Hypertrophic Cardiomyopathy

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Editor

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Second Edition

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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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