The 2009 International Hypertrophic Cardiomyopathy Summit

Barry J. Maron, MD*

In Minneapolis, Minnesota, on October 16 to 18, 2009, the fourth "International Summit on the Diagnosis and Management of Hypertrophic Cardiomyopathy and Prevention of Sudden Death: The Next 50 Years," was held and sponsored by the Minneapolis Heart Institute Foundation in recognition of the fiftieth Anniversary of this disease (Figure 1). During the previous half-century, hypertrophic cardiomyopathy (HC) persistently intrigued and challenged the cardiovascular community and, indeed, has periodically been the source of misunderstanding and even controversy. The 3 previous HC Summits held in Minneapolis were in 1997, 2002, and 2006 (with the meeting scheduled for September 14, 2001 canceled).

During the 2.5-day period, 215 attendees from 13 countries and 24 states heard 37 lectures from an international faculty of 25 speakers (Figures 2 and 3 and Table 1). This unique program was dedicated to relating the expansive HC "story" from basic molecular genetics to clinical presentation and natural history, and, most importantly, to management options and decision-making—from the earliest studies in the 1960s to the present context of HC within contemporary cardiovascular medicine. The program integrated the older and well-recognized data with the more recent insights in an interactive symposium format, with adequate time reserved after each lecture for questions and discussion.

Special appreciation is extended to Dr. Eugene Braunwald for his first-time participation, which strengthened the program considerably. Among Dr. Braunwald's many seminal contributions to cardiovascular medicine is the initial systematic description of HC with his colleagues at the National Institutes of Health 50 years ago (Figure 4).

Recalling this successful and important conference affords the opportunity to revisit many of the important principles and ideas relevant to HC, as presented by the assembled faculty.

Basic Principles

- HC is probably unrecognized clinically in most affected persons, with only the "tip of the iceberg" diagnosed.
- It is the most common genetic cardiovascular disease, with a prevalence of 1:500 in the general population, and about 600,000 affected individuals in the United States.
- HC is the most common cause of sudden death (SD) in the young, including trained athletes.
- HC is an important cause of cardiovascular disability, including heart failure and atrial fibrillation (AF)/stroke.
- Paradoxically, HC is often of little or no clinical significance and is frequently compatible with a normal life expectancy and longevity.
- The clinical, morphologic, and genetic expression is highly heterogeneous.
- It has a phenotypic expression, with asymmetric left ventricular (LV) hypertrophy that assumes diverse patterns, frequently including mild segmental hypertrophy (with normal LV mass).
- Other phenotypic features include disorganized cellular architecture, expanded interstitial matrix, replacement fibrosis, microvascular remodeling, enlarged/elongated mitral valve leaflets, and congenital anomalies of the mitral apparatus.

Genetics

- HC has extreme genetic heterogeneity, with 11 disease-causing genes and now >1,000 individual mutations, accounting for only 50% of patients with genetic testing.
- 80% of patients with positive genetic test results have MYBPC3 or MYH7 mutations.
- In China, the distribution of HC genes differs, with fewer MYBPC3 and MYH7 mutations and the apparent absence of some previously identified "malignant" mutations (i.e., Arg 403 Gln).
- A large proportion of HC mutations (about 2/3) are novel ("private"), occurring in only 1 family.
- Commercial genetic testing is now widely available; however, "variants of unknown significance" not uncommonly pose clinical dilemmas for interpretation.
- Family co-segregation studies represent the most productive strategy for resolving ambiguous mutations.
- Murine models offer potential clues to disease mechanisms, novel treatment strategies, and possible prevention of disease phenotypes.
- Sarcomeric mutations in the community might be associated with reduced penetrance and a lower risk of overt heart disease.
- Some HC-causing mutations (e.g., MyBPC3) might be more common variants responsible for cardiomyopathies in some parts of the world (e.g., Southeast Asia).
- Genetic testing of little value in predicting a patient's future prognosis but can provide a definitive HC diagnosis in at-risk family members or, selectively, when the clinical findings are ambiguous.
- HC phenocopies, with nonsarcomeric genetic substrates, can mimic true HC (e.g., Fabry's disease, lysosome-associated membrane protein-2 [LAMP2],

Minneapolis Heart Institute Foundation, Hypertrophic Cardiomyopathy Center, Minneapolis, Minnesota. Manuscript received November 19, 2009; revised manuscript received and accepted December 3, 2009.

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*Corresponding author: Tel: (612) 863-3996; fax: (612) 863-3875.

E-mail address: hcm.maron@mhif.org (B.J. Maron).

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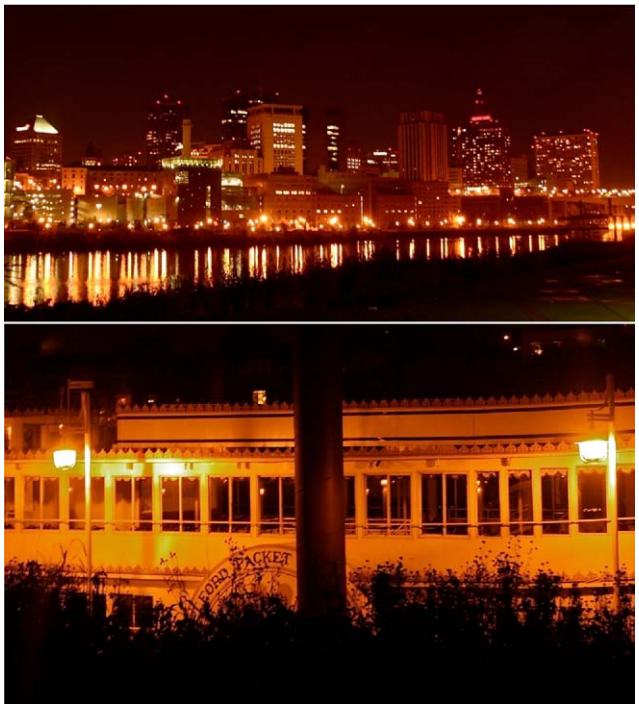

Figure 1. Twin Cities at night. *(Top)* St. Paul, Minnesota, panorama with Mississippi River in front. *(Bottom)* Mississippi River Boat, site of a dinner and excursion for faculty, guests, and registrants.

Figure 2. Faculty and other notables. *From upper left to right, top row:* Drs. Barry Maron, Iacopo Olivotto, Cristina Basso, and David Richmond; *second row from left:* Drs. Steve Ommen, Heidi Rehm, Franco Cecchi, Jinan Zhang, and Rick Nishimura; *third row from left:* Drs. Rutai Hui, Robert Hauser, Chris Semsarian, and Paolo Spirito; *bottom row from left:* Drs. Anna Woo, Joseph Dearani, Antonio Pelliccia, and Pravin Shah. Not shown: Mark Sherrid, Domenico Corrado, Christine Seidman, Michael Ackerman, Mark Estes, and Harry Lever.

Figure 3. Dr. Joseph Murgo *(Center)* with Drs. Martin Maron *(Left)* and Barry Maron *(Right).*

Table 1
Hypertrophic Cardiomyopathy Summit faculty and notable guests

Faculty/Guest Names	Location
Summit faculty*	
Barry J. Maron, MD (Director)	Minneapolis, MN
Christine E. Seidman, MD	Boston, MA
Heidi L. Rehm, PhD	Boston, MA
Martin S. Maron, MD	Boston, MA
Eugene Braunwald, MD	Boston, MA
E. Douglas Wigle, MD	Toronto, ON, Canada
Pravin M. Shah, MD	Newport, Beach, CA
Iacopo Olivotto, MD	Florence, Italy
Cristina Basso, MD	Padua, Italy
Franco Cecchi, MD	Florence, Italy
Paolo Spirito, MD	Genoa, Italy
Steven R. Ommen, MD	Rochester, MN
Michael J. Ackerman, MD, PhD	Rochester, MN
N. A. Mark Estes III, MD	Boston, MA
Robert G. Hauser, MD	Minneapolis, MN
Lisa Salberg	Rockaway, NJ
Christopher Semsarian, MD, PhD	Sydney, Australia
Rutai Hui, MD, PhD	Beijing, China
Antonio Pelliccia, MD	Rome, Italy
Domenico Corrado, MD, PhD	Padua, Italy
Mark V. Sherrid, MD	New York, NY
Joseph A. Dearani, MD	Rochester, MN
Anna Woo, MD	Toronto, ON, Canada
Rick Nishimura, MD	Rochester, MN
Harry Lever, MD	Cleveland, OH
Notable guests	
Joseph Murgo, MD	San Antonio, TX
David Richmond, MD	Sydney, Australia
Gunnar Gunnarsson, MD	Reykjavík, Iceland
Euan Ashley, MD	Palo Alto, CA
Charlene Day, MD	Ann Arbor, MI
Zinan Zhang, MD	Nanjing, China

* In order of their presentations.

Figure 4. "The Three Masters." Drs. Douglas Wigle (speaking at podium), Pravin Shah *(Center),* and Eugene Braunwald *(Right).*

protein kinase adenosine monophosphate-activated gamma regulatory-2 subunit [PRKAG2], Noonan syndrome.
- LAMP2 cardiomyopathy is a lysosome storage disease and HC phenocopy; it is associated with massive LV hypertrophy and death before 25 years of age; and it is refractory to implantable cardioverter-defibrillator (ICD) therapy.
- Family screening using echocardiography/cardiovascular magnetic resonance imaging and electrocardiography is recommended, usually beginning at 12 years of age and every 12 to 18 months thereafter through adolescence.
- A 2-month-old child, mutation-free by virtue of a preimplantation genetic diagnosis was presented to the conference by a HC patient (who is also the father).

Cardiovascular Magnetic Resonance Imaging

- Cardiovascular magnetic resonance imaging is a noninvasive, high-resolution, tomographic technique with considerable imaging power for HC.
- Cardiovascular magnetic resonance imaging can detect hypertrophy in regions of the left ventricle that are not reliably identified using echocardiography (i.e., anterolateral LV free wall/apex).
- The predominant site of hypertrophy is usually at the 1-o'clock position in the short-axis view at the confluence of the anterior septum with anterior free wall.
- Cardiovascular magnetic resonance imaging can detect LV apical aneurysms with regional scarring (with or without thrombi) that can alter management strategies.
- Elongated mitral valve leaflets represent a primary disease abnormality.
- Hypertrophy can also extend into contiguous portions of the right ventricle.
- Contrast-cardiovascular magnetic resonance imaging offers the opportunity for in vivo recognition of myocardial replacement fibrosis (as delayed enhancement).
- Delayed enhancement is related to the occurrence of ventricular tachyarrhythmias on ambulatory Holter electrocardiograms. No conclusive evidence is available at present that delayed enhancement is a reliable, independent marker for increased SD risk.

Figure 5. A 51-year-old Duluth, Minnesota, kindergarten teacher, Karen, with a primary prevention ICD (because of a family history of HC-related SD as the sole risk factor), which has terminated ventricular fibrillation 3 times in 6 years.

Clinical Course

- The presentation of HC includes a wide spectrum of ages, from infants to the elderly.
- The overall annual mortality rate has been 1%, greatly different from the 4% to 6% annually in skewed and now-obsolete tertiary center data.
- The pathways of disease progression in HC are distinct and diverse, including SD, progressive heart failure, end-stage phase, and AF.
- All complications are treatable with cardioactive drugs, ICDs, heart transplantation, and surgical septal myectomy (or, alternatively, alcohol ablation), depending on the patient's clinical profile.

Risk Stratification and SD

- Previous cardiac arrest/sustained ventricular tachycardia, with or without hemodynamic instability, are secondary prevention risk factors.
- No single dominant/quantitative risk factor has been found for primary prevention.
- The 5 major primary prevention risk factors are a family history of SD; unexplained, recent syncope; hypotensive/attenuated exercise blood pressure; multiple, repetitive, or prolonged nonsustained ventricular tachycardia on serial Holter electrocardiograms; and massive LV hypertrophy (wall thickness $\geq$30 mm).
- These risk factors are most applicable to patients $<$40 years old.
- Other disease features regarded as contributors to risk or arbitrators of ICD decisions include LV apical aneurysm with regional scarring; end-stage phase; intense competitive sports (modifiable); and alcohol septal ablation (selected patients).
- The risk markers are associated with high-negative, but low-positive, predictive value.

Prevention of SD

- Pharmacologic strategies do not provide absolute protection against SD.
- ICDs are reliable in terminating ventricular tachycardia/ventricular fibrillation in high-risk patients (11% annually for secondary and 4% annually for primary prevention).
- The principles of SD prevention: (1) current risk factors represent a useful and effective guide; (2) a single major risk factor can be sufficient to consider an ICD; (3) all risk factor patients may not be obligated to an ICD recommendation; (4) the risk factors cannot be summed numerically to ascertain risk level; (5) the absence of conventional risk factors does not confer immunity from SD; and (6) transparency is important, and ambiguous ICD decisions can be determined by individual physician clinical judgment and input from the fully informed patient.
- ICDs have altered the clinical course of HC and provide the possible opportunity for survival to normal or near-normal longevity for many patients (Figure 5).

Electrophysiologic Principles

- Device complications (5% annually, with a prevalence of 25%), in particular inappropriate shocks are most common in younger patients and those with AF, representing an important factor to be considered in implant decisions.
- The complication risks of ICD therapy are greater in young patients with HC.
- ICD complications can be minimized in experienced centers.
- Some early occurring ICD shocks for ventricular tachycardia/ventricular fibrillation might be pro-arrhythmic and not necessarily "life-saving" surrogates of SD.
- No evidence is available in HC that appropriate ICD interventions simply "trade" SD risk for future heart failure demise.
- The mechanisms of SD are multifactorial, complex, and incompletely defined.

Defibrillator Industry and HC

- Recent, numerous recalls related to ICD leads and generator failure (not confined to any single manufacturer) have significantly affected patients with HC.
- ICD lead models show important differences in performance; for instance, the small-diameter Sprint Fidelis (Medtronic, Minneapolis, Minnesota) lead failure rate is 6 times that of other leads.
- Because patients with HC tend to be young and long-lived, the design of ICD leads with proven effectiveness and durability is imperative.
- Proposed solutions to lead-related and other device problems include greater transparency in reporting by manufacturers, support for registries, understanding of past lessons, and long-term clinical testing before new products are introduced into widespread use.

Myocardial Ischemia

- Most patients have reported transient angina or atypical chest discomfort.
- Paradoxically, active myocardial ischemia is usually a clinically "silent," but an important HC disease mechanism associated with microvascular remodeling and dysfunction ("small vessel disease"), with resultant scarring (evident at autopsy and with contrast-cardiovascular magnetic resonance imaging).
- Ischemia is of clinical relevance in HC, as a determinant of outcome, with progressive heart failure, LV remodeling, and premature death.
- Myocardial ischemia can be detected quantitatively using positron emission tomography, but that is not yet a part of routine clinical assessment, nor is a treatment strategy available to mitigate ischemia.
- Coronary arterial myocardial bridging is a common morphologic component of HC; however, it is not a reliable SD risk factor.
- The pathways for progressive heart failure have been identified, i.e., end-stage with extensive scarring, diastolic dysfunction with or without restrictive LV filling, and LV outflow tract obstruction, with AF a common component of each.

LV Outflow Obstruction

- LV outflow obstruction is a determinant of progressive heart failure/cardiovascular death, which results from chronic elevation in LV pressure/wall stress.
- It is a common disease feature in 70% of patients, either at rest or with physiologic (exercise) provocation.
- The highest outflow gradients have been linked to severe heart failure.
- The relation between LV outflow obstruction and SD risk is relatively weak.

End-Stage HC

- End-stage HC is an uncommon but profound disease consequence in about 3% of patients (incidence 1% annually), with 10% annual mortality/event rate.
- It is characterized by systolic dysfunction and LV remodeling, often with cavity enlargement and/or wall thinning, and is evident at a wide age range (mean 45 years).
- End-stage HC appears to result from "small vessel disease" ischemia with widespread scarring evident with contrast-cardiovascular magnetic resonance imaging or at autopsy.
- End-stage disease is the only indication for heart transplantation in patients with HC; post-transplant survival is similar, if not slightly longer, than for patients with other cardiac diseases.

Atrial Fibrillation

- AF is the most prevalent sustained arrhythmia in patients with HC, affecting 20% of patients, most commonly those >50 years of age.
- AF is linked to left atrial dilation and is a determinant of progressive heart failure and embolic stroke (rather than SD).

- A combination of AF and outflow obstruction at rest is a particularly unfavorable finding.
- Aggressive management strategies, including drug therapy and, more recently, radiofrequency ablation to control the heart rate or maintain sinus rhythm, are similar to those used for AF in other structural heart diseases.
- Amiodarone is the most commonly used drug to prevent AF recurrence.
- For some symptomatic patients with drug-refractory AF, radiofrequency ablation may be potentially effective and can postpone the need for chronic pharmacologic treatment.
- Left atrial remodeling and dilation predict mortality and heart failure (independent of AF).
- A primary atrial myopathy responsible for AF in patients with HC is possible.

Surgical Septal Myectomy Versus Percutaneous Alcohol Ablation

- Septal myectomy is the preferred treatment option for the vast majority of patients with drug-refractory HC and marked obstruction.
- Surgery has been associated with substantial long-term clinical improvement in 85% of patients, with survival similar to that of the general population (including a reduced rate of SD and appropriate ICD intervention).
- The operative mortality rate at the most experienced surgical centers has been $<1\%$ during the past decade.
- Alcohol ablation is an alternative option for selected patients judged to be suboptimal operative candidates because of advanced age, substantial co-morbidities, or a strong preference for nonsurgical strategies.
- Alcohol ablation has been associated with sustained ventricular tachyarrhythmias in 10% of patients.
- Surgery at experienced myectomy centers conveys a lower operative mortality and morbidity and greater hemodynamic and symptomatic benefit compared to alcohol ablation.
- A randomized trial to resolve the surgery versus alcohol ablation debate is not feasible.

HC Worldwide

- HC is a global disease, reported from >50 countries, on all continents.
- China has an estimated 1 million patients with HC.
- The clinical and genetic expression is similar in patients worldwide, including, most commonly, North America, Europe, Australia, China, and Japan.
- Apical HC is more common in Japan than in the United States.
- In Italy, mandatory national screening of competitive athletes with electrocardiography has identified those with HC and reduced mortality from cardiomyopathy.
- Australia (population 21 million) has developed a comprehensive national HC referral center.

Patient Advocacy/Support

- The Hypertrophic Cardiomyopathy Association is an Internet-based organization dedicated to the accurate transmission of information about HC; they also hold regional meetings and an annual national conference in New Jersey.
- The Hypertrophic Cardiomyopathy Association provides support, advocacy, and education to patients, families, the medical community, and the public.
- It has been active since 1996 with $>200,000$ Web site visitors annually (available at: www.4HCM.org), and 4,700 families enrolled.
- It promotes the creation of Centers of Excellence focused on the diagnosis and management of this disease.

The 3 Masters

Eugene Braunwald, MD: Eugene Braunwald, MD (Figure 4) was responsible for the clinical identification of the first patient with HC (who has, in fact, survived to date), and the initial comprehensive description of this disease at the National Institutes of Health almost 50 years ago in the early 1960s. He reflected on the unique and remarkable experience (and challenge) of describing and characterizing this exceedingly complex disease for the first time, as well as the directions those observations have taken us.

Douglas Wigle, MD: Douglas Wigle, MD (Figure 4) played a key role in formulating the concept of LV outflow tract obstruction in HC, at a time when its very existence as a pathophysiologic principle in this disease was challenged. In 1987, he wrote: "To deny the presence of obstruction to LV outflow in HC is to deny patients appropriate medical and/or surgical therapy." A participant in the "Great Obstruction Debate" with Drs. Criley (Johns Hopkins) and Ross (National Institutes of Health) at the 1966 American Heart Association meeting in New York, New York.

Pravin Shah, MD: Pravin Shah, MD (Figure 4) was responsible for the novel description of systolic anterior motion of the mitral valve with early M-mode echocardiography, recognized as the mechanism by which dynamic outflow obstruction occurs in HC.

We also recollect another master of HC, Andrew G. Morrow, MD, of the National Institutes of Health, who developed and performed the septal myectomy operation, which, appropriately, bears his name.