

9-14-2010

## Research priorities in hypertrophic cardiomyopathy: report of a Working Group of the National Heart, Lung, and Blood Institute.

Thomas Force

*Center for Translational Medicine, Cardiology Division, Thomas Jefferson University*

Robert O Bonow

*Department of Medicine, Northwestern University School of Medicine*

Steven R Houser

*Department of Physiology, Temple University School of Medicine*

Follow this and additional works at: <https://jdc.jefferson.edu/transmedfp>

R. John Solaro

*Department of Physiology, University of Illinois School of Medicine*

[Let us know how access to this document benefits you](#)

Ray E Hershberger

*Cardiovascular Division, Department of Medicine, University of Miami Miller School of Medicine*

### Recommended Citation

Force, Thomas; Bonow, Robert O; Houser, Steven R; Solaro, R John; Hershberger, Ray E; Adhikari, See next page for additional authors

Bishow; Anderson, Mark E; Boineau, Robin; Byrne, Barry J; Cappola, Thomas P; Kalluri, Raghu;

LeWinter, Martin M; Maron, Martin S; Molkentin, Jeffery D; Ommen, Steve R; Regnier, Michael;

Tang, W H Wilson; Tian, Rong; Konstam, Marvin A; Maron, Barry J; and Seidman, Christine E,

"Research priorities in hypertrophic cardiomyopathy: report of a Working Group of the National Heart, Lung, and Blood Institute." (2010). *Center for Translational Medicine Faculty Papers*.

Paper 5.

<https://jdc.jefferson.edu/transmedfp/5>

This Article is brought to you for free and open access by the Jefferson Digital Commons. The Jefferson Digital Commons is a service of Thomas Jefferson University's [Center for Teaching and Learning \(CTL\)](#). The Commons is a showcase for Jefferson books and journals, peer-reviewed scholarly publications, unique historical collections from the University archives, and teaching tools. The Jefferson Digital Commons allows researchers and interested readers anywhere in the world to learn about and keep up to date with Jefferson scholarship. This article has been accepted for inclusion in Center for Translational Medicine Faculty Papers by an authorized administrator of the Jefferson Digital Commons. For more information, please contact: [JeffersonDigitalCommons@jefferson.edu](mailto:JeffersonDigitalCommons@jefferson.edu).

---

**Authors**

Thomas Force, Robert O Bonow, Steven R Houser, R John Solaro, Ray E Hershberger, Bishow Adhikari, Mark E Anderson, Robin Boineau, Barry J Byrne, Thomas P Cappola, Raghu Kalluri, Martin M LeWinter, Martin S Maron, Jeffery D Molkenin, Steve R Ommen, Michael Regnier, W H Wilson Tang, Rong Tian, Marvin A Konstam, Barry J Maron, and Christine E Seidman

## Research Priorities in Hypertrophic Cardiomyopathy Report of a Working Group of the National Heart, Lung, and Blood Institute

Thomas Force, MD; Robert O. Bonow, MD; Steven R. Houser, PhD; R. John Solaro, PhD;  
Ray E. Hersherberger, MD; Bishow Adhikari, PhD; Mark E. Anderson, MD, PhD; Robin Boineau, MD;  
Barry J. Byrne, MD, PhD; Thomas P. Cappola, MD; Raghu Kalluri, MD, PhD;  
Martin M. LeWinter, MD; Martin S. Maron, MD; Jeffery D. Molkenin, PhD; Steve R. Ommen, MD;  
Michael Regnier, PhD; W.H. Wilson Tang, MD; Rong Tian, PhD; Marvin A. Konstam, MD;  
Barry J. Maron, MD; Christine E. Seidman, MD

**H**ypertrophic cardiomyopathy (HCM) is a myocardial disorder characterized by left ventricular (LV) hypertrophy without dilatation and without apparent cause (ie, it occurs in the absence of severe hypertension, aortic stenosis, or other cardiac or systemic diseases that might cause LV hypertrophy). Numerous excellent reviews and consensus documents provide a wealth of additional background.<sup>1–8</sup> HCM is the leading cause of sudden death in young people and leads to significant disability in survivors. It is caused by mutations in genes that encode components of the sarcomere. Cardiomyocyte and cardiac hypertrophy, myocyte disarray, interstitial and replacement fibrosis, and dysplastic intramyocardial arterioles characterize the pathology of HCM. Clinical manifestations include impaired diastolic function, heart failure, tachyarrhythmia (both atrial and ventricular), and sudden death. At present, there is a lack of understanding of how the mutations in genes encoding sarcomere proteins lead to the phenotypes described above. Current therapeutic approaches have focused on the prevention of sudden death, with implantable cardioverter defibrillator placement in high-risk patients. But medical therapies have largely focused on alleviating symptoms of the disease, not on altering its natural history. The present Working Group of the National Heart, Lung, and Blood Institute brought together clinical, translational, and basic scientists with the overarching goal of identifying novel strategies to prevent the phenotypic expression

of disease. Herein, we identify research initiatives that we hope will lead to novel therapeutic approaches for patients with HCM.

### Epidemiology

The epidemiology of HCM suggests that it is present in  $\approx 1$  in 500 adults.<sup>9</sup> Because of the delay in phenotypic expression of the disease, HCM is not commonly recognized clinically in young children, but when it is, it is much more frequently recognized in males.<sup>10</sup> This is likely due to greater penetrance in young males.<sup>11,12</sup> HCM is underdiagnosed clinically in blacks and in women, yet women tend to present with more marked heart failure than men when they are diagnosed later in life.<sup>13,14</sup> There is no overall difference in mortality, including sudden cardiac death, between men and women, although sudden cardiac death on the athletic field predominantly occurs in men.

### Genetic Cause

Extensive investigation has shown that at least 50% of HCM cases can be traced to a specific genetic cause. This probably underestimates the true percentage of genetically based HCM, because current mutation-screening platforms typically examine only 8 to 10 genes because of unfavorable cost-benefit assessments. For example, current platforms do not examine titin (owing to its size) or myozenin-2 (because relatively few mutations have been defined in this gene).<sup>15</sup>

---

From the Center for Translational Medicine and Cardiology Division (T.F.), Thomas Jefferson University, Philadelphia, Pa; Department of Medicine (R.O.B.), Northwestern University School of Medicine, Chicago, Ill; Department of Physiology (S.R.H.), Temple University School of Medicine, Philadelphia, Pa; Department of Physiology (R.J.S.), University of Illinois School of Medicine, Chicago, Ill; Cardiovascular Division (R.E.H.), Department of Medicine, University of Miami Miller School of Medicine, Miami, Fla; National Heart, Lung, and Blood Institute (B.A., R.B.), National Institutes of Health, Bethesda, Md; Department of Medicine (M.E.A.), University of Iowa Carver College of Medicine, Iowa City, Iowa; Powell Gene Therapy Center (B.J.B.), College of Medicine, University of Florida, Gainesville, Fla; Cardiology Division (T.P.C.), University of Pennsylvania School of Medicine, Philadelphia, Pa; Division of Matrix Biology (R.K.), Department of Medicine, Beth Israel-Deaconess Medical Center, Harvard Medical School, Boston, Mass; Cardiology Unit (M.M.L.), Department of Medicine, University of Vermont College of Medicine, Burlington, Vt; Tufts Medical Center (M.S.M., M.A.K.), Tufts University School of Medicine, Boston, Mass; Howard Hughes Medical Institute (J.D.M.), Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio; Mayo Clinic (S.R.O.), Rochester, Minn; Department of Bioengineering (M.R.), University of Washington, Seattle, Wash; Cleveland Clinic Foundation (W.H.W.T.), Cleveland, Ohio; Mitochondrial and Metabolism Center (R.T.), University of Washington, Seattle, Wash; Hypertrophic Cardiomyopathy Center (B.J.M.), Minneapolis Heart Institute Foundation, Minneapolis, Minn; and Howard Hughes Medical Institute (C.E.S.), Brigham and Women's Hospital, Harvard Medical School, Boston, Mass.

Guest Editor for this article was Gregg C. Fonarow, MD.

**The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/cgi/content/full/122/11/1130/DC1>.**

Correspondence to Thomas Force, MD, Center for Translational Medicine and Cardiology Division, Thomas Jefferson University, College Bldg, Room 315, 1025 Walnut St, Philadelphia, PA 19107. E-mail [thomas.force@jefferson.edu](mailto:thomas.force@jefferson.edu)  
(*Circulation*. 2010;122:1130-1133.)

© 2010 American Heart Association, Inc.

*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.110.950089

Moreover, when strict clinical criteria are used for diagnosis, including family history, mutation detection approaches 70%.

HCM is a genetic disease of sarcomere proteins,<sup>5,16</sup> with mutations in the genes that encode  $\beta$ -myosin heavy chain (*MYH7*) and myosin binding protein C (*MYBPC3*) accounting for  $\approx$ 80% to 85% of cases with identified mutations in most series.<sup>4,17–19</sup> Mutations in the troponins cardiac troponin T (*TNNT2*) and troponin I (*TNNI3*) and  $\alpha$ -tropomyosin (*TPM1*) are also relatively common, collectively representing 10% to 15% of additional genetic causes for all HCM cases.<sup>4,17,19</sup> These and the myosin light chains (*MYL2*, *MYL3*) and  $\alpha$ -cardiac actin (*ACTC*) are the 8 genes most commonly involved in HCM.

### Rare Genetic Causes

Mutations in several other genes that encode sarcomere or sarcomere-related proteins have been implicated in HCM, including cardiac troponin C (*TNNC1*),  $\alpha$ -myosin heavy chain (*MYH6*), and cardiac myosin light chain kinase 2 (*MYLK2*). In addition, several other genes that encode non-sarcomere proteins, including caveolin 3 (*CAV3*), calreticulin (*CALR3*), junctophilin-2 (*JPH2*), phospholamban (*PLN*), and the mitochondrial tRNA-encoding genes *MTTG* and *MTTI*, produce clinical features that mimic HCM.<sup>4,20</sup> The relationship of HCM caused by sarcomere protein gene mutations to these disorders is unclear.<sup>5,16</sup>

### Unknown Causes

The apparent absence of mutations in patients with a clinical diagnosis of HCM indicates an important gap in our knowledge. Mutation testing can be particularly uninformative in 3 clinical scenarios in which family history is negative: (1) Hypertrophy that occurs very early in childhood; (2) hypertrophy that is only recognized after middle age; and (3) hypertrophy that is limited to the ventricular apex.<sup>21</sup> The cause of these conditions is not clear.

### Disease Mechanisms

The disease mechanisms of HCM remain incompletely understood. Postulated mechanisms include (1) a dominant negative function (ie, a “poison peptide,” wherein the mutant gene encodes a protein that interferes with the function of the normal allele); (2) haploinsufficiency (leading to an insufficient quantity of the normally functioning sarcomere protein); and/or (3) impaired myocardial energetics and decreased energy reserve.<sup>8,22,23</sup> The lack of a definitive link between mutations and an understanding of the pathogenesis/molecular mechanisms that drive the expression of the HCM phenotype is a significant gap in our understanding of the disease.

### Clinical Genetics

Allelic heterogeneity (each family having a so-called private mutation) is particularly common in HCM. Approximately 500 mutations have been noted in the medical literature, but the number of identified mutations in various private databases suggests the true number is more than 1000. HCM demonstrates age-dependent penetrance, affecting 50% to 80% and 95% of individuals by age 30 years and ages 50 to 60 years, respectively.<sup>24</sup> Recent estimates of 1% annual mortality in HCM differ significantly from earlier estimates (3% to 6%) that were

based on referral populations of high-risk groups to HCM centers.<sup>25–27</sup> Survival to 75 years or beyond has been estimated in  $\approx$ 25% of an unselected HCM cohort.<sup>28</sup>

### Compound Heterozygosity

Two to five percent of patients with HCM harbor 2 mutations (compound or double heterozygosity) or are homozygous for a mutation,<sup>4,18,29,30</sup> and these patients display more severe and/or earlier onset of disease.<sup>29,30</sup>

### Genotype/Phenotype Relationships

Despite the significant clinical heterogeneity observed even for the same mutation within families or between families,<sup>31–35</sup> as well as the variable penetrance, which alters clinical onset and severity of disease, genotype/phenotype relationships of sarcomere gene mutations clearly have advanced our understanding of the disease and, in some cases, have allowed identification of relatively low- versus high-risk patients.<sup>36,37</sup> Some genotype/phenotype relationships that have stood the test of time include *MYH7* mutations, which are associated with earlier onset and more extensive hypertrophy.<sup>8,33,35</sup> More specifically, the myosin 403 mutation is associated with increased risk of heart failure and sudden death, and the myosin 719 mutation leads to a marked increase in heart failure. Others include the relatively limited hypertrophic response with *TNNT2* mutations<sup>34,38,39</sup> and the incomplete penetrance and relatively later onset of HCM from *MYBPC3* mutations.<sup>31,36,40</sup> That said, multiple poorly understood mechanisms contribute to heterogeneity of presentation, and these include environmental inputs, sex,<sup>10</sup> and genetic and epigenetic modifiers.

### Key Morphological and Clinical Components of Genetically Mediated HCM

Cardiomyocyte and cardiac hypertrophy, myocyte disarray, interstitial and replacement fibrosis, and dysplastic intramyocardial arterioles characterize the pathology of HCM. Clinical manifestations include impaired diastolic function, tachyarrhythmia (both atrial and ventricular), and sudden death.<sup>41–44</sup> Accepted risk factors for sudden cardiac death include prior cardiac arrest from ventricular fibrillation, spontaneous sustained ventricular tachycardia, family history of premature sudden death, unexplained syncope, LV wall thickness  $\geq$ 30 mm, abnormal blood pressure response to exercise, and nonsustained ventricular tachycardia.<sup>28,43</sup> Additional predictors include the presence of LV apical aneurysms and the end stage of disease.<sup>45,46</sup>

A consensus document<sup>1</sup> and review<sup>47</sup> of clinical management of arrhythmias and sudden cardiac death in HCM are available. Clinically apparent atrial fibrillation develops in at least 20% of patients with HCM,<sup>48</sup> but the true incidence is likely higher than that. Atrial fibrillation is a risk factor for thromboembolic disease, including stroke.<sup>1</sup> Molecular mechanisms that regulate the phenotypic expression of the various pathologies and how these might drive arrhythmogenesis in HCM are poorly understood.

### Genetic Causes of LV Hypertrophy Not Involving Sarcomere Mutations

LV hypertrophy can result from gene mutations that alter proteins with functions that are unrelated to the sarcomere. These

include Fabry disease, glycogen storage disorders (PRKAG2 cardiomyopathy and Pompe disease), lysosomal disorders (X-linked lysosome-associated membrane protein gene cardiomyopathy), and several syndromes (ie, Noonan, lentiginos, ECG abnormalities, ocular hypertelorism, pulmonary valve stenosis, abnormal genitalia, retardation of growth, and deafness [LEOPARD], and Costello). The clinical manifestations and patient courses associated with these are different from HCM.<sup>8,17,49–51</sup> These phenocopies are not discussed further herein.

### Rationale for Investing in Research on HCM

The rationale for investing in research in HCM is supported by the following: (1) HCM is the most common genetic heart disease and affects individuals at every age; (2) HCM is the most common cause of sudden death in young people; (3) HCM is an important cause of heart failure disability; (4) HCM can be viewed as a paradigm for the potential opportunities provided by harnessing modern genetic science in medicine to make gene-based diagnosis and prediction a reality; (5) gaps in our basic understanding of mechanisms of disease are substantial, but already, insights provided by studies in patients and in animal models of HCM suggest creative strategies to alter the natural history of this disease; and (6) these insights also promise a greater understanding of the molecular pathophysiology of other, nongenetic causes of hypertrophy. Thus, we believe that there are unparalleled opportunities in the immediate and near future to translate basic insights about HCM into new clinical models for diagnosis, prevention, and therapy.

### Critical Deficits in Our Understanding of HCM Pathogenesis Define Research Initiatives

In the online-only Data Supplement to this report, we define key deficits in our understanding of HCM, thereby leading into a delineation of research initiatives for the future. The areas of research will be broken down into clinical, translational, and basic science sections, but these divisions are clearly arbitrary and only serve as an organizational (and not operational) tool. In fact, we will strive to maintain connections among the 3 divisions, focusing on common deficits in our understanding.

### Sources of Funding

The following receive research grants from the National Institutes of Health (NIH), Howard Hughes Medical Institute (HHMI), the Fondation Leducq (FL), The American Heart Association (AHA), or other sources: Dr Force (NIH, The Kahn Foundation, the Scarperi Family, and AHA), Dr Anderson (NIH, FL), Dr Houser (NIH), Dr LeWinter (NIH), Dr Molkentin (NIH, HHMI, and FL), Dr Seidman (NIH, HHMI, and FL), Dr Solaro (NIH), Dr Byrne (NIH), Dr Maron (NIH), Dr Tang (NIH), Dr Tian (NIH), Dr Regnier (NIH), Dr Hershberger (NIH), Dr Bonow (NIH), Dr Cappola (NIH), and Dr Kalluri (NIH).

### Disclosures

Dr Solaro serves on the scientific advisory board of Cytokinetics, Inc. Dr Byrne has received honoraria from Amicus Therapeutics and has ownership interest in AGTC, Inc. Dr Cappola has received other research support from Abbott Diagnostics. Dr M. Maron serves as a consultant/advisory board member for PGX Health and Genzyme. Dr Tang has received other research support from Abbott Labs and has served as a consultant to Medtronic Inc. Dr B. Maron received a research grant and honoraria from Medtronic, Inc and has served as

a consultant to Gene Dx. Dr Konstam has served as a consultant for or received research support from Merck and Co, Boehringer-Ingelheim, Johnson and Johnson, and Trevena. The remaining authors report no conflicts.

### References

1. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH III, Spirito P, Ten Cate FJ, Wigle ED. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol*. 2003;42:1687–1713.
2. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA*. 2002;287:1308–1320.
3. Ho CY, Seidman CE. A contemporary approach to hypertrophic cardiomyopathy. *Circulation*. 2006;113:e858–e862.
4. Marian AJ. Genetic determinants of cardiac hypertrophy. *Curr Opin Cardiol*. 2008;23:199–205.
5. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association scientific statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation*. 2006;113:1807–1816.
6. Taylor MR, Carniel E, Mestroni L. Familial hypertrophic cardiomyopathy: clinical features, molecular genetics and molecular genetic testing. *Expert Rev Mol Diagn*. 2004;4:99–113.
7. Ashrafian H, Watkins H. Reviews of translational medicine and genomics in cardiovascular disease: new disease taxonomy and therapeutic implications: cardiomyopathies: therapeutics based on molecular phenotype. *J Am Coll Cardiol*. 2007;49:1251–1264.
8. Keren A, Syrris P, McKenna WJ. Hypertrophic cardiomyopathy: the genetic determinants of clinical disease expression. *Nat Clin Pract Cardiovasc Med*. 2008;5:158–168.
9. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults: echocardiographic analysis of 4111 subjects in the CARDIA Study: Coronary Artery Risk Development in (Young) Adults. *Circulation*. 1995;92:785–789.
10. Morita H, Rehm HL, Menesses A, McDonough B, Roberts AE, Kucherlapati R, Towbin JA, Seidman JG, Seidman CE. Shared genetic causes of cardiac hypertrophy in children and adults. *N Engl J Med*. 2008;358:1899–1908.
11. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, Lurie PR, McCoy KL, McDonald MA, Messere JE, Colan SD. The incidence of pediatric cardiomyopathy in two regions of the United States. *N Engl J Med*. 2003;348:1647–1655.
12. Nugent AW, Daubeney PE, Chondros P, Carlin JB, Cheung M, Wilkinson LC, Davis AM, Kahler SG, Chow CW, Wilkinson JL, Weintraub RG. The epidemiology of childhood cardiomyopathy in Australia. *N Engl J Med*. 2003;348:1639–1646.
13. Olivetto I, Maron MS, Adabag AS, Casey SA, Vargiu D, Link MS, Udelson JE, Cecchi F, Maron BJ. Gender-related differences in the clinical presentation and outcome of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2005;46:480–487.
14. Maron BJ, Carney KP, Lever HM, Lewis JF, Barac I, Casey SA, Sherrid MV. Relationship of race to sudden cardiac death in competitive athletes with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2003;41:974–980.
15. Osio A, Tan L, Chen SN, Lombardi R, Nagueh SF, Shete S, Roberts R, Willerson JT, Marian AJ. Myozenin 2 is a novel gene for human hypertrophic cardiomyopathy. *Circ Res*. 2007;100:766–768.
16. Maron BJ, Seidman CE, Ackerman MJ, Towbin JA, Maron MS, Ommen SR, Nishimura RA, Gersh BJ. How should hypertrophic cardiomyopathy be classified? What's in a name? Dilemmas in nomenclature characterizing hypertrophic cardiomyopathy and left ventricular hypertrophy. *Circ Cardiovasc Genet*. 2009;2:81–85.
17. Cirino AL, Ho C. Familial hypertrophic cardiomyopathy overview. GeneTests Web site (<http://www.genetests.org>). University of Washington, Seattle. Available at: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=hyper-card>. Accessed August 13, 2008.
18. Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C, Benaiche A, Isnard R, Dubourg O, Burban M, Gueffet JP, Millaire A, Desnos M,

- Schwartz K, Hainque B, Komajda M. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation*. 2003;107:2227–2232.
19. Ackerman MJ. Genetic testing for risk stratification in hypertrophic cardiomyopathy and long QT syndrome: fact or fiction? *Curr Opin Cardiol*. 2005;20:175–181.
  20. Bos JM, Ommen SR, Ackerman MJ. Genetics of hypertrophic cardiomyopathy: one, two, or more diseases? *Curr Opin Cardiol*. 2007;22:193–199.
  21. Arad M, Penas-Lado M, Monserrat L, Maron BJ, Sherrid M, Ho CY, Barr S, Karim A, Olson TM, Kamisago M, Seidman JG, Seidman CE. Gene mutations in apical hypertrophic cardiomyopathy. *Circulation*. 2005;112:2805–2811.
  22. Marston S, Copeland O, Jacques A, Livesey K, Tsang V, McKenna WJ, Jalilzadeh S, Carballo S, Redwood C, Watkins H. Evidence from human myectomy samples that MYBPC3 mutations cause hypertrophic cardiomyopathy through haploinsufficiency. *Circ Res*. 2009;105:219–222.
  23. Crilley JG, Boehm EA, Blair E, Rajagopalan B, Blamire AM, Styles P, McKenna WJ, Ostman-Smith I, Clarke K, Watkins H. Hypertrophic cardiomyopathy due to sarcomeric gene mutations is characterized by impaired energy metabolism irrespective of the degree of hypertrophy. *J Am Coll Cardiol*. 2003;41:1776–1782.
  24. Charron P. Clinical genetics in cardiology. *Heart*. 2006;92:1172–1176.
  25. Elliott PM, Gimeno JR, Thaman R, Shah J, Ward D, Dickie S, Tome Esteban MT, McKenna WJ. Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. *Heart*. 2006;92:785–791.
  26. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almqvist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. *JAMA*. 1999;281:650–655.
  27. Maron BJ, Olivetto I, Spirito P, Casey SA, Bellone P, Gohman TE, Graham KJ, Burton DA, Cecchi F. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. *Circulation*. 2000;102:858–864.
  28. Maron BJ, Casey SA, Hauser RG, Aeppli DM. Clinical course of hypertrophic cardiomyopathy with survival to advanced age. *J Am Coll Cardiol*. 2003;42:882–888.
  29. Ingles J, Doolan A, Chiu C, Seidman J, Seidman C, Semsarian C. Compound and double mutations in patients with hypertrophic cardiomyopathy: implications for genetic testing and counselling. *J Med Genet*. 2005;42:e59.
  30. Olivetto I, Girolami F, Ackerman MJ, Nistri S, Bos JM, Zachara E, Ommen SR, Theis JL, Vaubel RA, Re F, Armentano C, Poggesi C, Torricelli F, Cecchi F. Myofibrillar protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. *Mayo Clin Proc*. 2008;83:630–638.
  31. Charron P, Dubourg O, Desnos M, Bennaceur M, Carrier L, Camproux AC, Isnard R, Hagege A, Langlard JM, Bonne G, Richard P, Hainque B, Bouhour JB, Schwartz K, Komajda M. Clinical features and prognostic implications of familial hypertrophic cardiomyopathy related to the cardiac myosin-binding protein C gene. *Circulation*. 1998;97:2230–2236.
  32. Charron P, Dubourg O, Desnos M, Isnard R, Hagege A, Bonne G, Carrier L, Tesson F, Bouhour JB, Buzzi JC, Feingold J, Schwartz K, Komajda M. Genotype-phenotype correlations in familial hypertrophic cardiomyopathy: a comparison between mutations in the cardiac protein-C and the beta-myosin heavy chain genes. *Eur Heart J*. 1998;19:139–145.
  33. Van Driest SL, Jaeger MA, Ommen SR, Will ML, Gersh BJ, Tajik AJ, Ackerman MJ. Comprehensive analysis of the beta-myosin heavy chain gene in 389 unrelated patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2004;44:602–610.
  34. Watkins H, McKenna WJ, Thierfelder L, Suk HJ, Anan R, O'Donoghue A, Spirito P, Matsumori A, Moravec C, Seidman JG, Seidman CE. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med*. 1995;332:1058–1064.
  35. Watkins H, Rosenzweig A, Hwang DS, Levi T, McKenna W, Seidman CE, Seidman JG. Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy. *N Engl J Med*. 1992;326:1108–1114.
  36. Erdmann J, Raible J, Maki-Abadi J, Hummel M, Hamann J, Wollnik B, Frantz E, Fleck E, Hetzer R, Regitz-Zagrosek V. Spectrum of clinical phenotypes and gene variants in cardiac myosin-binding protein C mutation carriers with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2001;38:322–330.
  37. Van Driest SL, Vasile VC, Ommen SR, Will ML, Tajik AJ, Gersh BJ, Ackerman MJ. Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2004;44:1903–1910.
  38. Moolman JC, Corfield VA, Posen B, Ngumbela K, Seidman C, Brink PA, Watkins H. Sudden death due to troponin T mutations. *J Am Coll Cardiol*. 1997;29:549–555.
  39. Mogensen J, Kubo T, Duque M, Uribe W, Shaw A, Murphy R, Gimeno JR, Elliott P, McKenna WJ. Idiopathic restrictive cardiomyopathy is part of the clinical expression of cardiac troponin I mutations. *J Clin Invest*. 2003;111:209–216.
  40. Niimura H, Bachinski LL, Sangwatanaroj S, Watkins H, Chudley AE, McKenna W, Kristinsson A, Roberts R, Sole M, Maron BJ, Seidman JG, Seidman CE. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. *N Engl J Med*. 1998;338:1248–1257.
  41. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Zamorano JL. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257–e354.
  42. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Smith SC Jr, Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). *J Am Coll Cardiol*. 2006;48:e247–e346.
  43. Miller MA, Gomes JA, Fuster V. Risk stratification of sudden cardiac death in hypertrophic cardiomyopathy. *Nat Clin Pract Cardiovasc Med*. 2007;4:667–676.
  44. Maron MS, Olivetto I, Maron BJ, Prasad SK, Cecchi F, Udelson JE, Camici PG. The case for myocardial ischemia in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2009;54:866–875.
  45. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, Mackey-Bojack S, Manning WJ, Udelson JE, Maron BJ. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation*. 2006;114:216–225.
  46. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, Lesser JR, Udelson JE, Ackerman MJ, Maron BJ. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. *Circulation*. 2008;118:1541–1549.
  47. Fifer MA, Vlahakes GJ. Management of symptoms in hypertrophic cardiomyopathy. *Circulation*. 2008;117:429–439.
  48. Olivetto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation*. 2001;104:2517–2524.
  49. Hershberger R, Cowan J, Morales A, Siegfried J. Progress with genetic cardiomyopathies: screening, counseling, and testing in dilated, hypertrophic, and arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circ Heart Fail*. 2009;2:253–261.
  50. Aoki Y, Niihori T, Narumi Y, Kure S, Matsubara Y. The RAS/MAPK syndromes: novel roles of the RAS pathway in human genetic disorders. *Hum Mutat*. 2008;29:992–1006.
  51. Maron BJ, Roberts WC, Arad M, Haas TS, Spirito P, Wright GB, Almqvist AK, Baffa JM, Saul JP, Ho CY, Seidman J, Seidman CE. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. *JAMA*. 2009;301:1253–1259.

KEY WORDS: calcium ■ genetics ■ cardiomyopathy, hypertrophic ■ hypertrophy ■ tachyarrhythmias