The epidemiologic evolution and present perception of hypertrophic cardiomyopathy

Iacopo Olivotto, Franco Cecchi

Regional Referral Center for Myocardial Diseases, Cardiology 2, San Luca, Azienda Ospedaliera Careggi, Florence, Italy

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Patients with rare diseases are confronted by limited attention from the scientific community, a delayed diagnosis, a limited availability of resources and high costs of treatment. Although hypertrophic cardiomyopathy (HCM) does not meet the criteria for rare diseases, many physicians are uncomfortable with the disease, and patients still pay a price for the perceived "rarity" of HCM. In the year 2000, as part of a large research project on cardiovascular disease prevention (Progetto Cuore), the Italian Institute of Health has approved and funded a National Registry of HCM. The aims of the registry included: the collection of clinical data for HCM patients in different geographical areas; the creation of a network of cardiologists involved in the care of HCM patients; and an improved access of patients to the most advanced treatment options. It is our hope that the registry will be imitated by other countries, and that it will contribute to overcome the limitations of "rarity" in HCM research.

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Address:

Dr. Iacopo Olivotto

Via Jacopo Nardi, 30
50132 Firenze
E-mail: iacopo.olivotto@virgilio.it

The burden of rare diseases

Rare diseases represent an important challenge to health organizations, due to the disadvantages deriving from the rarity itself, including limited attention from the scientific community, insufficient research initiatives, a delayed diagnosis due to the paucity of experts in the field, and the limited availability and high costs of effective treatment[1]. However, many incidental variables may contribute to the actual or perceived rarity of a given condition: e.g. a disease may be mistakenly judged to be rare because it represents the early epidemiological stage of an emerging disease.

Thus, the estimated prevalence of any disease in the population depends upon the sensitivity of the diagnostic techniques available at each time; moreover, the prevalence of a genetic disease also depends upon the number of disease genes involved and on their penetrance (i.e. the percentage of patients with phenotypic expression among disease gene carriers)[2-4]. As the knowledge of a disease increases, it is likely that both its estimated prevalence and the perceived complexity of its spectrum will also increase[5,6].

In this respect, the specific case of hypertrophic cardiomyopathy (HCM) is worth examining in detail because of its evolving epidemiology which has led to a new perception of the disease which is quite different from its initial descriptions.

The evolving perception of hypertrophic cardiomyopathy

Familial HCM is a genetically determined disease characterized by myocardial hypertrophy, most commonly asymmetric and involving the interventricular septum, occurring in the absence of cardiac or systemic causes of hypertrophy[5,6]. To date, ten disease genes have been identified, all encoding proteins that form part of the sarcomere[5-11]. Thus, under the label of HCM, at least ten different genetic diseases are included, sharing the common phenotypic denominator represented by asymmetric myocardial hypertrophy. Moreover, mutations in the gene for the γ_2 regulatory subunit of adenosine monophosphate-activated proteinkinase (PRKAG2) have recently been shown to cause a familial disease characterized by cardiac hypertrophy mimicking HCM, associated with electrophysiologic abnormalities such as ventricular preexcitation and atrioventricular conduction block[12]. Technically, PRKAG2 defects constitute a myocardial metabolic storage disorder and not HCM. In clinical practice, however, this finding means that not all patients with a HCM phenotype have a disease of the sarcomere.

The understanding of the clinical spectrum and epidemiology of HCM has evolved significantly since the initial clinical descriptions in the 1960s and 1970s (Fig. 1). In the early days, the disease was described exclusively in patients with severe forms of HCM characterized by a marked left ventricular outflow obstruction and a high incidence of sudden death[13,14]. In the following decades, however, the introduction of echocardiography in clinical practice has allowed researchers to unveil the marked clinical and morphological heterogeneity of HCM. It is now well established that HCM is often compatible with a normal lifestyle and life expectancy, and may remain dormant until late in life[5,6,15-18]: in a recent population-based study analyzing over 15 000 echocardiograms performed in rural communities, HCM had remained previously undetected in two thirds of identified patients, due to the lack of symptoms[19]. These findings are consistent with our experience on 330 unselected patients followed at five community-based hospitals in central and northern Italy, 59% of whom were asymptomatic and had a benign clinical course[16].

The development of genetic testing has the potential of further increasing the diagnostic sensitivity for HCM (Fig. 1). For example, systematic genetic screening in HCM families has been shown to have the potential of identifying apparently healthy individuals carrying HCM-related mutations[20]. A subgroup of these individuals, with late-onset HCM, will eventually develop clinical and morphological signs of the disease[2]; others, however, representing the benign extreme of the disease spectrum, may remain free of phenotypic or clinical manifestations of HCM. The possibility of a "healthy carrier" status poses challenging questions, ranging from diagnosis and risk stratification to possible future denominations of the disease (is the term *hypertrophic cardiomyopathy* acceptable in the absence of hypertrophy?). Moreover, in this new light the concept of the prevalence of HCM assumes a dynamic quality: single, cross-sectional echocardiographic studies are no longer sufficient to provide the final picture in a given population, and longitudinal evaluations become mandatory in subjects with a family history of HCM and/or known genetic mutations[2-6].

An increasing number of genotype-phenotype correlation studies performed with the aim of identifying the clinical and prognostic differences between the different sarcomere protein gene mutations, i.e. of segregating the diverse HCM, are being published[2-4,7-12]. Although fascinating and promising, these studies are as yet to be considered very preliminary, particularly with regard to the prognostic conclusions, due to the limited number of families included in the analyses.

Epidemiology of hypertrophic cardiomyopathy

A reliable estimate of the frequency of HCM may be difficult to obtain, due to several factors such as its incomplete penetrance, the variable age at onset, and

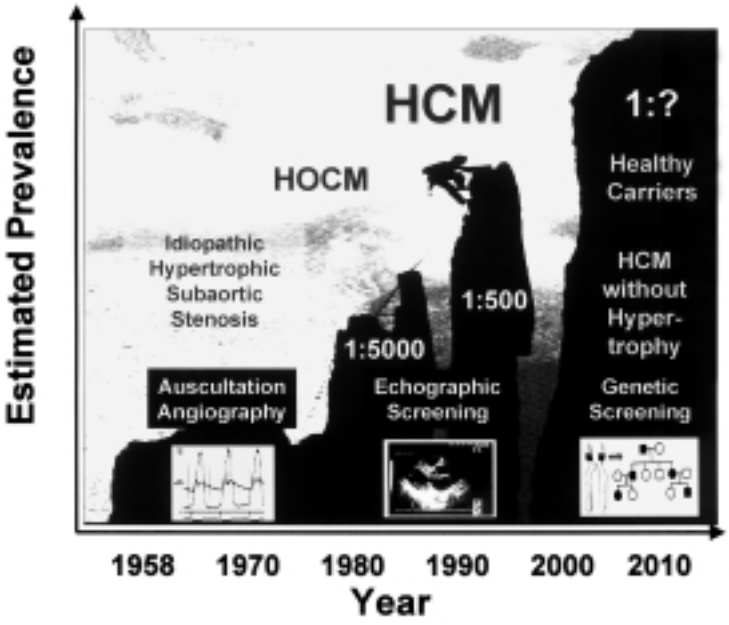

Figure 1. *Prevalence of hypertrophic cardiomyopathy (HCM) as estimated on the basis of the advent of different diagnostic techniques. The disease currently denominated HCM has received different denominations in the past, as different clinical and pathophysiological features were progressively highlighted by means of new instrumental techniques. Likewise, the perceived prevalence of HCM has changed over time, constantly increasing with the introduction of more sensitive diagnostic tools. Future epidemiological studies will have to address the prevalence of the latest subset identified within the HCM spectrum, namely "HCM patients without hypertrophy" (defined as patients with a known contractile protein mutation and ECG alterations or a history of arrhythmias, but with a normal echocardiographic appearance of the heart). Further possibilities may include the detection of "healthy carriers", i.e. those subjects who carry HCM-causing mutations in the absence of any morphologic or clinical expression of the disease. HOCM = hypertrophic obstructive cardiomyopathy.*

the common phenotypic presentation (i.e. myocardial hypertrophy), which may be mimicked by other cardiac diseases. Genetic screening is not feasible on a population scale, and the frequency of gene defects may vary among different geographic areas. Finally, studies addressing the prevalence of HCM in the general population have been limited, particularly in Europe[19,21-26].

Despite these limitations, recent evidence suggests that HCM is more common than previously believed. In the United States, a population-based study performed in the late 1980s in Olmsted County, Minnesota, based on hospital records, reported a prevalence of about 1:5000[25]. Only a decade later, two echocardiographic screening studies performed in the same state of Minnesota reported prevalence rates ranging from 1:500 to 1:300[19,26]. The 10-fold increase in the estimated prevalence of HCM presumably reflects the decisive impact of echocardiography in clinical practice (Fig. 1) as well as the progressive unveiling of patients with clinically latent disease in the community.

Studies on relatively unselected, community-based patient populations have also led to relevant changes in the *qualitative* perception of HCM[5,6,16-19,27-33]. For example, it is now well documented that obstructive forms of the disease represent a minority, occurring in about one fifth of patients; that heart failure-related complications, including atrial fibrillation and embolic stroke, are common and represent important predictors of an adverse prognosis; and that the degree of myocardial hypertrophy is liable to dynamic changes over time, ranging from the possibility of progressive ventricular wall thinning and remodeling, to significant increases in thickness[5,6,16-19,27-36]. Of utmost importance, it has been repeatedly documented that the overall clinical outcome in HCM patients is more benign than originally reported in highly selected patient populations followed at tertiary referral centers[13-18]. The annual HCM-related mortality among community-based patient populations is now estimated at around 1% for all cardiac causes, and at less than 0.5% for sudden unexpected death[5,6,16-18,27]. Moreover, in five Italian community-based regional cohorts, only about one third of patients progressed to severe limiting symptoms or presented with acute cardiovascular events requiring urgent hospitalization during a 9.5 year average follow-up[16]. Therefore, the profile of HCM has progressively evolved from that of a rare and malignant disease, to that of a relatively common and not invariably severe pathology.

Is hypertrophic cardiomyopathy a rare disease?

Technically, HCM is not a rare disease. On the basis of the estimated prevalence of 1:500 observed in the United States, there may be up to 1 million subjects with HCM in Europe alone, an unknown proportion of whom remain undiagnosed. Indeed, HCM is more common than other chronic conditions that are receiving larger attention worldwide (Table I)[26,37-42]. Therefore, it is important that the relevance of HCM be perceived in its true dimensions, and not be considered as somewhat of a curiosity in the huge sea of cardiovascular diseases. Furthermore, HCM should receive the deserved attention in health care planning and in the attribution of resources.

On the other hand, even though HCM may be relatively common, one cannot overlook the fact that many physicians are uncomfortable with the disease, and that patients and their families pay a price for the perceived "rarity" of HCM. Indeed, HCM still shares many features typical of rare diseases, and many of their "rarity-related" problems (Table II). Specifically, some of the most severe manifestations of HCM are rare and require highly specialized management (e.g. cardiac surgery or septal alcohol ablation for the relief of outflow obstruction) that can only be properly provided by a limited number of selected centers worldwide[43-45]. Likewise, routine genetic testing for all known sarcomere contractile protein mutations is not yet feasible, and genetic screening is usually confined to selected families studied at referral centers for research purposes[3-6].

Finally, to date a very limited number of properly designed, prospective studies including HCM patients has been performed, due to the relatively small number of patients followed at each center and to the problems related to the organization of multicenter studies[46]. As a consequence, most treatments commonly used in

Table I. Estimated prevalence of hypertrophic cardiomyopathy as compared with other chronic conditions receiving wider worldwide attention.

Condition	Estimated prevalence	Reference
Epilepsy	0.5-2:100	Dichter[37], 1991
Rheumatoid arthritis	1:100	Lipsky[38], 1991
Hypertrophic cardiomyopathy	1:500	Maron et al.[26], 1995
Inflammatory bowel disease	1:1000	Targan and Shanahan[39], 1994
Multiple sclerosis	1:1000-1:3390	Ford et al.[40], 1998 Milonas et al.[41], 1990
Cystic fibrosis	1:1600-1:2000	Davis[42], 1985

Table II. Hypertrophic cardiomyopathy (HCM) as a rare disease.

Reasons why HCM should not be considered a rare disease	Reasons why HCM is perceived as a rare disease
A prevalence 1:500 based on echocardiographic screening[26], i.e. possibly 1 million patients in Europe alone. Widespread genetic screening may increase this value.	Primary care physicians as well as many cardiologists rarely diagnose the disease. Physicians are often not familiar with the condition and may misdiagnose or mismanage patients, or be unaware of the treatment options.
Most cases have a benign prognosis and may be managed in community-based institutions.	A significant minority of patients die prematurely and/or suddenly, or experience severe disease progression and recurrent cardiac events. High-risk patients are not easily identified and the prevention of sudden death remains a major challenge.
International networks and registries have the potential of gathering large numbers of patients for designing appropriate clinical trials.	Patient populations followed at single centers have so far proved too small to allow satisfactory clinical trials for the accurate evaluation of the efficacy of old and new treatments.
In many patients the management strategies overlap with those employed for patients affected by more common cardiac conditions (e.g. the management of atrial fibrillation and heart failure). Invasive procedures are not usually required for the management of low-risk patients.	In a selected group of severely symptomatic or high-risk patients, specific invasive management strategies, including defibrillator and pacemaker implantation, alcohol septal ablation, and cardiac surgery are required; most of these are available only in a limited number of specialized centers.
The disease gene can now be identified in a substantial proportion of patients with HCM.	Routine genetic testing is not available; in most institutions appropriate genetic counseling is still not offered to patients. The prevalence and natural history of "healthy" carriers of a diseased gene is still unknown.

HCM patients have been introduced empirically or by default assimilation to other cardiovascular diseases, and are not evidence-based[5,6,30].

Therefore, despite significant advances in the knowledge of the disease, critical issues in terms of patient management and prognosis remain unresolved. Of particular relevance is the disappointingly low accuracy in the identification of those HCM patients who are at higher risk of sudden premature death[31-33]. Moreover, HCM may represent a progressive condition with a heavy burden in terms of the related limiting symptoms, acute cardiovascular events and impaired quality of life[47].

Future perspectives

Based on a new perception of HCM as a relevant health problem, the future management of HCM requires adequate strategies at different levels. Above all, multidisciplinary units specifically devoted to genetic myocardial diseases including HCM are necessary in selected referral institutions. Their aim should be that of providing state-of-the-art care and of promoting research initiatives, including long overdue prospective treatment studies. These units should also promote the diffusion of updated information, provide genetic testing and counseling facilities and constitute the backbone of an extensive network connecting all physicians involved in the care of HCM patients. They should be part of international networks involved in the organization of patient registries and clinical trials. This goal involves adequate health care planning and the attribution of resources to the specific problem of HCM.

A second level of intervention should be aimed at the community-based institutions and primary care physicians, in order to improve baseline care and the knowledge of the disease. At one end of the spectrum, primary care physicians and cardiologists should avoid the overtreatment of low-risk patients and excessive restrictions to their lifestyle; at the other end, they should be well aware of the risk stratification strategies for the prevention of sudden death and of newly developed treatment opportunities. These achievements are possible via constant feedback with referral institutions.

Thirdly, it is important that patients and their relatives be encouraged to set up HCM organizations, with the aim of providing advice and help to those patients and families with special problems, exchange information and promote fund raising. The web now allows the rapid diffusion of information and patient-oriented sites have already been established (e.g. www.hcma-heart.com and www.cardiomiopatiaipertrofica.it).

The implementation of multicenter patient registries for HCM is instrumental to each of these goals, and has repeatedly been advocated in the past[48,49].

The Italian registry of hypertrophic cardiomyopathy

In the year 2000, as part of a large research project on cardiovascular disease prevention (Progetto Cuore), the Italian Institute of Health (ISTISAN) has approved

and funded a national registry of HCM. The aims of the registry include: the collection of clinical data for HCM patients followed at referral centers and community-based hospitals in different Italian regions; the creation of a national network of cardiologists involved in the care of HCM patients; an increased access of patients to the most advanced treatment options; and an improved diffusion of updated information among physicians.

The initiative has been promoted by direct contacts with numerous cardiology units and national scientific associations. Information about the registry and data collection forms has been made available on a dedicated web site (www.cardiomiopatiaipertrofica.it). A dedicated software for data storage and analysis has been developed. Patient enrollment started in May 2000. By May 2002, at the conclusion of the enrollment phase, the registry had acquired data regarding 1677 patients from over 50 Italian provinces, representing approximately 1 to 2% of the estimated total HCM population in Italy. Future developments and subprojects are being considered for the second phase of the registry, including the implementation of a national network for DNA banking and genetic screening. Moreover, study protocols on patient subgroups are currently being planned. Their aim is to focus on specific issues, such as risk stratification for sudden cardiac death. It is our hope that the registry will constitute a prototype which will be imitated by other countries. Moreover, we strongly support the implementation of a European network leading to a HCM registry under the aegis of the Working Group for Myocardial and Pericardial Diseases of the European Society of Cardiology. Indeed, such an initiative may for the first time allow researchers to prospectively address important questions in HCM patient management and overcome the limitations of "rarity" in HCM research.

Conclusions

HCM is not as rare as previously believed. Indeed, due to the improved sensitivity of the diagnostic techniques the frequency of diagnosis of the disease is on the increase. However, patients and primary care physicians often perceive HCM as a rare condition; this discrepancy creates important practical and psychological problems to patients and their families. HCM should receive the deserved attention in health care planning and in the attribution of resources. Patients and physician networks are required for a better understanding and care and for the implementation of clinical trials that are urgently needed. On the basis of the promising experience of the Italian registry, we strongly support the creation of a European registry devoted to HCM patients.

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References

1. http://www.rarediseases.org
2. Charron P, Carrier L, Dubourg O, et al. Penetrance of familial hypertrophic cardiomyopathy. Genet Couns 1997; 8: 107-14.
3. Bonne G, Carrier L, Richard P, Hainque B, Schwartz K. Familial hypertrophic cardiomyopathy. From mutations to functional defects. Circ Res 1998; 83: 580-93.
4. Towbin JA. Molecular genetics of hypertrophic cardiomyopathy. Curr Cardiol Rep 2000; 2: 134-40.
5. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. JAMA 2002; 287: 1308-20.
6. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. N Engl J Med 1997; 336: 775-85.
7. Watkins H, Rosenzweig T, Hwang DS, et al. Characteristic and prognostic implications of myosin missense mutations in familial cardiomyopathy. N Engl J Med 1992; 326: 1106-14.
8. Thierfelder L, Watkins H, MacRae C, et al. α-Tropomyosin and cardiac troponin T mutations cause familial hypertrophic cardiomyopathy: a disease of the sarcomere. Cell 1994; 77: 701-12.
9. Watkins H, McKenna WJ, Thierfelder L, et al. Mutations in the genes for cardiac troponin T and α-tropomyosin in hypertrophic cardiomyopathy. N Engl J Med 1995; 332: 1058-64.
10. Charron P, Dubourg O, Desnos M, et al. Diagnostic value of electrocardiography and echocardiography for familial hypertrophic cardiomyopathy in a genotyped adult population. Circulation 1997; 96: 214-9.
11. Coviello DA, Maron BJ, Spirito P, et al. Clinical features of hypertrophic cardiomyopathy caused by mutation of a "hot spot" in the alpha-tropomyosin gene. J Am Coll Cardiol 1997; 29: 635-40.
12. Arad M, Benson DW, Perez-Atayde AR, et al. Constitutively active AMP kinase mutations cause glycogen storage disease mimicking hypertrophic cardiomyopathy. J Clin Invest 2002; 109: 357-62.
13. Braunwald E, Lambrew CT, Rockoff SD, Ross J Jr, Morrow AG. Idiopathic hypertrophic subaortic stenosis. I. A description of the disease based upon an analysis of 64 patients. Circulation 1964; 30 (Suppl 4): 3-217.
14. Shah PM, Adelman AG, Wigle ED, et al. The natural (and unnatural) history of hypertrophic obstructive cardiomyopathy. Circ Res 1974; 35 (Suppl II): II179-II195.
15. Shapiro LM, Zezulka A. Hypertrophic cardiomyopathy: a common disease with a good prognosis - five year experience of a district general hospital. Br Heart J 1983; 50: 530-3.
16. Cecchi F, Olivotto I, Montereggi A, et al. The Italian multicenter study on hypertrophic cardiomyopathy: I. Natural history and clinical course of unselected patients. In: Camerini F, Gavazzi A, De Maria E, eds. Advances in cardiomyopathies. Milan: Springer, 1997: 22-8.
17. Cecchi F, Olivotto I, Montereggi A, Santoro G, Dolara A, Maron BJ. Hypertrophic cardiomyopathy in Tuscany: clinical course and outcome in an unselected regional population. J Am Coll Cardiol 1995; 26: 1529-36.
18. Maron BJ, Casey SA, Poliac L, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopa-

thy in a regional United States cohort. JAMA 1999; 281: 650-5.
19. Maron BJ, Mathenge R, Casey SA, Poliac LC. Clinical profile of hypertrophic cardiomyopathy identified de novo in rural communities. J Am Coll Cardiol 1999; 33: 1590-5.
20. Nagueh SF, Bachinski LL, Meyer D, et al. Tissue Doppler imaging consistently detects myocardial abnormalities in patients with hypertrophic cardiomyopathy and provides a novel means for an early diagnosis before and independently of hypertrophy. Circulation 2001; 104: 128-30.
21. Bjarnason I, Jonsson S, Hardarson T. Mode of inheritance of hypertrophic cardiomyopathy in Iceland. Echocardiographic study. Br Heart J 1982; 47: 122-9.
22. Hada Y, Sakamoto T, Amano K, et al. Prevalence of hypertrophic cardiomyopathy in a population of adult Japanese workers as detected by echocardiographic screening. Am J Cardiol 1987; 59: 183-4.
23. Bagger JP, Baandrup U, Rasmussen K, Moller M, Vesterlund T. Cardiomyopathy in western Denmark. Br Heart J 1984; 52: 327-31.
24. Miura K, Nakagawa H, Morikawa Y, et al. Epidemiology of idiopathic cardiomyopathy in Japan: results from a nationwide survey. Heart 2002; 87: 126-30.
25. Codd MB, Sugrue DD, Gersh BJ, Melton LJ III. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975-1984. Circulation 1989; 80: 564-72.
26. 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: 785-9.
27. Maron BJ, Olivotto I, Spirito P, et al. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. Circulation 2000; 102: 858-64.
28. Olivotto I, Maron BJ, Montereggi A, Mazzuoli F, Dolara A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. J Am Coll Cardiol 1999; 33: 2044-51.
29. Maron MS, Olivotto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 2003; 348: 295-303.
30. Olivotto 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: 2517-24.
31. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med 2000; 342: 1778-85.
32. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. Lancet 2001; 357: 420-4.
33. Elliott PM, Poloniecki J, Dickie S, et al. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. J Am Coll Cardiol 2000; 36: 2212-8.
34. Maron BJ, Spirito P, Wesley Y, Arce J. Development and progression of left ventricular hypertrophy in children with hypertrophic cardiomyopathy. N Engl J Med 1986; 315: 610-4.
35. Spirito P, Maron BJ, Bonow RO, Epstein SE. Occurrence and significance of progressive left ventricular wall thinning and relative cavity dilatation in patients with hypertrophic cardiomyopathy. Am J Cardiol 1987; 60: 123-9.
36. Maron BJ, Niimura H, Casey SA, et al. Development of left ventricular hypertrophy in adults in hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutations. J Am Coll Cardiol 2001; 38: 315-21.
37. Dichter MA. The epilepsies and convulsive disorders. In: Harrison's principles of internal medicine. 12th edition. New York, NY: McGraw-Hill, 1991: 1968-77.
38. Lipsky PE. Rheumatoid arthritis. In: Harrison's principles of internal medicine. 12th edition. New York, NY: McGraw-Hill, 1991: 1437-43.
39. Targan SR, Shanahan F. Inflammatory bowel disease: from bench to bedside. Baltimore, MD: Williams and Wilkins, 1994.
40. Ford HL, Gerry E, Airey CM, Vail A, Johnson MH, Williams DR. The prevalence of multiple sclerosis in the Leeds Health Authority. J Neurol Neurosurg Psychiatry 1998; 64: 605-10.
41. Milonas I, Tsounis S, Logothetis I. Epidemiology of multiple sclerosis in northern Greece. Acta Neurol Scand 1990; 81: 43-7.
42. Davis PB. Cystic fibrosis. Seminars in Respiratory Medicine 1985; 6: 243-71.
43. Maron BJ, Nishimura RA, Danielson GK. Pitfalls in clinical recognition and a novel operative approach for hypertrophic cardiomyopathy with severe outflow obstruction due to anomalous papillary muscle. Circulation 1998; 98: 2505-8.
44. Seggewiss H, Gleichmann U, Faber L, Fassbender D, Schmidt HK, Strick S. Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: acute results and 3-month follow-up in 25 patients. J Am Coll Cardiol 1998; 31: 252-8.
45. Spirito P, Maron BJ. Perspectives on the role of new treatment strategies in hypertrophic obstructive cardiomyopathy. J Am Coll Cardiol 1999; 33: 1071-5.
46. Maron BJ, Nishimura RA, McKenna WJ, Rakowski H, Josephson ME, Kieval RS. Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy. A randomized, double-blind, crossover study (M-PATHY). Circulation 1999; 99: 2927-33.
47. Cox S, O'Donoghue AC, McKenna WJ, Steptoe A. Health related quality of life and psychological wellbeing in patients with hypertrophic cardiomyopathy. Heart 1997; 78: 182-7.
48. Spencer WH III, Roberts R. Alcohol septal ablation in hypertrophic obstructive cardiomyopathy: the need for a registry. Circulation 2000; 102: 600-1.
49. Braunwald E. A new treatment for hypertrophic cardiomyopathy? Eur Heart J 1997; 18: 709-10.