy and worsening diastolic dysfunction less likely, and cardiac output is not usually as affected. In addition, there is usually no accompanying mitral regurgitation. However, a subset of patients may either develop obstruction later in life or progress to severe diastolic dysfunction requiring transplantation, as in the current case. This is in part also due to reduced cavity size available for LV filling, especially in patients with severe apical HCM and cavity obliteration. Management of these severely symptomatic

patients is extremely difficult given the absence of good medical therapy and standard invasive options. Verapamil and diltiazem may improve LV diastolic filling, increase exercise capacity, and help improve symptoms, especially in beta-blocker-intolerant patients [2, 34–38]. Pacemakers to optimize AV delay and medications to improve congestion and relaxation are the mainstay of therapy until transplantation is required. In such patients, active involvement by family, physicians, and others is required to get the patient ready for transplantation and through the system to obtain a heart. In addition, a proactive stance, including VO2 testing and exercise invasive hemodynamics, as well as serial right heart catheterization, may be needed to arrive at the diagnosis of severe diastolic dysfunction. Once confirmed, multiple transplant waiting lists might be required, as hearts are more readily available to patients with ischemic or dilated cardiomyopathy.

Case 4: Congestive Heart Failure in an Elderly Woman with Long-Standing HCM

Ms. B.P. is an 82-year-old woman with known long-standing history of hypertrophic obstructive cardiomyopathy, in addition to hypertension and one episode of atrial fibrillation. She had been managed conservatively for her arrhythmia, without anticoagulation, due to risk of falls. She had also been labeled to have chronic obstructive lung disease despite being a nonsmoker. She was referred to our cardiology service during a hospital admission for congestive heart failure in the setting of atrial fibrillation, at which time she had significant dyspnea and lower extremity swelling. Two-dimensional echocardiography (Fig. 31.13a–c) revealed an ejection fraction of 60–65%, severe mitral regurgitation with systolic anterior motion of the mitral valve, and asymmetric septal hypertrophy with a septum measuring 17 mm. Accordingly, she was evaluated by the HCM center and treated with beta-blockers and diuretics.

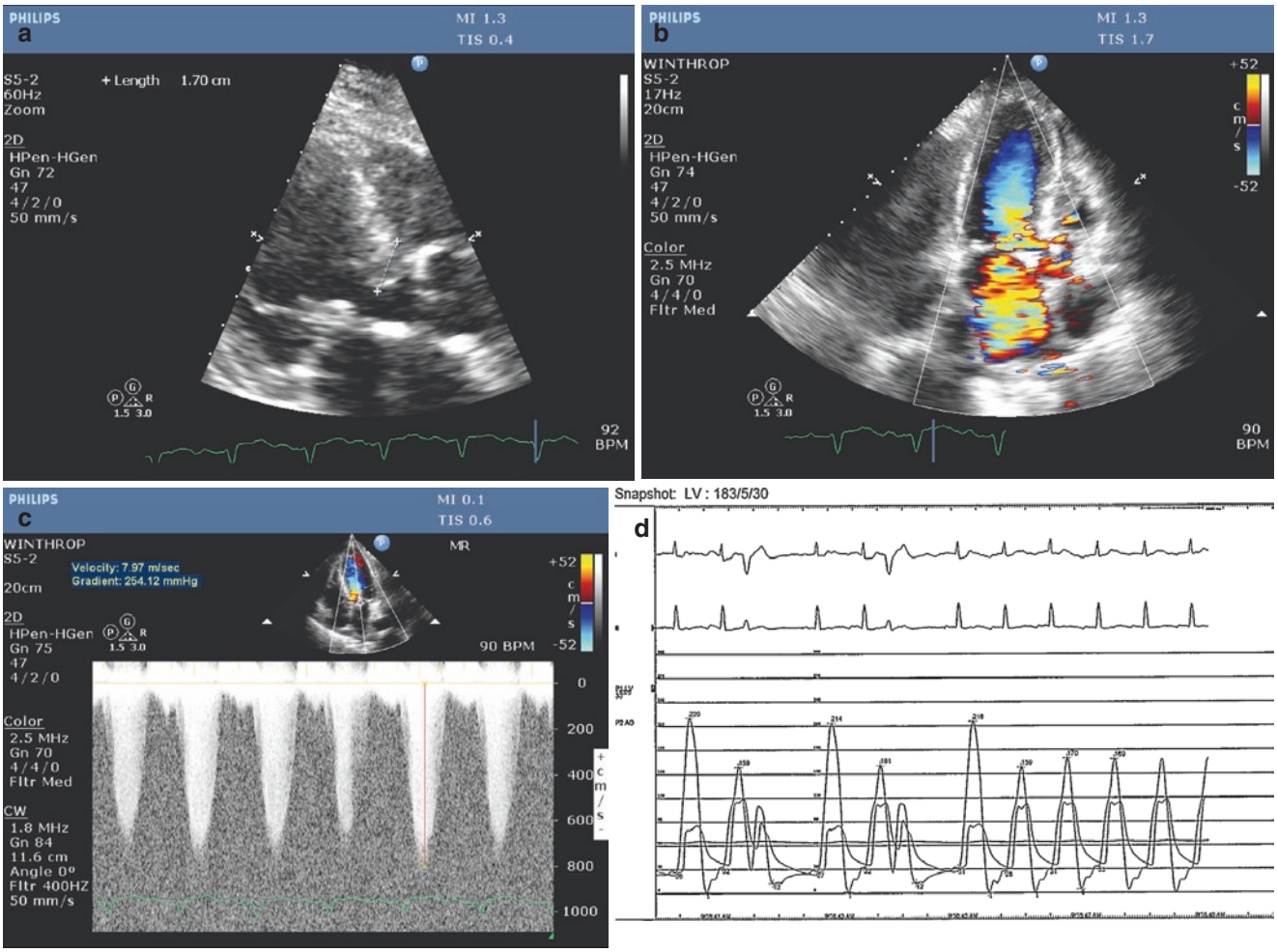

Fig. 31.13 Case 4: Measurements on presentation. (**a**) TTE parasternal long-axis view depicting asymmetric septal hypertrophy, (**b**) TTE three-chamber view depicting severe mitral regurgitation, (**c**) spectral Doppler on TTE consistent with severe mitral regurgitation, (**d**) hemodynamic data on cardiac catheterization revealing significant resting and provoked LVOT gradients

Clinical Decision-Making: What Is the Role of Diuretics in HCM?

It is important to avoid use of high-dose diuretics in patients with obstructive HCM for other concomitant conditions like hypertension. Diuretics (similar to alcohol intake and dehydration from reduced oral fluid intake) can reduce preload and thus exacerbate dynamic LVOT obstruction, especially in patients with preexisting resting or provocable LVOT gradients [1], in effect leading to worsening of symptoms. However, ACCF/AHA guidelines support addition of diuretics to symptomatic patients when congestion (volume overload) is present. This may be the case in nonobstructive forms but also is common with long-standing obstructive disease. However, in the latter, care must be taken to avoid over-diuresis which might precipitate worsening obstructive symptoms. Accordingly, invasive hemodynamics to document extent of congestion and choose type and dose of diuretic may be needed. In such patients, hydrochlorothiazide or combination of triamterene with hydrochlorothiazide may be ideal choices in patients with mild degrees of congestion, whereas loop diuretics together with metolazone may be required in severe cases.

After adequate diuresis the HCM service decided to do a right and left heart catheterization as an outpatient. At this time, she was in normal sinus rhythm. Cardiac catheterization (Fig. 31.13d) revealed severe resting and provocable obstructive physiology with resting gradient of greater than 40–50 mmHg and provocable gradient greater than 100 mmHg. There was mild noncritical disease in the coronaries. There was also moderate pulmonary hypertension and moderately elevated right and left filling pressures despite diuretic therapy. PVR was only mildly elevated, confirming that the primary problem was HCM and not COPD.

Clinical Decision-Making: When to Perform Cardiac Catheterization in HCM Patients?

Patients with HCM should undergo cardiac catheterization to assess for epicardial coronary stenosis, define coronary anatomy including septal perforators, and assess hemodynamics. In addition, catheterization can aid in determining the relative contributions of pulmonary and cardiac disease to heart failure, including the assessment of filling pressures. This is particularly relevant in a patient with obstructive physiology and congestion, in whom diuretics have been employed, as overshooting or undershooting the dose can result in continued or even new symptoms. Cardiac catheterization is an ACCF/AHA Class I recommendation in patients with HCM with chest discomfort who have an intermediate to high likelihood of CAD when the identification of concomitant CAD will change management strategies. In addition, catheterization should be performed before surgical myectomy or alcohol septal ablation [1]. In addition, cardiac catheterization is reasonable for patients with severe symptoms on optimal medical therapies, in order to fully understand cardiopulmonary function, evidence of heart failure (including cardiac output and volume status), and pulmonary contribution and assess whether severe obstructive physiology is present. Meticulous hemodynamics are required in order to fully elucidate underlying physiology.

Diuresis was continued, and disopyramide twice daily was added to the above therapy both for improvement in obstructive physiology and prevention of recurrent atrial fibrillation. Despite these additions and a short-term stay in cardiac rehab, she remained in New York Heart Association Class III symptoms and began losing weight consistent with cardiac cachexia. Following this, her treatment strategy was reevaluated, and a recommendation for permanent pacemaker implantation was made.

Clinical Decision-Making: Why Was a Permanent Pacemaker Recommended for This Patient?

Given her elderly and frail status, she did not appear to be a good candidate for invasive septal reduction therapy. Surgical myectomy would be too high risk, and it was not clear whether resolution of gradient at this late stage would be enough to reverse the course of disease. In such patients who are already on first- and second-line pharmacotherapy, implantation of a permanent pacemaker may be reasonable. Pacemakers with RV leads paced at the apex using a short AV delay may alleviate obstructive physiology [39] in a subset of patients, particularly the elderly (as observed in patients ≥65 years in the M-PATHY trial) [40], and also may allow higher doses of beta-blockers. Given lack of history of sudden cardiac death in the patient, history of ventricular tachycardia or non-sustained ventricular tachycardia, recent unexplained syncope, or left ventricular hypertrophy >30 mm, she was not at high risk for sudden cardiac death. Therefore, an implantable cardioverter defibrillator was not implanted.

On follow-up after pacemaker placement, she continued to have New York Heart Association Class III symptoms, however, despite augmented beta-blocker dosage. A review of systems revealed absence of other cardiac complaints besides significant shortness of breath, including palpitations, dizziness, syncope, or lower extremity swelling. She was a nonsmoker and has complaint with her medications, which included aspirin 81 mg q.d., furosemide 40 mg q.d., disopyramide sustained release 150 mg b.i.d., metoprolol succinate 25 mg b.i.d., and spironolactone 25 mg q.d. Physical exam in the outpatient office was significant for blood pressure 92/52 mmHg, heart rate 80 beats per minute, absence of jugular venous distension, presence of regular rate and rhythm, grade 3/6 systolic ejection murmur at the left sternal border which increased with Valsalva maneuver, and absence of rales on lung exam or edema in lower extremities. An echocardiogram revealed asymmetric septal hypertrophy 1.5 cm with significant outflow tract obstruction and moderate mitral regurgitation that appeared to be due to systolic anterior motion of the mitral valve, while there was no significant aortic stenosis. Alcohol septal ablation was discussed.

Clinical Decision-Making: When to Recommend Alcohol Septal Ablation in HCM Patients, and What Are the Risks?

Alcohol septal ablation was contemplated for this patient for multiple reasons. First, she had refractory symptoms after maximal medical therapy, including (in this case) pacemaker placement. Second, she was a poor surgical candidate due to her advanced age and frail status. Third, her septum was measured to be greater than 15 mm in thickness, and there was severe obstructive physiology due to systolic anterior motion of the mitral valve, and thus the morphology was amenable to alcohol septal ablation. And fourth, her anatomy indicated a high chance of success, with focal septal bulge, an appropriate septal perforator, and a lack of intrinsic mitral regurgitation. An in-depth discussion was held involving patient and family informing them of potential complications including high-grade heart block requiring a permanent pacemaker of 8.9% [41], approximately 1% risk of sustained ventricular tachyarrhythmias during hospitalization, and in-hospital mortality rate up to 1% [42]. In this patient, with a pacemaker implanted, the risks are reduced. However, given the septal thickness is borderline at 1.5 cm, the risk of creating a VSD was discussed and estimated at roughly 1%. After explanation of all risk and benefits, decision was made to proceed with the alcohol ablation, although it was recognized that it would be very difficult to determine what percent of her symptoms the procedure would alleviate given her overall functional status and comorbidities and long-standing disease. In effect, the therapy was felt to be palliative in an effort to improve quality of life.

Alcohol septal ablation was performed using standard technique via the first septal perforator. The provocable gradient reduced from 160 mmHg prior to ablation to 0 mmHg post ablation (Fig. 31.14). The procedure was marked by complete AV nodal block during which she required 100% pacing from her permanent pacemaker. The rest of the hospital course was unremarkable. She was discharged on day 3 and followed up as an outpatient 3 weeks later and reported significant improvement, now at NYHA Class I. Follow-up echocardiograms did not reveal any left ventricular outflow tract obstruction (Fig. 31.15). By 6 months of follow-up, dyspnea was completely resolved, and she reported being able to dance at her granddaughter's wedding "all night." Her appetite returned, and she had gained 10 pounds within 3 months, with no evidence of congestion. The permanent pacemaker interrogation did not reveal any further atrial fibrillation episodes. Her medical regimen was revisited, and her beta-blocker dosage was slightly decreased, disopyramide was stopped 2 months post ablation, and spironolactone was switched to hydrochlorothiazide 25 mg q.d. at 6 months. At last office visit, consideration was given to start an angiotensin receptor blocker in the future for better blood pressure control in this patient with resolution of obstructive physiology. The patient and family were extremely grateful that we had taken a chance on someone that most would have considered end-stage.

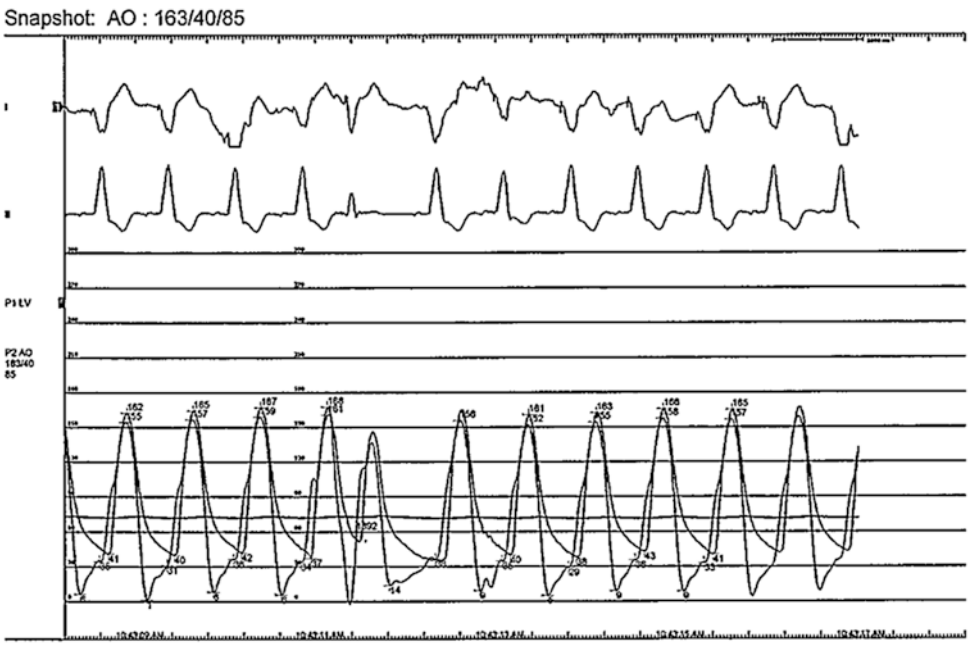

Fig. 31.14 Case 4: No significant resting or provocable gradient post alcohol septal ablation on cardiac catheterization

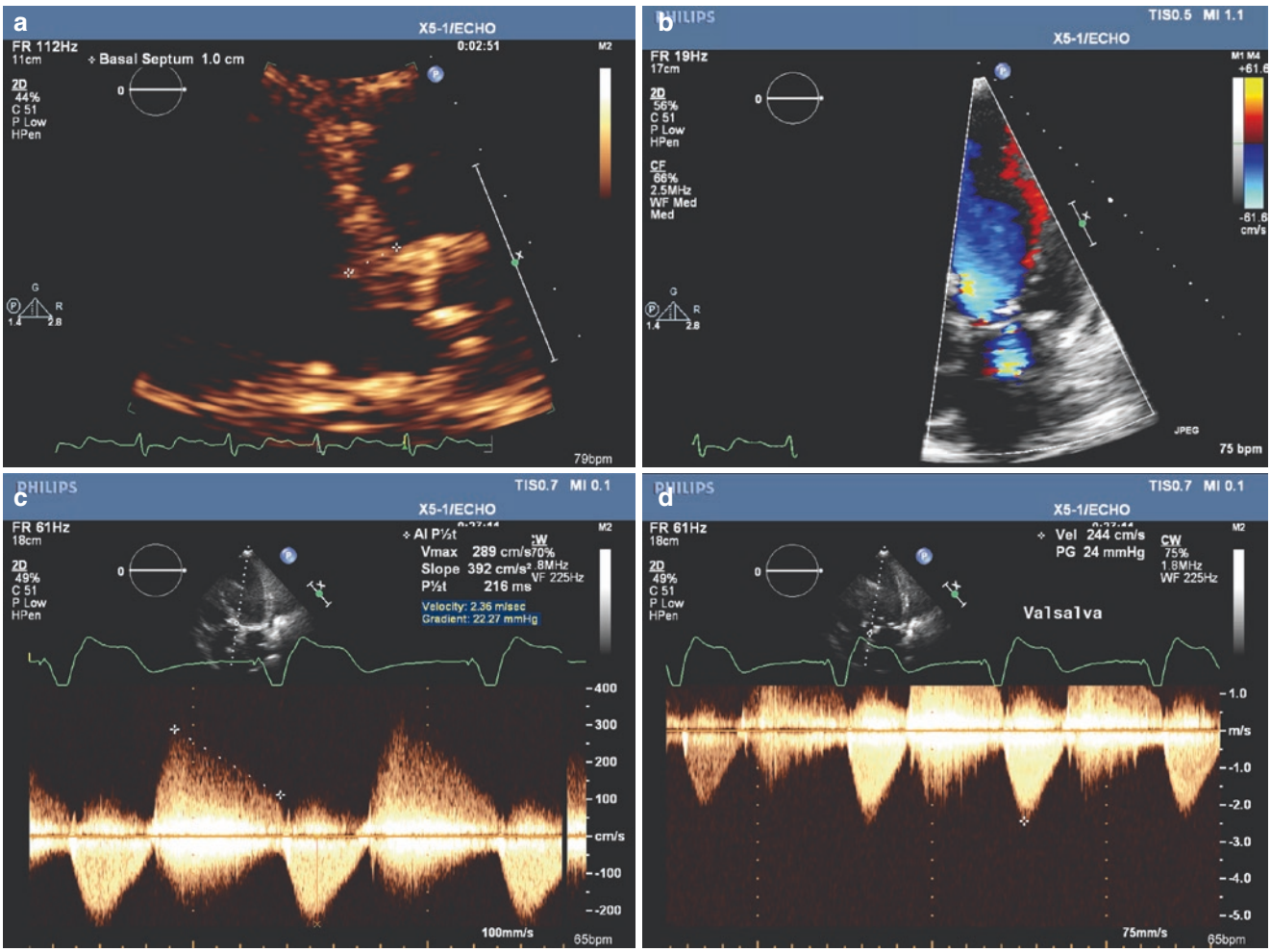

Fig. 31.15 Case 4: Post-ablation TTE images. (**a**) Reduction in basal septal thickness on PLAVX view (1 cm), (**b**) mild mitral regurgitation reduced from severe mitral regurgitation pre-ablation, (**c**, **d**) reduced LVOT gradient post-ablation, not worsened with Valsalva maneuver

Clinical Pearl

Patients with long-standing HOCM physiology may deteriorate from both a physical and functional status, including frailty and cachexia from chronic heart failure symptoms. Such patients may see significant improvement in overall status with aggressive HCM therapy including medications, pacemakers, and invasive therapies. In older patients such as these, alcohol septal ablation is a particularly palatable option as the risks are lower than surgery, and the patient may be willing to take this risk to see whether the HOCM physiology is the largest contributor to their overall debility. Patients with a prior permanent pacemaker have overall low risk with alcohol septal ablation and may only need to be monitored for 3 days in the hospital post-procedure, barring other unforeseen complications.

Case 5: A 52-Year-Old Woman with Nonobstructive HCM and SCD

Patient R.C. presented to the Hypertrophic Cardiomyopathy Center at the age of 52 in January of 2008. She had originally been diagnosed with HCM in 2006 when she had an episode of sudden cardiac death. This event was preceded by lightheadedness, and she was found to have ventricular tachycardia in the ambulance. An echocardiogram revealed severe asymmetric septal hypertrophy and HCM, without obstructive physiology. She noted that at the time of the initial diagnosis, she was not told this condition was hereditary. She had also not undergone structured risk stratification for SCD prevention.

Clinical Pearl: Genetic Basis of HCM

HCM is caused by an autosomal dominant mutation in genes that encode sarcomere proteins or sarcomere-associated proteins [1]. Informing patients of the genetic basis of HCM is crucial as HCM mutations have high penetration >95% and an affected parent has 50% chance to transmit the mutation to the child, thus warranting genetic counseling and screening of the patient and all first-degree relatives, who accordingly have roughly a 50% risk of sharing the disease-causing mutation [43]. This patient has one son, who was a teenager involved in high-risk sports at the time of her initial presentation and diagnosis, and therefore he should have been screened for HCM morphology or symptoms. If diagnosed with HCM, he would have been advised against competitive athletics, and an ICD would have been implanted. It is important to provide relatives who are asymptomatic counseling before they are tested about the consequences of a lifetime diagnosis of HCM, as it could affect their insurance policies, occupation, eligibility for adoption, participation in certain sports (as described in above example), etc [2]. Sporadic cases are rare, measuring roughly 5% at most of patients with HCM.

Besides HCM, she reported a history of dyslipidemia and asthma and was an ex-smoker (7 pack-years) who had quit tobacco 25 years ago. She reported her father was alive with a history of acute MI at age 72 and her mother was alive and well.

Patient denied previous symptoms, including specifically no dyspnea, edema, palpitations, chest pain, or syncope. Workup during the hospitalization included an electrocardiogram which revealed a right bundle branch block (Fig. 31.16), an echocardiogram (Fig. 31.17a, b), which was significant for severe asymmetric septal wall hypertrophy, an ejection fraction of 60–65%, grade 1 diastolic dysfunction, a mildly dilated left atrium, and mild mitral valvular regurgitation. There was no provocable gradient on the Valsalva maneuver and no exacerbation of MR. A diagnostic cardiac catheterization revealed normal coronary anatomy and a hyperkinetic ventricle (Fig. 31.17c, d). Following this an implantable cardioverter defibrillator was placed. No electrophysiology testing was performed.

Clinical Pearl: When to Do Electrophysiology Testing for Risk Stratification?

Electrophysiology studies (EPS) for risk stratification are not recommended by ACCF/AHA clinical guidelines [1], due to the poor sensitivity and specificity. Accordingly, inducibility of VT at EPS is not an indication for ICD placement. EPS may be helpful in patients with supraventricular tachycardias such as atrial flutter, atrial tachycardia, AV nodal reentry tachycardia, and AV reentry tachycardia [2] or in patients with heart block or high-degree block after surgical myectomy or alcohol septal ablation, in whom permanent pacemaker placement is being considered. The decision to place an ICD is based on clinical algorithms of elevated risk. EPS may be utilized to check device thresholds, especially with addition of new antiarrhythmic medications, or for ablation or treatment of arrhythmias such as monomorphic sustained ventricular tachycardia [44, 45] by catheter ablation.

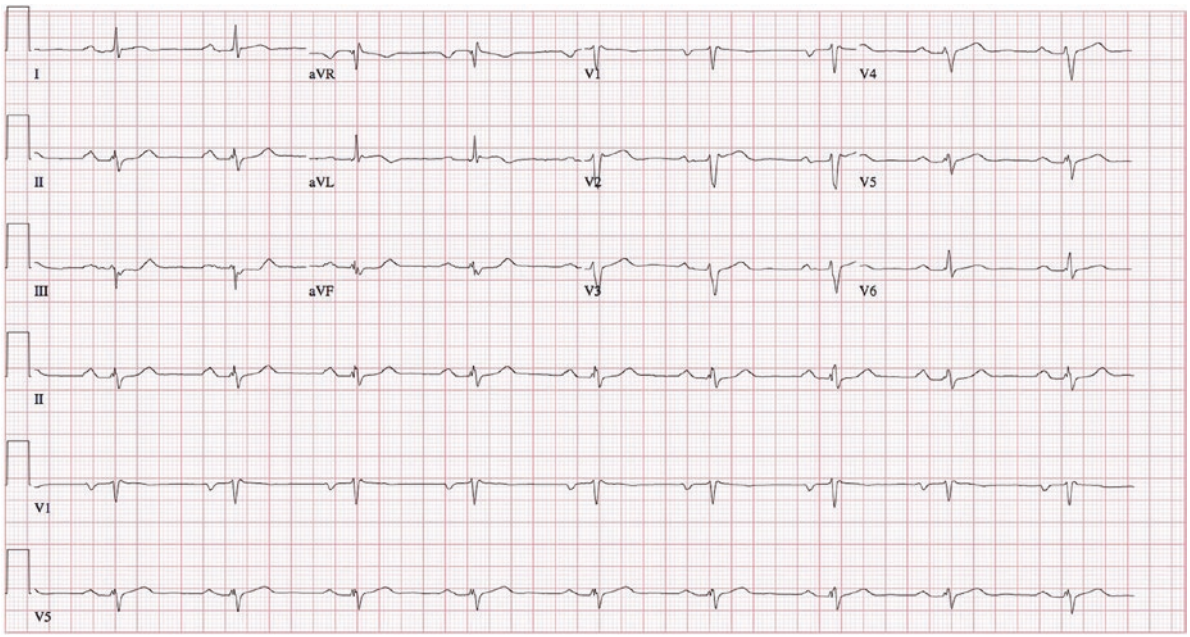

Fig. 31.16 Case 5: Initial 12-lead electrocardiogram depicting an incomplete right bundle branch block

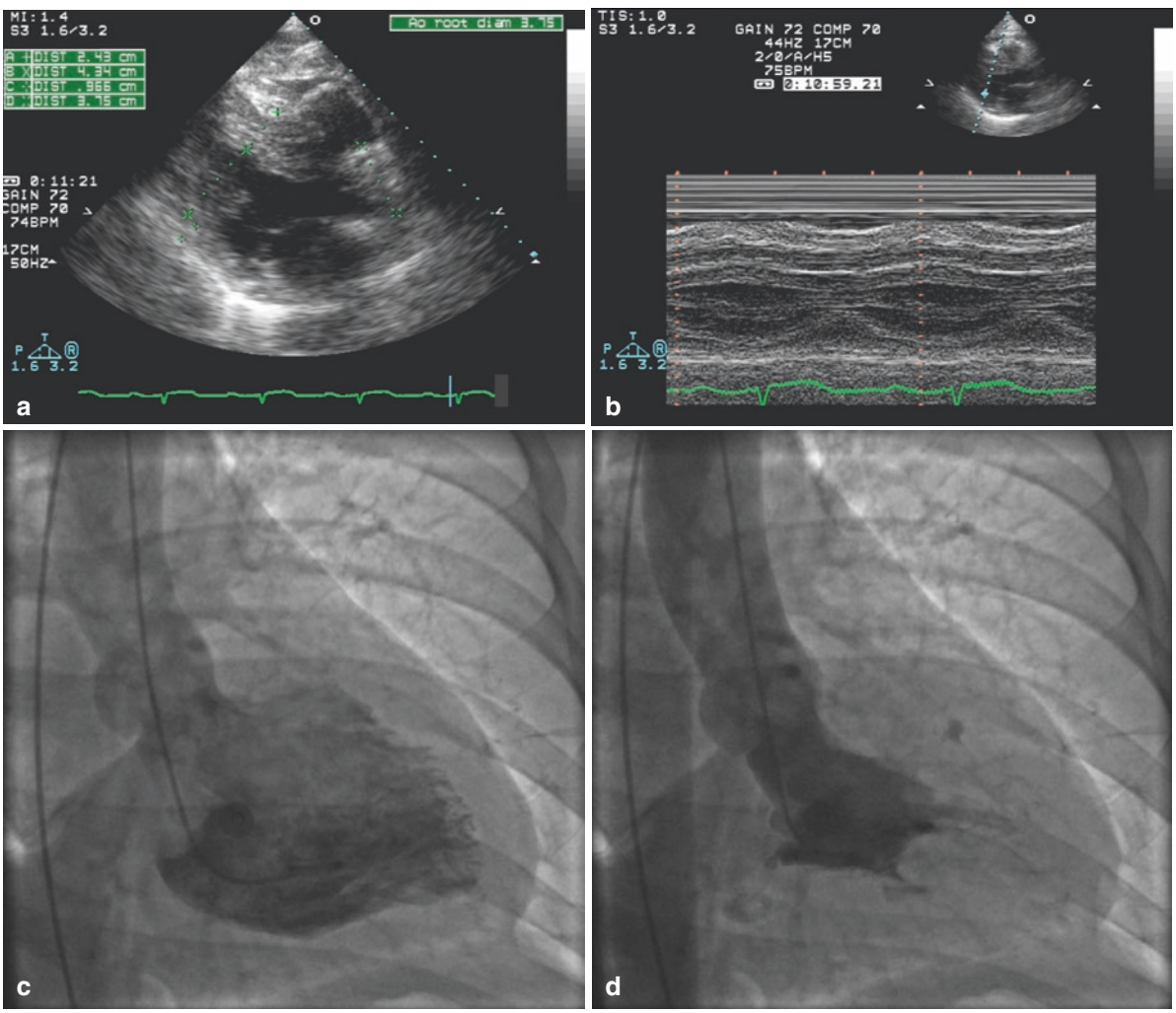

Fig. 31.17 Case 5: Baseline measurements. (**a**) TTE in parasternal long-axis view depicting asymmetric septal hypertrophy (2.4 cm), (**b**) M-mode TTE depicting complete obliteration of LV cavity in systole, (**c**, **d**) cardiac catheterization depicting hyperkinetic ejection fraction secondary to severe septal hypertrophy

The patient did well for the next 2 years and denied symptoms. At presentation to the HCM clinic, a repeat two-dimensional echocardiogram showed similar findings as above significant for marked septal wall hypertrophy without systolic anterior motion of the mitral valve. Review of medications revealed she was taking atorvastatin 10 mg q.d., verapamil extended release 360 mg q.d., aspirin 81 mg q.d., montelukast 10 mg q.d., and tamoxifen 10 mg once daily.

Clinical Decision-Making: Choosing Verapamil vs. Beta-Blocker

Verapamil therapy is recommended for the treatment of symptoms (angina or dyspnea) in patients with obstructive or nonobstructive HCM who do not respond to beta-blocking drugs or who have side effects or contraindications to beta-blocking drugs [1]. Our patient had a history of reactive upper airway disease and was using bronchodilator therapy; hence verapamil therapy was instituted from the beginning. In addition, some clinicians prefer calcium channel blockers in patients with nonobstructive HCM, due to theoretic potential to better improve diastolic function. However, diltiazem is poorly studied, and therefore the preferred calcium blocker is verapamil. Care should be taken to avoid high-dose verapamil in patients with obstructive physiology or congestion, as verapamil may have a profound effect on afterload and result in worsening of obstructive physiology, hypotension, syncope, and death in some patients. Accordingly, some clinicians prefer to not increase verapamil to doses over 240 mg daily.

She was categorized as New York Heart Association Class I heart failure based on lack of any symptoms, and she was advised to continue her current medication regimen. Exercise testing revealed good exercise tolerance without arrhythmia or hypotension. At this point various options were available if symptoms developed, including decreasing the AV delay in order to improve diastolic filling, changing medications to b.i.d., and adding metoprolol succinate. No changes were made at the next 6-month follow-up as she continued to be doing well on her medical regimen. She was advised against competitive athletics and instructed on appropriate exercise to maintain ideal weight. By the next visit, she continued to do well, but her genetic testing confirmed a positive mutation consistent with hypertrophic cardiomyopathy, and she was advised to have her son tested.

Roughly 2 years later, ICD interrogation revealed a short episode of atrial flutter, even though she did not report any significant palpitations. Anticoagulation was discussed, but given the opportunity to interrogate her ICD more frequently for monitoring of recurrence, the patient elected to not initiate warfarin. Five months after the previous visit, she presented to the HCM center outpatient office after receiving an inappropriate ICD shock—her ICD lead was found to be on a recent manufacturer recall and was replaced.

Clinical Pearl: ICD Complications in HCM Patients

ICD lead implants in relatively young HCM patients are not benign as the younger patients may live many years and the collective morbidity for ICD complications including lead malfunctions, perforations, dislodgement, pocket site complications, and generator malfunctions/changes is not inconsequential as is demonstrated by this case. In addition, HCM patients with ICDs may suffer from T-wave oversensing [46] due to high-amplitude T waves leading to spurious ICD detection and unnecessary therapy, which can reduce the quality of life of these patients [47]. In one multicenter study, these extraneous shocks were observed more frequently in patients <30 years old who met the criteria for the highest clinical risk stratification; however, by extrapolation it was determined one in four patients experienced an appropriate ICD shock over the initial 5 years post-ICD implantation, thus making ICDs a reliable way to reduce mortality in high-risk patients [48]. The vast majority of patients with >1 risk marker however will not experience SCD. In the same study, the number of risk factors did not correlate with the rate of subsequent appropriate ICD discharges among the presumably high-risk patients selected for ICD placement. Lead fracture is another major complication in HCM patients and may be more common due to hyperdynamic LV and RV function and the more vigorous activities that younger individuals participate in.

In addition to lead malfunction, the ICD interrogation in our patient also revealed several episodes of atrial fibrillation, subsequent to which her aspirin was stopped and warfarin started with a goal to keep the international normalized ratio 2–3 for cardioembolic stroke prevention, given her CHADS2-VASc score of 2. On follow-up a month later, she had gained 7 pounds now weighing 216 pounds. She had paroxysmal atrial fibrillation but still no obstructive physiology on the echocardiogram. In July of 2010, the patient presented to the emergency room with another ICD shock following an episode of rapid atrial fibrillation. At this point her verapamil was increased to b.i.d. dosing, and she was discharged home.

The next year was unremarkable. In June of 2011, however, an ICD check revealed four episodes of atrial fibrillation and five beats of non-sustained ventricular tachycardia. She reported feeling well. She had lost some weight (weighing now at 205 pounds). In December of 2011, the patient came in for an ICD check, which revealed six beats of NSVT but no episodes of AF. She had started dabigatran 150 mg b.i.d. instead of warfarin, and metoprolol succinate 25 mg q.d. was added to her regimen. A follow-up echocardiogram 6 months later was unchanged.

Clinical Decision-Making: Anticoagulants in HCM with AF

Patients with HCM are at increased risk of atrial fibrillation-related strokes, perhaps more than the general population. Stroke is the third leading cause of death in HCM patients after SCD and progressive heart failure, with an estimated risk of 4% annually. It is important to discuss anticoagulation with the patients. All HCM patients with paroxysmal, persistent, or permanent atrial fibrillation should be fully anticoagulated with warfarin even if sinus rhythm is restored [2]. Choices include warfarin and the newer oral anticoagulants like dabigatran, although the latter have not been studied specifically in the HCM population. Left atrial appendage occlusion devices could also be considered for such patients as these patients were not excluded specifically in the PROTECT AF and PREVAIL trials [49, 50]. Our patient did have mild diastolic dysfunction with mildly dilated left atrium in absence of any significant mitral regurgitation. She also was hesitant in the beginning to initiate warfarin. A frequent reason cited by patients is the need to closely monitor INR levels by invasive blood testing. Given her paroxysmal atrial fibrillation and CHADS2-VASc score of 2, she would have been a reasonable candidate for the newer oral anticoagulants like dabigatran, rivaroxaban, or apixaban. However, patients should be counseled about the lack of data for these agents in the HCM population. In addition, it is not clear that the CHADS2 and CHADS2-VASc scores are validated in HCM; therefore, patients may be reasonably anticoagulated with any episodes of atrial fibrillation, regardless of the presence or absence of modifying risk factors for thromboembolism.

At 3.5 years after initial presentation, she continued to do well overall symptomatically, but an ICD check demonstrated several episodes of NSVT with the longest one with 27 beats at a heart rate of 166 beats per minute, terminating spontaneously. There were no further episodes of AF. Remarkably, the addition of low-dose metoprolol resulted in cessation of all AF. Her electrocardiogram now showed sinus rhythm with right bundle branch block, left anterior fascicular block, and first-degree atrioventricular delay. An echocardiogram revealed stable nonobstructive HCM with a septal thickness of 2.4 cm (Fig. 31.17a, b). Her weight, electrocardiogram, and medications were unchanged, and she was referred for an exercise stress test to evaluate her exercise tolerance.

Clinical Decision-Making: Why and Which HCM Patients to Refer for Exercise Stress Testing?

Exercise treadmill is useful to determine functional capacity and response to therapy in patients with HCM, besides risk stratifying for sudden cardiac death [1] (if abnormal blood pressure response or ventricular arrhythmia is found, see chapter on risk stratification for SCD). In patients with HCM who do not have a resting peak instantaneous gradient of greater than or equal to 50 mmHg, ACCF/AHA guidelines suggest exercise echocardiography is reasonable for the detection and quantification of exercise-induced dynamic LVOT obstruction [1]. Both of these conditions were met in our patient, although once an ICD is already in place, patients who are asymptomatic likely can forego annual exercise treadmill tests solely for risk stratification.

At the stress test, she demonstrated a good exercise capacity of 9:31 min of the Bruce exercise protocol and achieved 10.45 metabolic equivalents (METS) with a peak heart rate of 130 bpm which was 79% of her age-predicted maximal heart rate (while on calcium channel blockers and beta-blockers). Stress electrocardiogram revealed only sinus tachycardia without stress-induced obstructive physiology on the echocardiographic portion, confirming nonobstructive HCM.

On her last follow-up, she had NYHA Class II symptoms, but no changes to her medical regimen were made. A repeat echocardiogram (Figs. 31.18 and 31.19) revealed no progression of septal hypertrophy and absence of any significant resting or provocable gradient. Over the years, genetic tests became available for her family, and her mother, brother, and son are all positive for the same HCM mutation. Her son was found to also have the phenotype and therefore underwent ICD implantation based on the fact that our patient, a first-degree relative, had suffered SCD due to HCM.

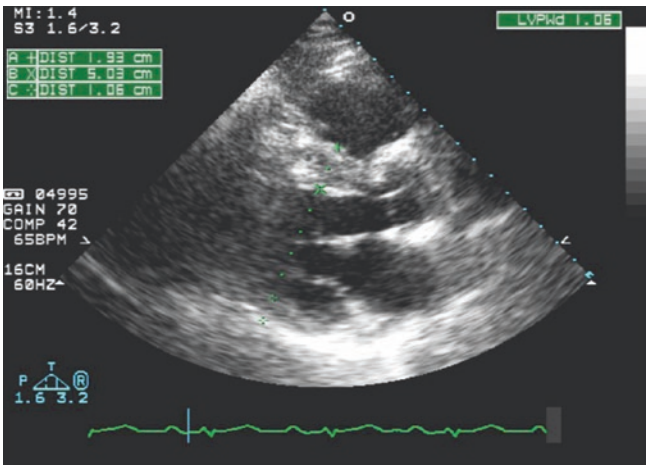

Fig. 31.18 Case 5: TTE parasternal long-axis view, 5-year follow-up, on medical therapy. Mild regression in septal hypertrophy (1.9 cm) compared to baseline measurements (see Fig. 31.17a)

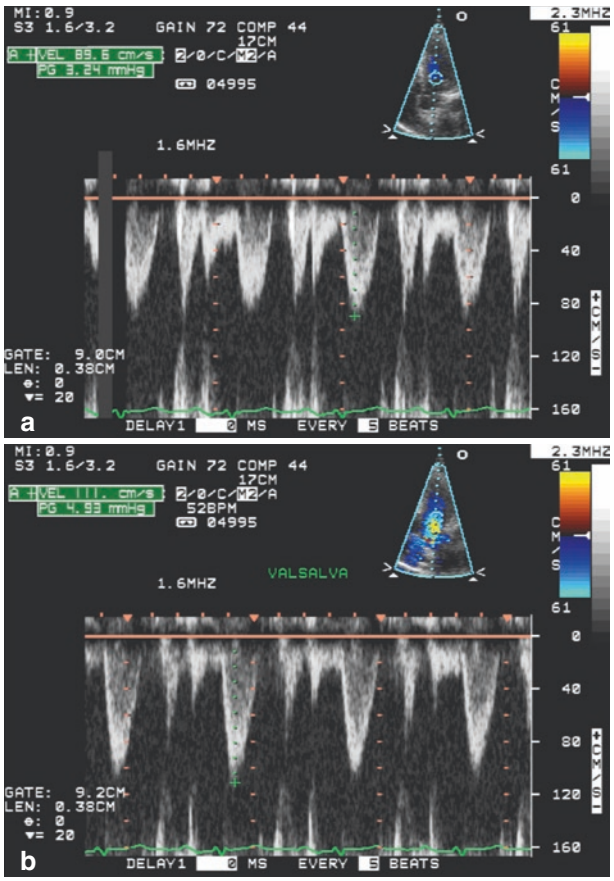

Fig. 31.19 Case 5: TTE parasternal long-axis view, 5-year follow-up, on medical therapy. (**a**) Resting LVOT gradient = 3 mmHg, (**b**) LVOT gradient at Valsalva maneuver = 5 mmHg

Clinical Pearl: How to Use Genetic Testing?

Genetic testing is now increasingly utilized in HCM patients. The main power of genetic testing is in tracing the gene's passage through the family and in both confirming and excluding the presence of this genetic disease. In this case, the mother of our patient was found to be the individual who transmitted the gene to RC, and therefore it is the maternal side of the family that should be further tested and, most importantly, informed. In addition, the son was found to be positive for the gene. In all cases of gene positivity, imaging including echocardiogram and sometimes MRI is required to ascertain whether gene positivity is accompanied by phenotype positivity, as it is presently believed that it is the presence of the phenotype that confers risk of SCD [51]. There is no data available regarding rate of SCD in genotype-positive and phenotype-negative individuals with HCM [52]. By consensus opinion, therefore, these genotype-positive and phenotype-negative patients may be managed conservatively, and they are not typically excluded from competitive sports. However, any phenotypic abnormality that might be consistent with HCM would prompt the full battery of annual testing and visits and exclusion from competitive sports. This includes, in most cases, the presence of any maximal thickness >1.5 cm or other abnormalities that are highly suggestive of clinical disease (i.e., significant LGE on cardiac MRI typical of HCM, significant asymmetric hypertrophy, or the presence of outflow tract obstruction).

Case 6: Exertional Dyspnea in a 61-Year-Old Male with Severe LVOT Obstruction

Mr. A.H. presented to the HCM center in late 2007 as a 61-year-old male with known history of hypertension, dyslipidemia, peptic ulcer disease, gastroesophageal reflux disorder, and hypertrophic cardiomyopathy. HCM was first diagnosed 9 months prior to referral to our center by his primary cardiologist when he had started experiencing exertional dyspnea on walking one block, in addition to frequent lightheadedness on exertion, consistent with NYHA Class III symptoms. He had been managed with atorvastatin for dyslipidemia and atenolol for hypertension that was later switched to amlodipine with little relief of his symptoms. A two-dimensional echocardiogram several years earlier was interpreted as "normal." This was followed by a cardiac catheterization in Jan 2007, which was reported as "normal coronary anatomy."

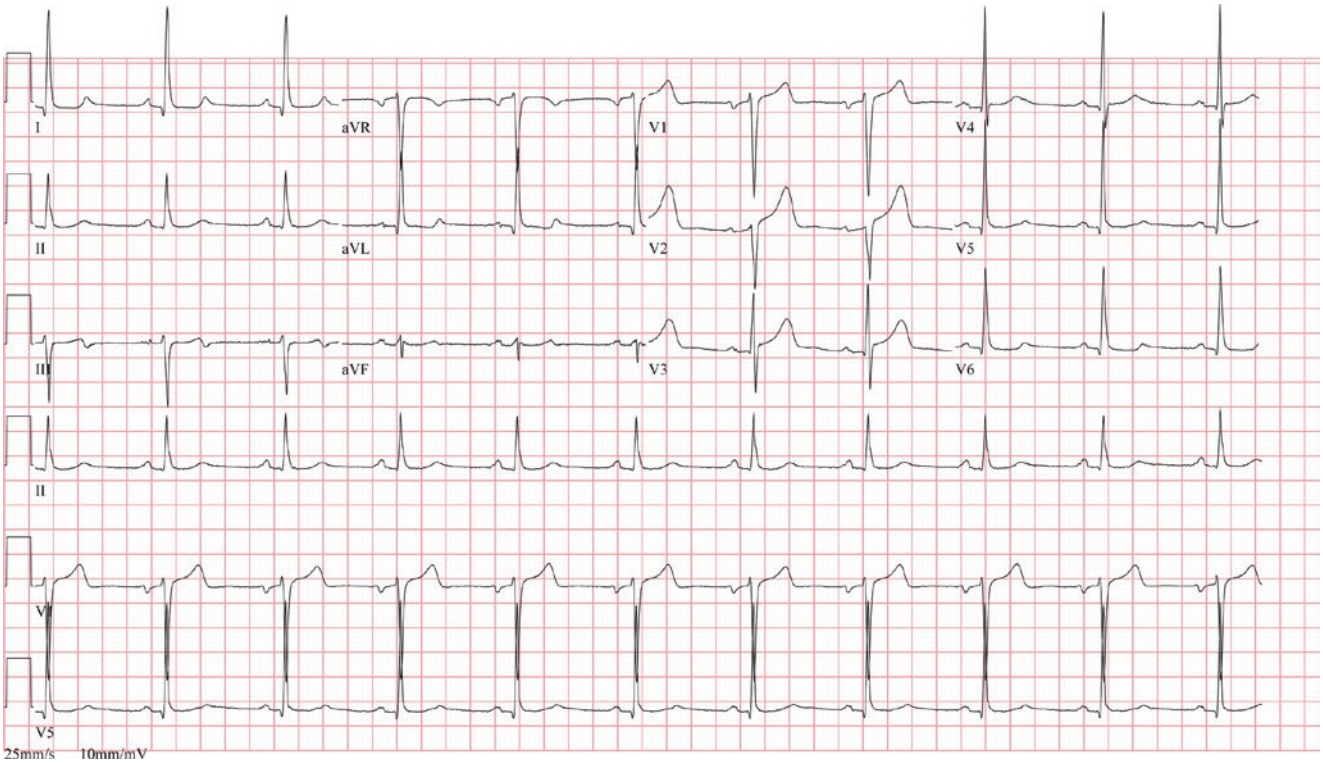

Fig. 31.20 Case 6: 12-lead electrocardiogram depicting left ventricular hypertrophy and repolarization abnormality

He denied tobacco or alcohol use. His family history was significant for death of his mother at age 67 from "heart failure," and his brother had died at age 37 of an unknown cause. Physical examination revealed blood pressure 112/70 and a regular heart rate at 90 beats per minute. Cardiovascular exam revealed a grade 3/6 systolic ejection murmur at the left sternal border and a hyperdynamic left ventricle. Chest exam was clear to auscultation bilaterally, and the rest of his exam was unremarkable. Notably, there was no edema.

His electrocardiogram in the office revealed normal sinus rhythm with left ventricular hypertrophy and repolarization abnormality (Fig. 31.20). On this initial visit, due to likely obstructive physiology based on his examination and his significant heart failure symptoms, the amlodipine was discontinued and beta-blocker therapy initiated with metoprolol succinate 25 mg b.i.d. In addition a 24-hour ambulatory electrocardiogram monitor was placed for assessing risk for sudden cardiac death and possible consideration for implantable cardioverter defibrillator given his significant family history. He was also advised lifestyle modification measures including avoiding alcohol, dehydration, and competitive athletic activities and ensuring aggressive oral fluid hydration.

Clinical Pearls: Approach to the Initial Visit

Patients with HCM and presumed obstructive physiology should undergo a comprehensive echocardiogram to diagnosis HCM, presence or absence of obstructive physiology, and the maximal thickness. If there is doubt, a cardiac MRI is often useful. Once diagnosed, patients should be counseled on their initial visit on multiple areas. First, a description of HCM must be given in detail, including the variety of symptoms that may be present. Patients with systolic ejection murmurs indicative of obstructive physiology should be told to avoid any medications that could reduce the afterload or preload or increase contractility. They should be educated on situations that could lead to dehydration and advised to avoid alcohol, caffeine, or other stimulants. Phosphodiesterase inhibitors for erectile dysfunction are contraindicated, as are nitrates. They should be told to run any new medications by their cardiologist directly, as many antihypertensives are relatively contraindicated due to their primary afterload-reducing effects or their tendency to cause reflex tachycardia, both of which can worsen obstruction. Accordingly, during the initial visit, medications are usually adjusted or eliminated.

Patients should avoid any athletic activities that can cause a sudden increase in left ventricular outflow tract gradient or arrhythmia like sprinting, tennis, basketball, lifting free weights, or soccer [53]. In addition to discussing lifestyle modification as above, risk of sudden cardiac death should be discussed, including the annual screening that is required. Finally, the family inheritance pattern and genetic testing aspects should be discussed. In general, the first visit concentrates on understanding the patient's symptoms, physiology, and adjusting medications while educating regarding lifestyle modification and compliance. Subsequent visits can focus on the issues surrounding genetic testing and risk of SCD. However, as in the present case, initiating the SCD risk stratification protocol, for example, with Holter monitoring, may be reasonable. Other tests such as exercise treadmill testing for risk stratification might be better timed after appropriate beta-blockade has been initiated.

An echocardiogram was performed and revealed systolic anterior motion of the mitral valve with mild to moderate mitral regurgitation, a normal left ventricular systolic function, echogenic contact region at the SAM septal contact point, and asymmetric septal hypertrophy with basal septum 2.2 cm and 1.7 cm left ventricular posterior wall. The resting left ventricular outflow tract gradient was 12 (Fig. 31.21) mmHg, and with Valsalva maneuver, it increased to 26 mmHg. The ambulatory electrocardiogram recorder had revealed normal sinus rhythm besides sinus bradycardia and seven couplets but no non-sustained ventricular tachycardia or atrial arrhythmia. The beta-blocker dose was doubled due to continued NYHA Class III symptoms, and a decision was made to perform an exercise treadmill test both to continue his risk stratification and to assess his exercise tolerance on medication.

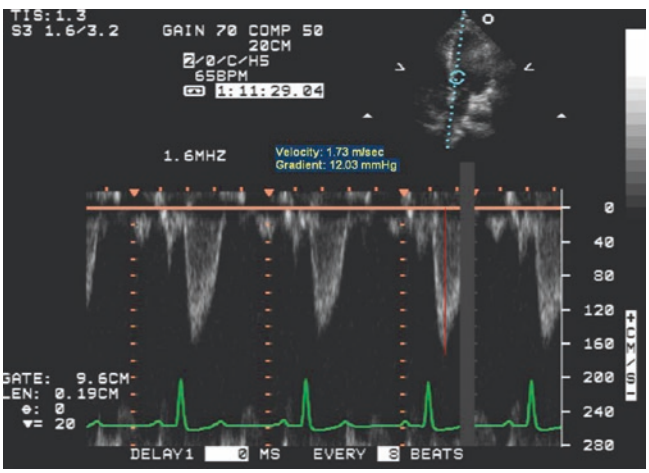

Fig. 31.21 Case 6: Initial TTE, spectral Doppler revealing 12 mmHg resting LVOT gradient

Clinical Decision-Making: Why Would an Exercise Treadmill Test (ETT) Be Helpful in This Patient?

Besides helping determine exercise tolerance, which can confirm or refute a patient's subjective assessment, an ETT would help risk stratify this patient. Although he has a family member who died at a young age, HCM was not known in this person, and therefore the family history alone cannot be used to justify ICD implantation. Thus, any indication for ICD placement would be based on the confluence of other risk factors, as in all patients with HCM. Given his maximal septal thickness is 2.2 cm (less than the 3.0 cm cutoff point) and the absence of NSVT, SCD, or VT, an abnormal blood pressure response during the ETT would help assign risk [54, 55]. Patients with a 20 mmHg drop in systolic blood pressure or less than 20 mmHg rise in this pressure during the ETT are considered at increased risk of sudden cardiac death and may warrant ICD placement as a Class IIb in the 2011 ACCF/AHA guidelines [1]. An exercise stress echocardiogram may also be considered in patients with resting gradients less than 50 mmHg to determine if there is a significant exercise-induced gradient or an increase in the mitral regurgitation [1]. Finally, exercise tolerance can help determine whether to increase medications or maintain the current dose; in general, NYHA Class I–II patients typically can be maintained on medications, while higher degrees of debilitation often require escalation of medications or contemplation of invasive therapies once medications have been exhausted or limited by side effects.

The patient continued to have NYHA Class III symptoms despite augmented medical therapy. Options included increasing medications further or proceeding to invasive therapies. However, it remained unclear the extent of obstruction and whether provocable gradients qualify for invasive therapies. After a thorough and balanced discussion, including surgical and interventional consultation, the patient requested a minimally invasive approach, and thus an alcohol septal ablation was considered. During the cardiac catheterization, no resting gradient was present, but a peak gradient of 300 mmHg was found, confirming severe obstructive physiology. Alcohol septal ablation was performed and resulted in acute reduction in the provocable gradient to 120 mmHg. The first septal artery was diminutive and deemed not suitable for septal ablation, so the procedure was performed via an anomalous septal artery arising from the right coronary artery (Fig. 31.22).

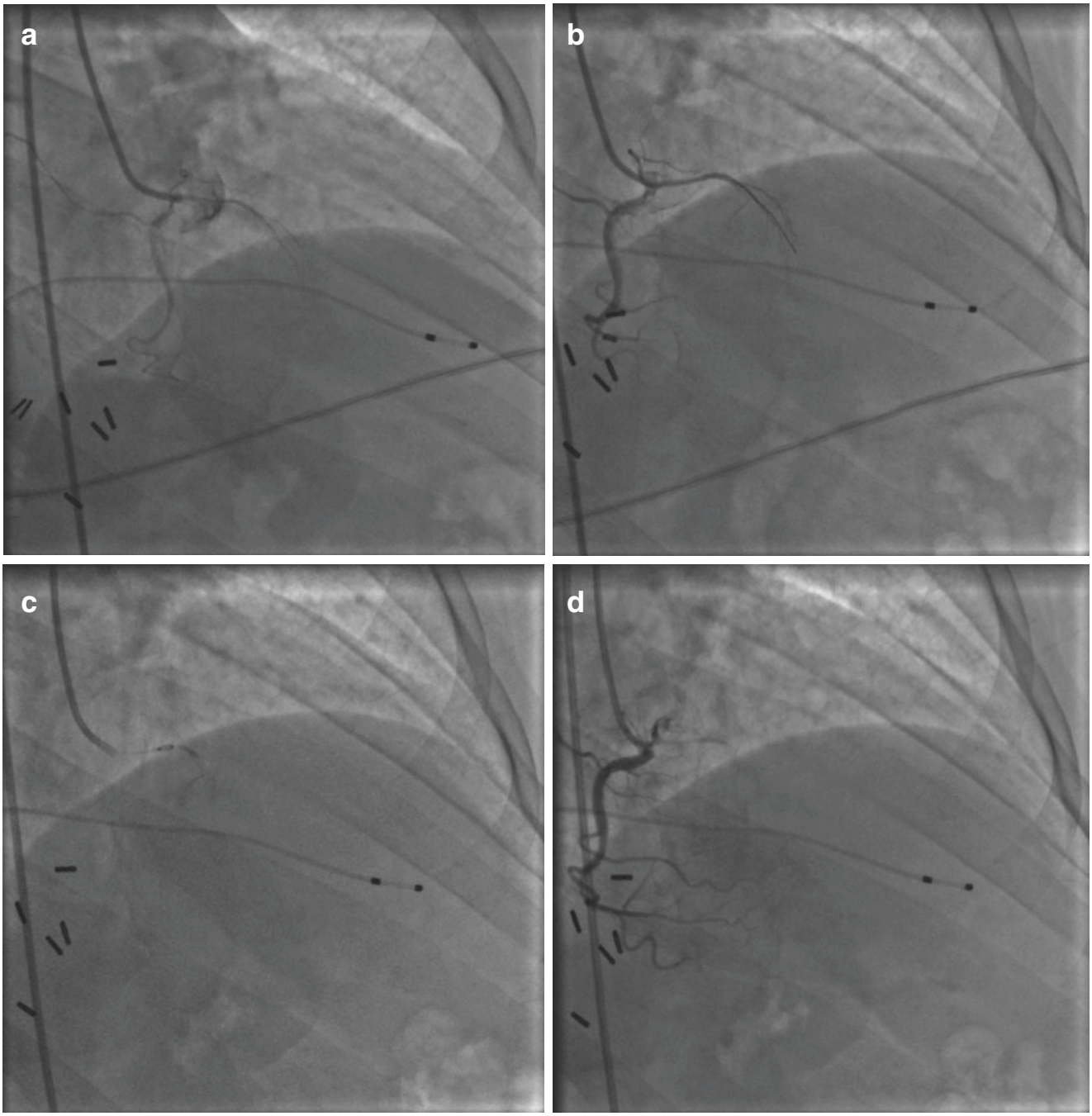

Fig. 31.22 Case 6: Initial alcohol septal ablation via first basal septal perforator originating from the right coronary ostium. (**a**) Engaging the septal perforator with a Judkins right guiding catheter, (**b**) wire inserted into the septal perforator, (**c**) balloon inflated and ethanol injected into the branch, (**d**) post-ablation obliterated perforator branch

Echocardiographic guidance was utilized for the ablation. Peak creatinine phosphokinase level was 900. A dual-chamber implantable cardioverter defibrillator was placed for complete heart block, the significant family history of sudden cardiac death, and monomorphic non-sustained ventricular tachycardia >48 h post-procedure (Class 2b indication). A week post-procedure, the patient reported feeling "100%" better in the office and had New York Heart Association Class I symptoms. He was able to engage in low-level exercises and walk several city blocks without any symptoms. No changes to his medical regimen were made at this time.

Clinical Decision-Making: When to Conclude an Alcohol Septal Ablation Procedure?

Historically, alcohol septal ablation was deemed successful when a >50% reduction in resting and peak gradient was achieved, as in this patient. More recently, many experts have advocated for continuing to ablate additional septal perforators (if present) in order to leave a residual resting gradient of <10 mm Hg (which mirrors surgical results) and a >50% reduction in peak gradient. Our patient met this criteria, as there was no resting gradient after the procedure. While this more stringent goal may increase the risk of complete heart block requiring pacemaker placement, a more effective and durable result may be obtained. This remains a point of controversy, however, within the field. In the current patient, a decision was made to conclude the procedure and follow the patient clinically.

The patient was seen again in the office 1 month post ablation and was only reporting some fatigue with exertion. ICD interrogation did not reveal any ventricular tachycardia or atrial fibrillation, and he was less than 1% of the time atrial and ventricular paced. By this time, the patient's ICD lead had been recalled by the manufacturer but had no signs of fracture, and therefore it was not extracted.

Three months post ablation, the patient was again seen in the office, this time complaining of intermittent lightheadedness, dizziness, palpitations, and shortness of breath with minimal exertion, reporting occasional dizziness at rest besides a 10-pound weight gain. An echocardiogram (Fig. 31.23) at this time revealed a resting gradient of 19 mmHg and a provoked gradient of 45 mmHg, while the basal septum measured 1.8 cm (down from 2.2 cm). An echo 2 months ago had revealed the resting gradient to be 11 mmHg and the provoked gradient to be 18 mmHg. At this point the patient was conservatively managed and seen frequently as an outpatient and symptoms monitored, given ongoing expected remodeling from the ablation that might continue to improve over time. However, at 8 months post ablation, due to worsening symptoms, a repeat echocardiogram revealed a gradient of 100 mmHg with systolic anterior motion of the mitral valve causing LVOT obstruction and mild mitral regurgitation. A right and left heart cardiac catheterization was repeated, and while no resting gradient was again noted, a provoked gradient of 180 mmHg was discovered, and the first septal perforator had increased in size. This was thought to be due to the demand arising from the first ablation, and a second alcohol septal ablation was therefore planned.

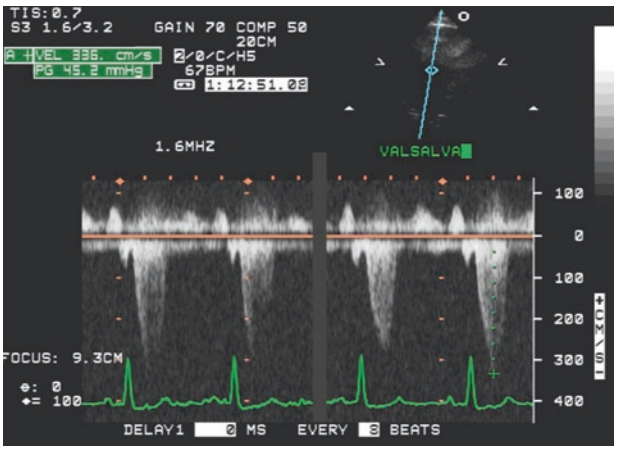

Fig. 31.23 Case 6: Symptoms persisted after initial ablation leading to a TTE study. Spectral Doppler revealed persisted LVOT provocable gradient on the Valsalva maneuver

Clinical Decision-Making: How Frequently Is a Second Alcohol Ablation Needed?

Studies report 2.7–12.8% incidence of repeat alcohol septal ablations and 1.1–2.8% incidence of referral to septal reduction surgery, after an initial alcohol septal ablation [41, 42, 56], as patients may have refractory symptoms due to severe hypertrophy, inability to adequately ablate the entirety of the obstructive area, or recurrence of obstruction due to collateral vessels as in our patient. Patients should therefore be told that a second invasive therapy may be required in a small subset of patients. In order to improve the initial efficacy, it is now thought that resting gradient should be reduced to less than 10 mm Hg and peak gradient at least 50% reduced, if not more; in this manner, there appears to be little risk of recurrence. However, care must be taken to not infuse too much alcohol and instead focus on targeting the exact area of septal contact by contrast echo guidance, so as to improve efficacy while maintaining safety. In fact in the Multicenter North American Registry, higher volume of injected alcohol was associated with higher mortality as was a larger number of arteries injected with ethanol [41]. Patients should also be considered for septal myectomy after an initial failed alcohol ablation. However, although successful, surgical myectomy in this setting has a high incidence of permanent pacemaker (10–20%). In the case of our patient, due to the focal nature of the septal bulge contributing to his symptoms, the more proximal LVOT obstruction that appeared to align with the now available first septal perforator, and the presence of an ICD already in place, a repeat alcohol septal ablation was chosen. Importantly, the patient continued to have septal thickness sufficient to justify ablation (>1.5 cm). This may not always be the case, and when significant thinning is present, a surgical myectomy may be safer as the surgeon can take care to avoid resection near the thinned septum.

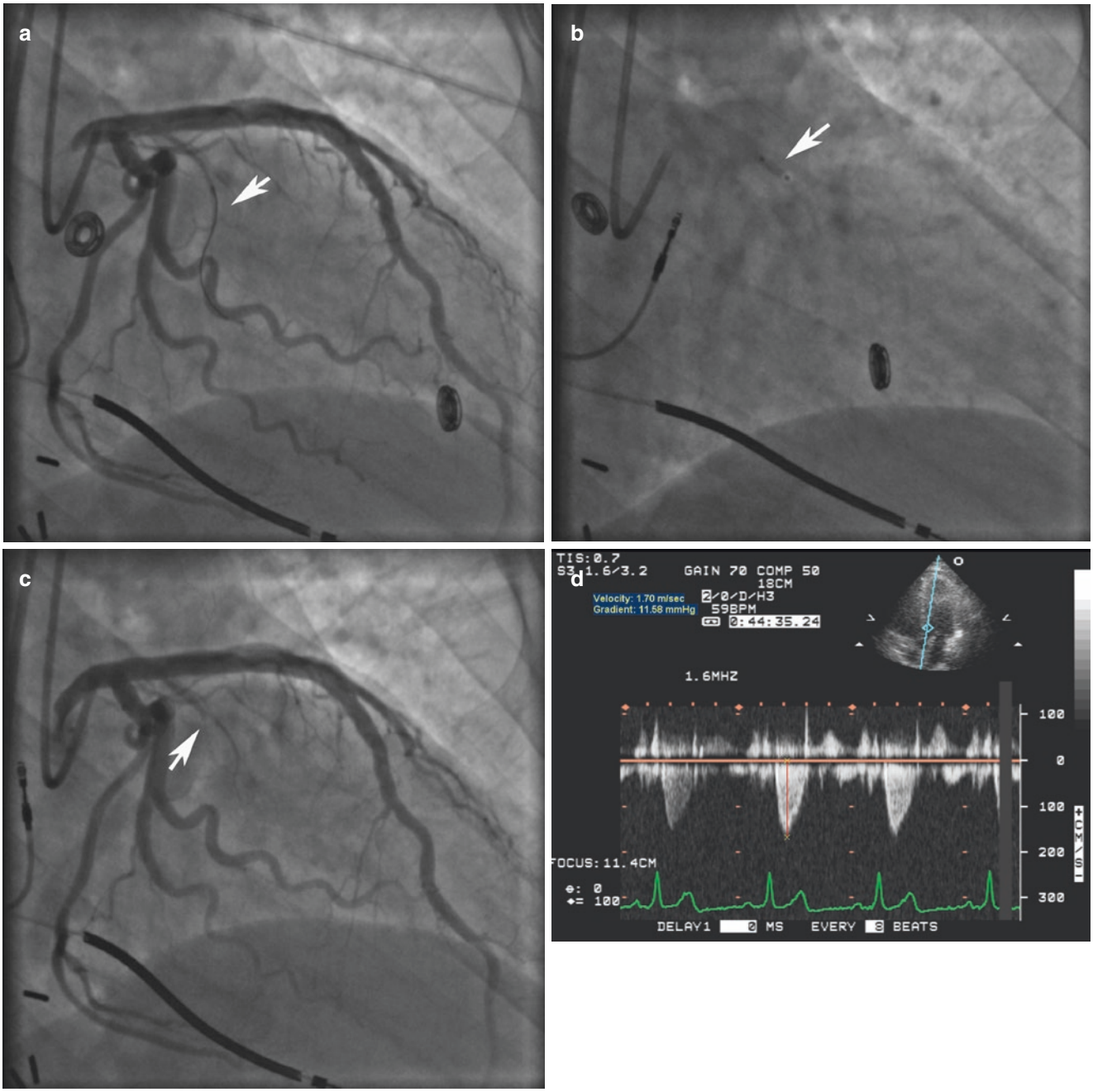

Fig. 31.24 Case 6: Repeat alcohol septal ablation. (**a**) Basal septal perforator from the LAD (*arrow*) engaged with a wire, (**b**) balloon (*arrow*) inflated in the branch and alcohol injected distal to the balloon, (**c**) ablated perforator branch (*arrow*), (**d**) TTE spectral Doppler post-ablation revealing reduced resting gradient across the LVOT (12 mmHg). Arrow head points toward

The second ablation (Fig. 31.24) was done via the first septal perforator and resulted in disappearance of the provocable LVOT gradient with Valsalva and Brockenbrough maneuver completely. The patient was seen frequently as an outpatient after this ablation and has had complete resolution of his symptoms with no residual dyspnea on exertional or dizziness. Echocardiograms show no LVOT obstruction either at rest or with provocation and absence of SAM.

Five years later, the patient remained in NYHA Class I and was asymptomatic without lightheadedness or dyspnea. An interrogation revealed lead noise, and the ICD lead was revised for lead fracture. At 6 years follow-up, he continued to do well from the cardiac perspective. His echocardiogram revealed no LVOT obstruction or systolic anterior motion of mitral valve, and he had mild to moderate mitral regurgitation.

Clinical Pearls: ICD Lead Complications in HCM Patients Are Not Inconsequential

HCM patients with ICD implants may lead long productive lives, and these patients may outlast the life span of any given device system. While ICDs have been shown to be effective at aborting SCD in patients with HCM, the benefits and risks of an ICD implantation should be carefully considered and preferred only in patients with high risk for sudden cardiac death. This is especially the case for the very young, in whom multiple revisions may be required over their lifetime. In very young patients, single-chamber defibrillation may suffice and reduce complications [57]. HCM patients are prone to T-wave oversensing and other lead malfunctions due to the hypertrophied heart with hyperdynamic contraction. Conversely, the risk of SCD is such that patients may benefit from ICD implantation many years afterward, and the risk stratification protocol is not perfect. Thus the decision to implant an ICD should be individualized in patients considering both the potential benefits and the potential long-term morbidity of living with these devices.

Case 7: A 57-Year-Old Man with Dyspnea on Exertion and Chest Heaviness

A 57-year-old Caucasian male presented to our HCM center with a diagnosis of HCM, dyslipidemia, and mitral valve prolapse. HCM had been diagnosed after a year of progressive dyspnea on exertion associated with chest heaviness. There were no reports of palpitations, lightheadedness, or syncope. At the time of his initial evaluation, he was unable to perform light housework or climb one flight of stairs, consistent with NYHA Class III. An electrocardiogram revealed a left bundle branch block (Fig. 31.25), while an echocardiogram demonstrated preserved left ventricular systolic function with asymmetric basal septal wall hypertrophy measuring 1.9 cm, a posterior wall thickness measuring 1.3 cm, and a left ventricular outflow tract obstruction with a resting gradient of 65 mmHg augmenting to 140 mmHg with provocation. Systolic anterior motion (SAM) of the anterior mitral valve leaflet was present associated with moderate eccentric mitral regurgitation. Turbulence in the outflow tract, which is associated with obstructive physiology, appeared to be both at the area of septal hypertrophy but also somewhat higher in the outflow tract right below the aortic valve, raising concern for subaortic membrane. Following a

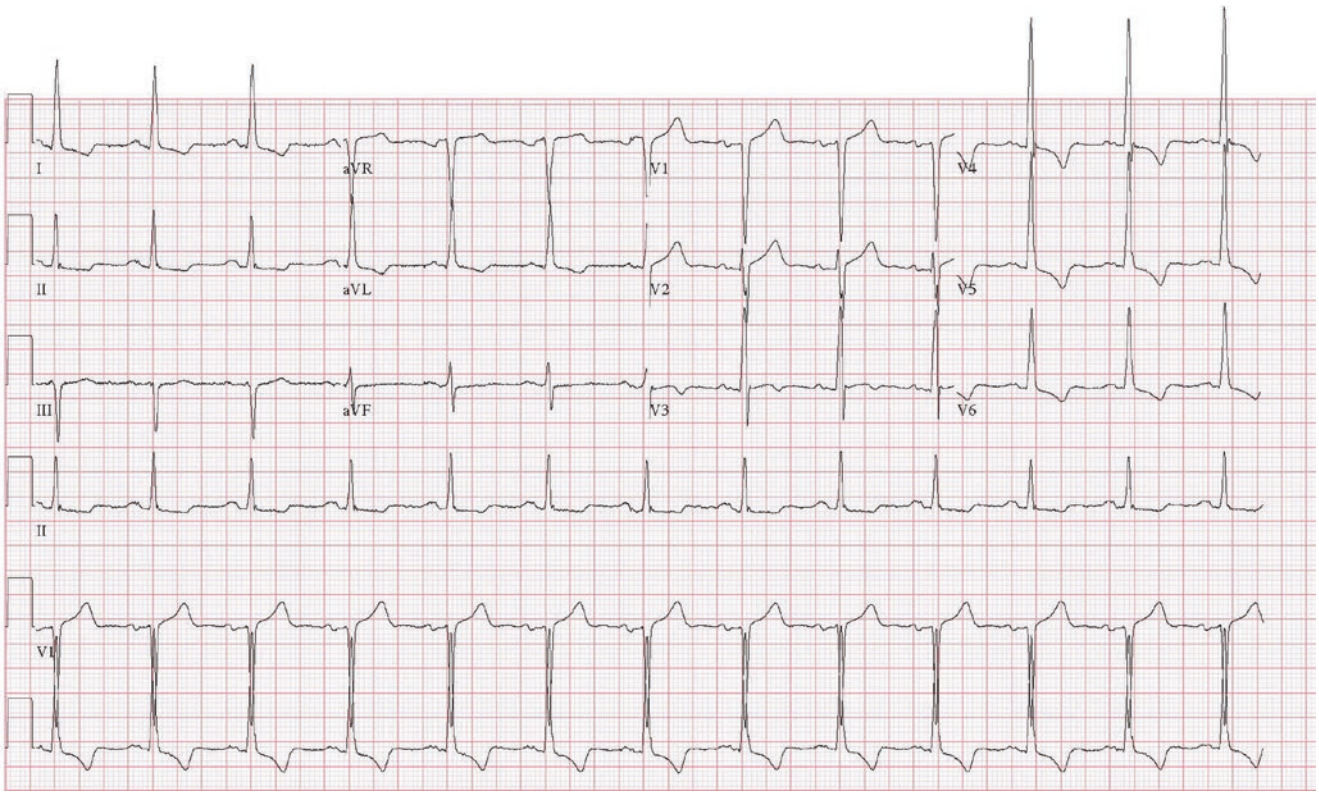

Fig. 31.25 Case 7: 12-lead electrocardiogram depicting left bundle branch block

normal 24-hour ambulatory electrocardiogram monitor study and an exercise treadmill test showing no evidence of ischemia or ectopy, the patient was referred for cardiac catheterization to further assess the gradient and the etiology of symptoms, including dyspnea and chest pain.

Clinical Decision-Making: When Is Cardiac Catheterization Recommended for HCM Patients?

Coronary angiography is an ACCF/AHA Class I recommendation in HCM patients with chest discomfort who may have an intermediate to high likelihood of coronary artery disease (CAD) when the identification of concomitant CAD will change approaches to management [1]. While chest discomfort is a common complaint in patients with HCM, it is important to assess whether symptoms are due to HCM itself or instead related to epicardial obstructive CAD, as CAD as a comorbid disease entity signifies a higher risk for adverse outcomes [58]. Such patients are candidates for revascularization. Ischemia however in HCM can also be secondary to severe hypertrophy itself or due to microvascular dysfunction. In addition, coronary angiography is essential to delineate the coronary anatomy, and this can be an important factor in considering management options for septal reduction therapy in highly symptomatic patients. For example, the presence of multivessel disease or left main disease may prompt surgical septal myectomy instead of alcohol septal ablation.

In addition to coronary angiography, hemodynamic evaluation with cardiac catheterization can aid in the determination of right and left heart filling pressures, contribution of pulmonary disease, presence or absence of resting or provocable outflow tract obstruction, as well as evidence for diastolic dysfunction. In patients with significant heart failure, angina, or pre-syncope or syncope, a comprehensive cardiac catheterization can therefore aid in determining and prioritizing etiologies and organizing treatment scheme. For example, patients with congestive heart failure or dyspnea may benefit from augmented diuretics, whereas patients with normal filling pressures and pulmonary circulation but severe obstruction may benefit from augmented beta-blockers, initiation of disopyramide, or contemplation of invasive septal reduction therapies. Exercise hemodynamics may also be of benefit in elucidating diastolic dysfunction or subclinical pulmonary disease as contributions to patient symptoms.

Cardiac catheterization can also aid in determining the components of subvalvular versus valvular obstruction in patients with HOCM and valvular aortic stenosis; in such patients, standard transthoracic echocardiography is often not definitive. The relative contributions of valvular and subvalvular obstruction can be quantified and actual valve area calculated based on the isolated valvular gradient and Fick equation-derived cardiac output.

The patient underwent diagnostic cardiac catheterization revealing normal coronary arteries, a hyperkinetic left ventricle, and a subaortic valvular gradient of 30 mmHg, which increased to >50 mmHg with Brockenbrough maneuver. There was no valvular gradient. Filling pressures and pulmonary pressures, including pulmonary vascular resistance, were normal. A transesophageal echocardiography (TEE) was recommended for further evaluation of the left ventricular outflow tract obstruction given the presence of a subvalvular gradient during hemodynamic assessment and equivocal etiology (two areas of turbulence in the outflow tract, concerning for concomitant muscular and membrane components).

Clinical Decision-Making: When Is a TEE Recommended for Patients with HCM?

ACCF/AHA guidelines [1] indicate that TEE (1) can aid clinical decision-making when imaging from TTE is inconclusive, (2) can guide surgical planning by helping delineate hypertrophied septum that needs to be removed surgically, (3) can be useful to study any structural abnormalities of the mitral valve apparatus in patients with mitral regurgitation, (4) can be used to help decide feasibility of alcohol septal ablation, (5) can identify the presence of a subaortic membrane causing fixed obstruction with or without coexisting dynamic obstruction, and (6) can be useful in patients with atrial fibrillation contemplating cardioversion or anti-arrhythmic therapy, in order to exclude left atrial appendage thrombus. Patients considered for left atrial appendage closure will also need a protocol-driven TEE.

In the evaluation of mitral regurgitation, central or anterior jets indicate an intrinsic abnormality of the mitral valve, whereas posterior jets timed with SAM are indicative of mitral regurgitation related to HOCM physiology. The latter would be expected to resolve with isolated surgical myectomy or alcohol septal ablation. It is pertinent to point out that in HCM patients with a subaortic membrane who are undergoing invasive management for drug-refractory symptoms, the treatment of choice is surgical myectomy, during which the membrane can be resected.

The TEE (Fig. 31.26) confirmed the systolic anterior motion of the anterior mitral valve leaflet with left ventricular outflow tract obstruction and posteriorly directed MR. However, a subvalvular membrane was also identified (Fig. 31.27). At this point, the patient continued to experi-

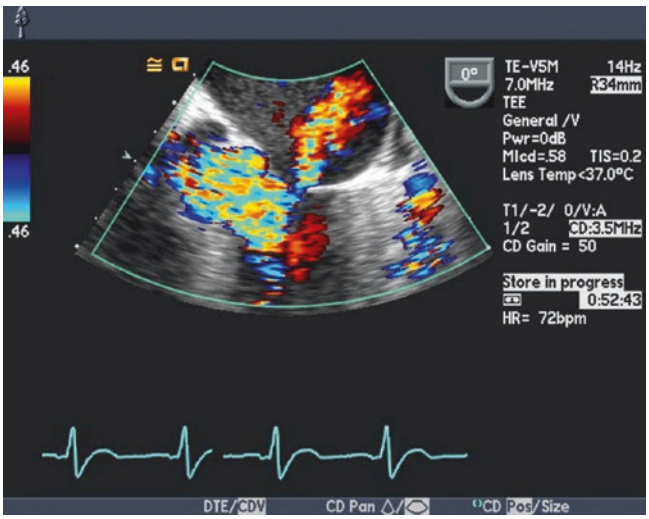

Fig. 31.26 Case 7: TTE depicting moderate mitral regurgitation secondary to systolic anterior motion with a mosaic pattern visualized from turbulent flow in the LVOT secondary to the systolic anterior motion and the subaortic membrane resulting in elevated LVOT gradients (see text for details)

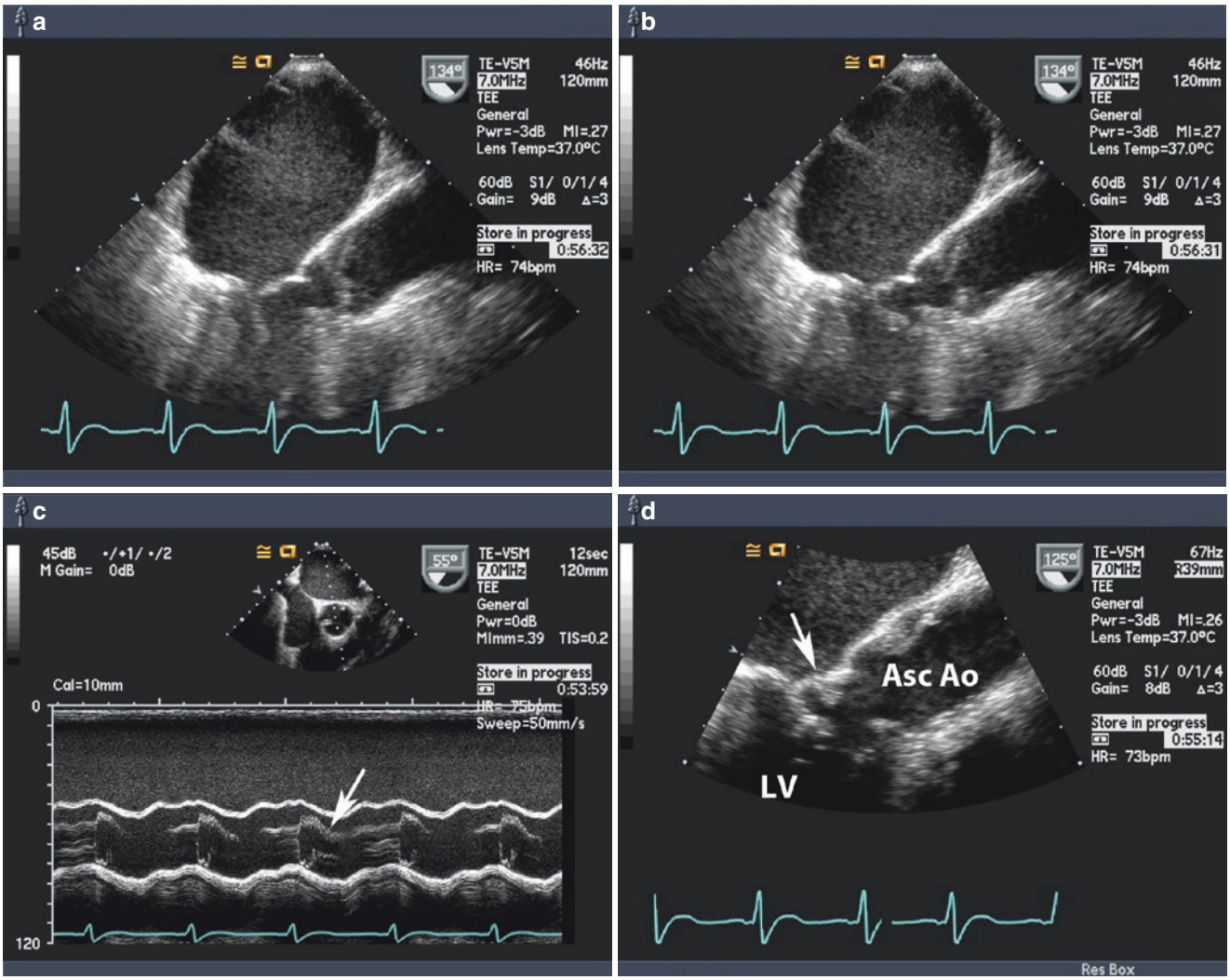

Fig. 31.27 Case 7: TEE depicting systolic anterior motion of mitral valve (**a**–**b**), (**c**) M-mode finding suggesting sub-aortic valve membrane (white arrow head) and (**d**) the systolic anterior motion is confirmed (white arrow head) on the long axis view of the left ventricle

ence severe drug-refractory symptoms despite combination therapy with optimal doses of metoprolol succinate and verapamil. A decision was therefore made to proceed with septal reduction therapy and membrane excision.

Clinical Decision-Making: How to Appropriately Select HCM Patients Requiring Septal Reduction Therapy to Either Surgical Myectomy or Alcohol Septal Ablation

ACCF/AHA guidelines [1] recommend that septal reduction therapy should be performed only by experienced operators—20 cumulative procedures for an individual operator or 50 cumulative procedures for an individual operator working in a dedicated HCM center in the context of a comprehensive clinical HCM program (Class I recommendation). This treatment should be restricted to patients with evidence of LVOT obstruction and severe drug-refractory symptoms who meet strict anatomic and hemodynamic criteria.

Currently surgical septal myectomy is the first consideration for patients who require invasive therapy due to its long track record and safety data, as long as it can be performed in an experienced center (Class IIa indication). When comorbidities exist, including advanced age, that increase the risks of surgery, alcohol septal ablation is useful as an alternative (Class IIa indication). Finally, when both options are available, the principle of patient autonomy dictates that a patient should be able to choose between the two procedures after a balanced and thorough discussion (Class IIb indication). However, the more recent ESC guidelines consider both therapies roughly equivalent, with choice of therapy based on patient anatomy and risk profile primarily.

Factors favoring surgical septal myectomy include younger age (<30–40), greater septal thickness (>3.0 cm), and concomitant surgical cardiac disease (e.g., structural heart disease requiring surgery or CAD requiring coronary artery bypass grafting). Preexistent LBBB also favors surgery. Factors that favor alcohol septal ablation include older age, significant comorbidity that increases surgical risk, and the patient's strong preference to avoid open-heart surgery after a careful discussion with the patient. Preexistent RBBB favors alcohol septal ablation.

In the present case, the subaortic membrane is an absolute contraindication to alcohol septal ablation, and thus surgical myectomy was required. In general, patients with unusual subvalvular anatomy, including redo myectomy, prior alcohol septal ablation, and membranes, as well as abnormal papillary muscles or mitral valvular contributors, should be treated by surgeons at HCM centers with a large surgical experience.

Given the patient's age, persistent NYHA Class III symptoms with coexisting dynamic LVOT obstruction, and presence of a subvalvular aortic membrane, the patient was referred for surgery. A successful circumferential excision of the fibrous ridge/membrane along with septal myectomy was performed without complications. Consequently, the patient's symptoms improved, and he now remains in NYHA Class I functional status 5 years later. He continues to be evaluated annually for SCD risk stratification and family counseling and tracking.

Clinical Pearl: When to Suspect a Membrane?

The vast majority of patients with subvalvular outflow tract obstruction have SAM and obstruction due to mitral leaflet contact with the septum. Such obstruction is dynamic and based on preload, afterload, and contractility. Turbulence in the outflow tract on the parasternal long axis view is seen at the point of septal/SAM contact. In patients with a membrane, the obstruction may be fixed (as opposed to dynamic), associated with aortic regurgitation, and the turbulence will be at a distinct or separate location compared to SAM, usually higher but still beneath the aortic valve. These raise suspicion of a membrane and prompt TEE or other imaging to rule out its presence, such as cardiac MRI. In general, however, TEE is the gold standard. As such, the clinician must have a heightened sense of awareness in order to pick up a membrane. Failure to do so might result in inadvertent alcohol septal ablation, which would fail to eliminate the gradient.

Case 8: Worsening Heart Failure in a Patient with Hypertrophic Cardiomyopathy and Prior Myectomy

Ms. S.J. is a 40-year-old woman with a long-standing history of hypertrophic cardiomyopathy (HCM) managed surgically with myectomy 3 years ago. Her past medical history also includes a history of hypothyroidism, dyslipidemia, depression, and type II diabetes mellitus. She was referred for evaluation and management of progressively worsening dyspnea on exertion over the past 6 months; on presentation, she was NYHA (New York Heart Association) Class III. She also complained of orthopnea and dizziness on minimal exertion. She was on metoprolol succinate 50 mg twice a day, disopyramide 100 mg twice a day, and furosemide 20 mg once a day. She denied angina or syncope. On examination, she had

normal sinus rhythm 60/min, blood pressure 100/70 mmHg, body mass index 22 kg/m^2, a harsh 3/6 crescendo-decrescendo systolic murmur heard best at the left upper sternal border which worsened during Valsalva maneuver, faint bibasilar crackles, and bilateral lower extremity edema. A 12-lead electrocardiogram demonstrated normal sinus rhythm with a left bundle branch block (QRS > 200 msec) and first-degree AV delay (PR = 232 msec)—findings consistent with prior myectomy (Fig. 31.28). Two-dimensional transthoracic echocardiography revealed an ejection fraction (EF) of >65%, asymmetric septal hypertrophy of 27 mm, no papillary muscle hypertrophy, grade 2 diastolic dysfunction, mild to moderate mitral regurgitation with systolic anterior motion (SAM), and left ventricular outflow tract (LVOT) gradients of 84 mmHg during Valsalva maneuver (Figs. 31.29 and 31.30). Her furosemide dose was carefully increased, and she was referred for a cardiac catheterization to further assess for epicardial obstructive coronary artery disease, hemodynamics, and septal perforator anatomy. Cardiac catheterization confirmed absence of obstructive coronary artery disease, significant LVOT obstruction (LVOTO) (resting gradient of 30 mm Hg and a PVC-provoked gradient of 90 mm Hg), and septal perforator anatomy amenable to alcohol septal ablation.

Ms. S.J. underwent successful alcohol septal ablation under myocardial contrast echocardiographic guidance—2.5 cc in first septal perforator followed by 1 cc in second septal perforator. The provoked gradients decreased from 80 mmHg to 45 mmHg (Fig. 31.31). She developed complete AV dissociation after first septal ablation requiring permanent pacing during and after the case. She was taken off disopyramide and discharged home the following day. On 1-month follow-up, she had a dramatic improvement in her symptoms and was NYHA Class I–II. There was no discernable LVOTO on rest or provocation on repeat transthoracic two-dimensional echocardiogram 3 months after the procedure. This case demonstrates that in carefully selected symptomatic HCM patients, alcohol septal ablation is safe and effective for abolishing residual gradients after surgical myectomy.

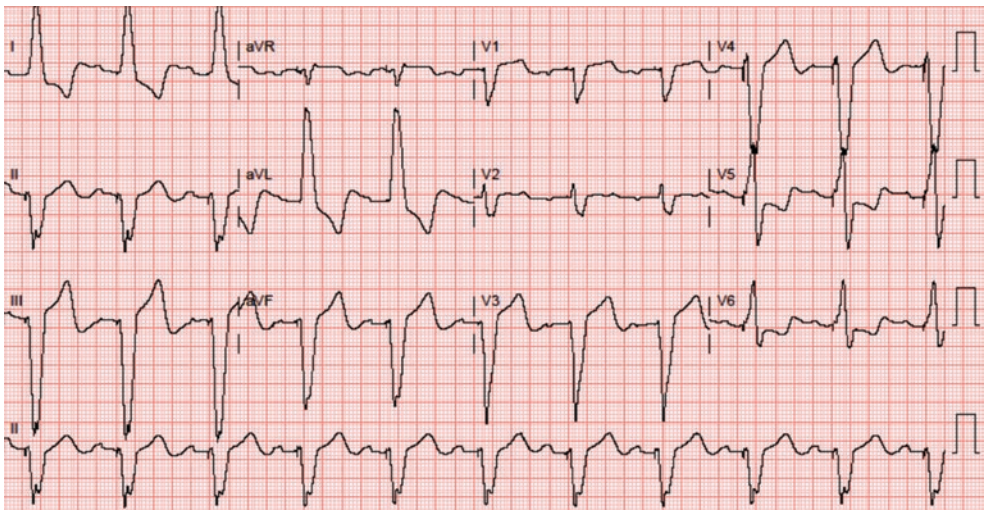

Fig. 31.28 A 40-year-old female with HCM and myectomy 3 years ago. Baseline electrocardiogram—normal sinus rhythm with first-degree AV delay and left bundle branch block

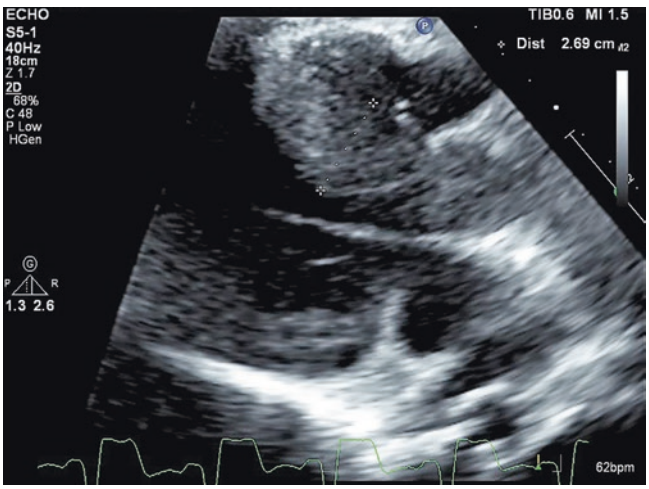

Fig. 31.29 A 40-year-old female with HCM and myectomy 3 years ago. Asymmetric septal thickness of 27 mm

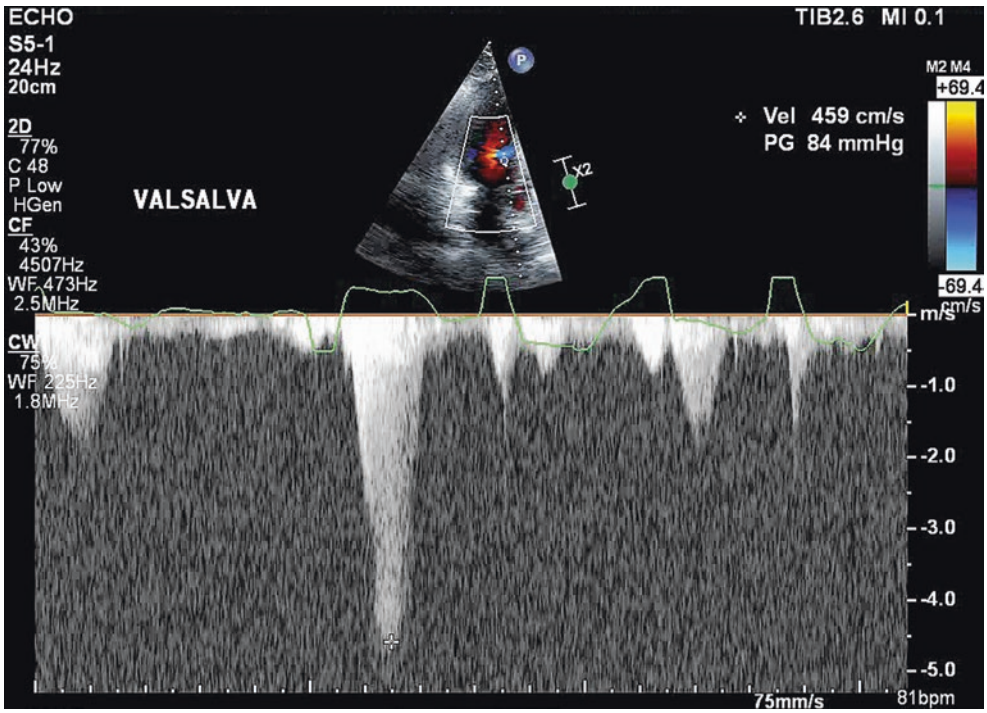

Fig. 31.30 A 40-year-old female with HCM and myectomy 3 years ago. Left ventricular outflow tract gradient (provoked, Valsalva) of 84 mmHg

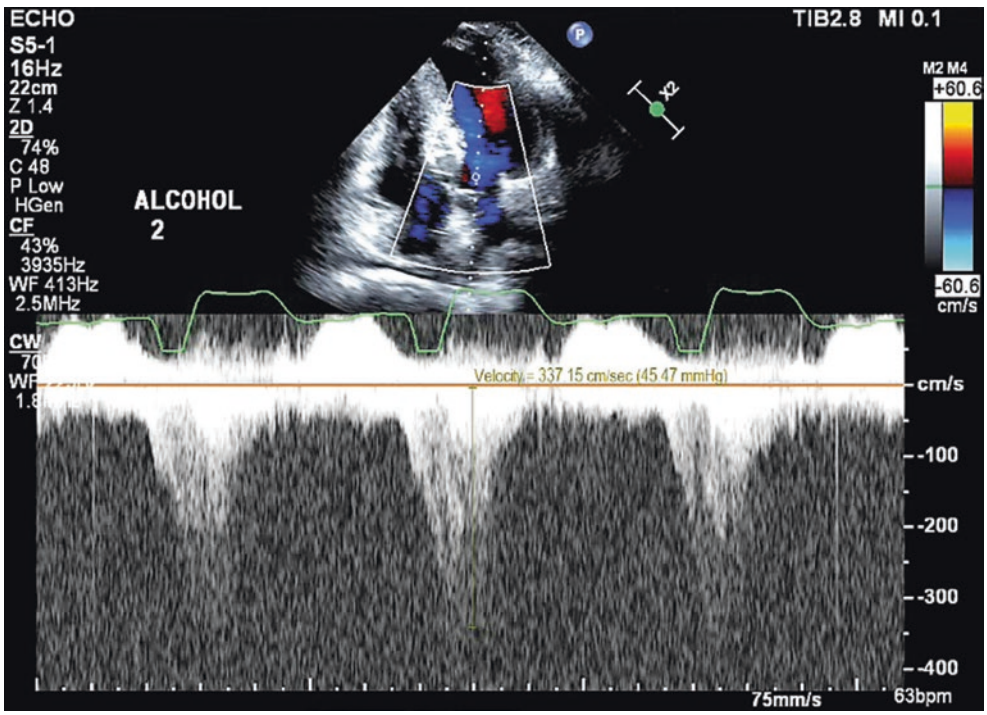

Fig. 31.31 A 40-year-old female with HCM and myectomy 3 years ago. Reduction in gradient and septal thickness post-alcohol septal ablation

Clinical Pearl: Mechanisms of Residual LVOTO After Septal Myectomy

Surgical myectomy to reduce SAM and LVOTO has been in existence for several decades. The classic Morrow procedure involved resection of small amount of muscle from the proximal interventricular septum to relieve LVOTO [59]. Today, the procedure involves wider and deeper resection of the interventricular septum and, in selected patients, resection of anomalous chordae, mitral valve plication, or mitral valve replacement [25, 60, 61]. Procedural/early mortality has decreased exponentially from 4–5% to <1% since the early years, especially at high-volume centers of excellence [60, 62]. Surgical myectomy is the accepted invasive therapy for young patients who are highly symptomatic despite maximally tolerated medical therapy and elevated outflow tract gradients. Residual LVOTO after septal myectomy is rare, and 1–2% patients require reoperative myectomy for residual gradients and symptoms at highest-volume centers [63]. In a large series of reoperative myectomy from the Mayo Clinic, mean time to symptoms after first procedure and mean time to reoperation were 22 ± 42 months and 43 ± 51 months, respectively [63]. The most common etiology of residual gradients was inadequate length of previous subaortic septal excision in 59% of patients, followed by inadequate length and an inadequate depth of septectomy in 25% of patients. Mid-ventricular obstruction was seen in some cases but was a relatively rarer cause of residual gradients [63]. Of note, reintervention rates were higher in patients treated with alcohol septal ablation versus septal myectomy (7.7% versus 1.6%, $p = 0.001$) [64].

Clinical Decision-Making: How to Manage Symptomatic Residual LV Outflow Tract Obstruction in Patients with Prior Myectomy?

Ms. S.J. had symptomatic residual LVOTO despite maximally tolerated medical therapy. The residual gradient was primarily due to inadequate length and depth of excision at time of myectomy as a mid-ventricular gradient was ruled out on echocardiogram. The management options included reoperative myectomy or alcohol septal ablation. Data from the largest series of repeat myectomies report excellent clinical outcomes—93.8% NYHA Class I or II post-procedure and 98% survival at 10 years following a reoperative myectomy [63]. As our patient was an excellent surgical and alcohol septal ablation candidate, we offered both therapeutic modalities to the patient. We discussed in great detail the likelihood of improvement in gradients and lower rates of permanent pacemaker implantation with reoperative septal myectomy. Despite an exhaustive conversation regarding the excellent rates of reoperative success and the consequences (and possible long-term complications) of permanent pacemaker implantation at her young age, she decided to pursue alcohol septal ablation. Her preference to choose septal ablation over repeat myectomy was driven by her fear of perioperative morbidity and length of stay associated with a reoperation. According to the most recent European Society of Cardiology guidelines, all patients 40 and over, planned for alcohol septal ablation, should undergo invasive or CT coronary angiography (Class IIa) [2]. This recommendation is not dependent on symptomatic angina.

Clinical Decision-Making: Pacemaker or Implantable Cardioverter Defibrillator Prior to Alcohol Septal Ablation

Alcohol septal ablation is conceptually designed to induce myocardial injury in the territory supplied by the septal arteries and can be associated with iatrogenic conduction disturbances. The most common conduction abnormality is right bundle branch block seen in 50–85% of patients, post-procedure [65–67]. The rates of complete heart block and permanent pacemaker implantation are higher with septal ablation versus myectomy (OR, 2.6; 95% CI, 1.7–3.9) and range from 10 to 30% (12% in more recent European data) [7, 68, 69]. The most important independent risk factor for post-alcohol septal ablation complete heart block is preexisting left bundle branch block. Female gender, bolus alcohol injection, first-degree AV delay, and injecting more than one septal artery are other important risk factors for development of post-procedure complete heart block [70]. Our patient had three major risk factors (first-degree AV delay, left bundle branch block, and female gender); hence, we decided to proceed with permanent pacemaker implantation prior to alcohol septal ablation.

Indications for a primary or secondary prevention implantable cardioverter defibrillator include history of sudden cardiac death, history of ventricular tachycardia or non-sustained ventricular tachycardia, abnormal blood pressure response, left ventricular hypertrophy >30 mm, or a history of sudden unexplained syncope. Our patient had severe left ventricular hypertrophy of 27 mm but did not meet criteria for implantable cardioverter defibrillator.

Conclusions

HCM patients present in many ways, and the course of their disease may result in a myriad of phenotypes. These include presentations early and late in life, during pregnancy, or as a result of family screening. These also include a vast array of arrhythmias from SCD to atrial fibrillation. As patients are brought in, they are evaluated in a comprehensive manner to include optimal imaging to make the diagnosis and understand the physiology, medication titration to control symptoms, initial and annual testing to understand their risk of SCD, and ongoing discussions with their families to protect their loved ones. Moreover, as patients age, they may develop new diseases that need to be treated or may have their disease progress to the point of needing new therapies, including pacemakers, ICDs, or septal reduction treatment. Conversely, they may experience long periods of stability, during which routine visits simply confirm stability of symptoms and minimal risk factors for SCD.

The preceding cases were chosen as a representative cohort to elucidate long-term management and all of the factors that are seen in the context of an HCM program and how they were handled. While practice patterns may differ, the goal was to give the reader an understanding of the nuances of care, both diagnostic and therapeutic, that are required when caring for this challenging yet rewarding patient population. It also gives the reader an understanding of how to integrate all the preceding chapters into the practical management of the patient with HCM.

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