Hypertrophic Cardiomyopathy: An Important Global Disease

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Over the past 45 years since the first modern report by Teare (1), hypertrophic cardiomyopathy has been of great interest to clinicians (and more recently to molecular biologists) largely due to its broad clinical spectrum, genetic etiology, and strong association with sudden death in the young (including trained athletes) (2–8). Most reports have come from tertiary referral centers in North America and Western Europe, but also from the Far East (mostly Japan), the Middle East (Israel), South America, and Australia. Taken together, these reports have generally suggested a similar clinical presentation and course regardless of geographic region (2,5,9).

Certainly, hypertrophic cardiomyopathy has for the most part been considered somewhat of an oddity—an uncommon but "interesting" disease that can be a source of anxiety to patients and physicians alike. Indeed, it is recognized as an often unpredictable genetic heart disease that may present unique challenges for diagnosis and management (5). Furthermore, it is apparent that most cardiology practices comprise relatively few patients with hypertrophic cardiomyopathy (5,10), compounding the challenges inherent in appreciating the heterogeneous morphologic and clinical expression of this disease (2,5,6,8).

Furthermore, it has become much more difficult to achieve sufficient exposure and clinical experience with the genetic cardiovascular diseases, such as hypertrophic cardiomyopathy, as the overall volume of patients within cardiology practice has greatly increased due to dramatic therapeutic advances that have enhanced the longevity of patients with coronary artery disease and heart failure. In the United States, only a small number of centers are dedicated to the study and management of hypertrophic cardiomyopathy; these include the Minneapolis Heart Institute Foundation, the Mayo Clinic, Tufts-New England Medical Center (Boston), St. Luke's-Roosevelt Hospital Center (New York), and the Cleveland Clinic. Resources for these patients have been reduced by the recent permanent closure of the long-standing hypertrophic cardiomyopathy program at the National Institutes of Health.

But . . . how rare is hypertrophic cardiomyopathy? Certainly, the issue of prevalence is fundamental to establishing the importance and management of any disease within the population. Recent epidemiologic studies in the United States, which are based on echocardiographic identification of the disease phenotype (i.e., otherwise unexplained left ventricular hypertrophy in the absence of ventricular dilatation), place its prevalence at about 0.2% (1 in 500) in the general population (11–13) (Figure). This suggests that as many as 500,000 persons in the United States may have hypertrophic cardiomyopathy (7). Still, such figures likely underestimate the true occurrence of this disease, given that the available data do not account for the many undiagnosed but affected family members who may be related to an identified proband.

Furthermore, to place these numbers into some perspective, hypertrophic cardiomyopathy has an estimated prevalence that is 10- to 50-fold greater than other familial diseases affecting the heart and great vessels, such as long QT, Brugada, and Marfan syndromes, as well as other noncardiac diseases with greater visibility in the lay and physician communities, such as cystic fibrosis, amyotrophic lateral sclerosis, multiple sclerosis, and muscular dystrophy. Finally, based on the available risk stratification and prevalence data, it is possible for 50,000 to 100,000 patients with hypertrophic cardiomyopathy in the United States to be presently at an unacceptably high risk of sudden death (7), including many who could be candidates for primary prevention of sudden death with an implantable defibrillator (16).

In this context, the two reports from China in this issue of the *Journal* have particular importance for our understanding and awareness of hypertrophic cardiomyopathy (14,17). China is the most populous country in the world with 1.3 billion citizens, or 20% of the world population. Consequently, the total number of Chinese patients affected by any important disease represents a public health problem of considerable magnitude. In the first of these studies, Zou et al (14) report the results of an ambitious cross-sectional epidemiologic survey that comprised more than 8000 residents from nine geographically diverse urban communities and medical centers (including Beijing) and used echocardiography with a random sampling recruitment design. In this community-based sample, the disease phenotype for hypertrophic cardiomyopathy was identified in 0.16% of subjects. This prevalence is almost identical to that previously reported with echocardiography in the Coronary Artery Risk Development In Young Adults (CARDIA) study (11), which comprised

Am J Med. 2004;116:63–66.
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0002-9343/04/$–see front matter
doi:10.1016/j.amjmed.2003.10.012

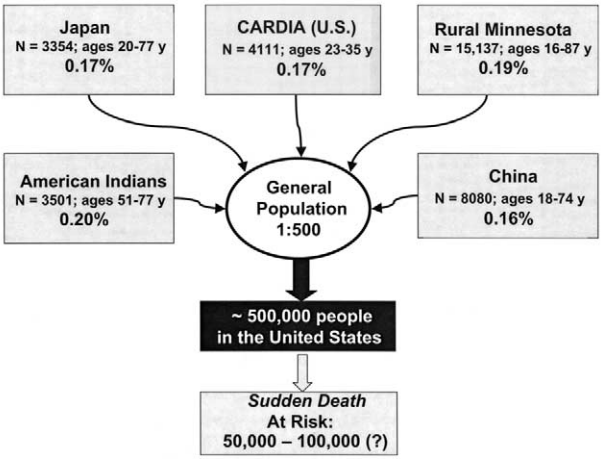

Figure. The worldwide prevalence of hypertrophic cardiomyopathy and its clinical implications. Population prevalence data from references 11 to 15. CARDIA = Coronary Artery Risk Development In Young Adults.

a biracial cohort of 4111 men and women, aged 23 to 35 years, enrolled from four urban centers (Figure). These prevalence figures are also similar to that reported by Hada et al (15) who documented hypertrophic cardiomyopathy by echocardiography in 0.2% of Japanese workers (Figure). Extrapolating from their data, Zou et al have concluded that there are potentially 1 million persons in China with hypertrophic cardiomyopathy. It may also be assumed that there is a substantial proportion of that population who remain undiagnosed and unaware of their disease, including many persons who are undoubtedly at increased risk of sudden death (7).

Of note, Zou et al (14) defined the disease phenotype by an echocardiographically determined left ventricular wall thickness ≥13 mm. This is a somewhat less restrictive criteria than the cutoff of ≥15 mm that was used in the CARDIA study (11), and could represent a potential source of overestimation of prevalence. Indeed, more than one third of their subjects with hypertrophic cardiomyopathy had borderline left ventricular wall thicknesses of only 13 and 14 mm, including 2 with systemic hypertension (of whom 1 also had a normal electrocardiogram).

Recognition of such a large group of Chinese patients with hypertrophic cardiomyopathy represents a potential burden on medical resources, and in this regard raises a number of considerations. These include the need for widespread dissemination of echocardiography necessary for clinical diagnosis, development of interventions for control of heart failure (e.g., surgical septal myectomy or alcohol septal ablation [2,5] and implantable defibrillators for prevention of sudden death [2,5,7,16]), as well as laboratory-based genetic testing for formulating family screening strategies and understanding the basic mechanisms of disease.

In the second study, Ho et al (17) followed a clinical cohort of 118 patients with hypertrophic cardiomyopathy for up to 30 years at the Queen Mary Hospital in Hong Kong. The major prognostic implications for hypertrophic cardiomyopathy in this group of patients were not dissimilar to those reported over the last 10 years in largely community-based, regional, and nontertiary referred cohorts (2,5,18). In particular, Ho et al report an overall relatively benign clinical course for their patients with an annual mortality rate of 1.6%. This contrasts sharply with the mortality rates of up to 5% to 6% that were cited in the older literature (2,5,18). Those studies, however, consisted mostly of highly selected cohorts that comprised a disproportionate number of high-risk or severely symptomatic patients, which exaggerated the overall severity of the disease (2,5,7,18).

The report of Ho et al (17) is also notable for describing other demographic and morphologic features of hypertrophic cardiomyopathy, which are distinctive from prior reports from other countries (2,5,8,9). For example, the authors found certain clinical features to be particularly common in their cohort, such as atrial fibrillation (35% of their patients vs. about 20% in most other studies [2,5]) and apical hypertrophy confined to the most distal portion of the left ventricle (41% of their patients vs. 3% reported in non-Asians and 15% in Japanese [8,19]). This high frequency of the apical variant, which is a nonobstructive form of the disease, probably accounts in large measure for the low prevalence of outflow obstruction reported, and also supports the view that this particular phenotypic expression of hypertrophic cardiomyopathy is probably most prevalent in Asian patients (2,5,19). Ho et al also found the disease to be more severe in women (female sex was the only independent predictor of mortality), an observation which differs from the experience in non-Asian patients (20). These unique features of hypertrophic cardiomyopathy in this cohort could be attributable to racial/ethnic differences, or perhaps to patient selection factors since there is evidence that the cohort may have been subject to referral center bias (almost 75% of patients were symptomatic at first evaluation).

The two papers in this issue of *the Journal* reporting on hypertrophic cardiomyopathy in China represent a landmark in the 45-year history of this disease. Although frequently undiagnosed, it is now evident that hypertrophic cardiomyopathy is a not uncommon form of inherited heart disease, and affects several million people of many races (and both sexes) throughout the world. This awareness substantiates the emerging appreciation of hypertrophic cardiomyopathy as the most common cause of sudden cardiac death in the young, as well as a cause of

disability or death due to heart failure and stroke at any age.

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