Hypertrophic Cardiomyopathy

The Therapeutic Role of Calcium Antagonists

Edited by
M. Kaltenbach and S. E. Epstein

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Preface

First described in 1907 by Schicke but recognized as a clinical entity only as recently as 1958, when Teare published the pathologic findings in patients with hypertrophic cardiomyopathy (HCM), an explosion of knowledge about this fascinating disease has occurred, which has caused a profound evolution of our understanding of its broad pathophysiologic and clinical spectrum. Progress has been particularly rapid in the past few years when M-mode echocardiography, and more recently 2-dimensional echocardiography have been applied to the study of HCM.

In addition to new insights as to what the disease is, there has been enormous progress concerning its treatment, with the application of beta-adrenergic blocking agents and surgical relief of left ventricular outflow tract obstruction. Although these approaches have led to great strides in the symptomatic control of the disease, many patients' symptoms have remained refactory to medical and surgical therapy. Most discouragingly, sudden death still occurs, even in patients on large doses of beta-blocking agents and in patients who have had surgical relief of left ventricular outflow tract obstruction.

Therapy of HCM with calcium antagonists was initiated in 1973 in Frankfurt/Main. Independently, several years later, the group in Bethesda started with the same therapeutical approach. Many assumptions had to be made to justify this new form of treatment, e.g.:

- High doses of verapamil can be given over a long period of time without severe side effects
- Cardiomyopathy or its clinical effects relates to calcium ion overload or increased intramyocardial availability of calcium
- The negative inotropic action of verapamil is not of major clinical importance.

In the meantime our understanding of the disease as well as of the basic principle of calcium antagonism as defined by Fleckenstein has considerably increased. Most importantly, therapeutic experience with the use of verapamil in treating patients with HCM has increased markedly, and data relating to its effects have been collected at different institutions throughout the world.

This volume is aimed to represent our up-to-date knowledge of the topic. It offers for the first time an international overview on a new therapeutic approach to HCM.

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Synopsis

J. F. Goodwin

Epstein and colleagues comment on terminology (listing 58 names that have been given to hypertrophic cardiomyopathy) and emphasize the importance of abnormalities of diastolic function and reinforce the view that "obstruction" to outflow is only one aspect of this disease. The spectrum of hypertrophic cardiomyopathy is broader than originally suspected.

Echocardiographic studies have shown that hypertrophy can occur in all parts of the ventricle and may be found throughout the length of the ventricular septum, or in its upper or in its lower portions only. Hypertrophy, though usually asymmetrical, can be symmetrical. These variations have led to suggestions that hypertrophic cardiomyopathy is not one but many diseases or is even a nonspecific reaction of the myocardium with hypertrophy. This is not true: Hypertrophic cardiomyopathy is undoubtedly a major disease entity but with many forms and variations.

Sudden death is the most common type of death. Neither hemodynamic nor electrocardiographic findings are helpful in identifying the patient destined to die; nor does any type of ventricular morphology appear to be predictive. However, there may be a trend relating septal thickness to sudden death. A strong family history, young age, and massive cardiomegaly would suggest a poor prognosis, while one subset of hypertrophic cardiomyopathy is the so-called malignant familial type alluded to by Epstein and Maron.

The identification of occult arrhythmias by ambulatory ECG monitoring has greatly added to our knowledge. The experience of Maron and Epstein, supported by our own experience at the Royal Postgraduate Medical School, indicates that ventricular arrhythmias are common, and a direct relationship has been demonstrated between ventricular tachycardia and sudden death.

Cellular disorganization can be found in hypertrophic cardiomyopathy but also in a variety of cardiac diseases and even in healthy persons. In contrast to these cases with only small foci of cellular disorganization, patients with hypertrophic cardiomyopathy show large areas of the ventricular septum and also of the free left ventricular wall with cellular disorganization. It is not the finding itself but the widespread occurrence that is considered characteristic for hypertrophic cardiomyopathy. In the study of Maron et al. the most widespread cellular abnormalities were found in patients dying suddenly without prior functional limitations. It is therefore speculated that widespread cellular disorganization could provide a substrate for malignant ectopy.

The careful studies by Kunkel and colleagues show the value of endomyocardial biopsy in assessing the severity of the disease but less so in making a diagnosis. The patchy nature of the myofibrillar disarray in hypertrophic cardiomyopathy and the presence of similar lesions in other forms of ventricular hypertrophy secondary to

other cardiac disorders make diagnosis by endomyocardial biopsy extremely difficult. It is suggested that the severity of hypertrophy in the biopsy from the left ventricular free wall of patients with hypertrophic cardiomyopathy may provide information concerning the stage and progress of the disease and also the response of the myocardium to the abnormal anatomical and functional situation. Thus, although endomyocardial biopsy may provide additional information about this disease, it should not be used to diagnose hypertrophic cardiomyopathy.

Hypertrophic Cardiomyopathy: An Overview*

STEPHEN E. EPSTEIN and BARRY J. MARON

Hypertrophic cardiomyopathy presents extraordinary challenges to the investigator, partly because of the extreme diversity in its clinical, hemodynamic, and anatomical presentation, and partly because of the rapid changes that have occurred in our understanding of its pathophysiology, natural history, and treatment since it was first recognized as a clinical entity in 1958 [1]. The profound changes that have occurred in our concepts of the disease are reflected in Table 1, which lists the names that have been appended to this entity at one time or another over the years.

The multiplicity of descriptive names given to this disease relate primarily to several factors. First, several centers were involved more or less simultaneously in the pioneering studies that characterized the disease and each, understandably, developed names for this newly discovered clinical entity based on those aspects of the disease that were most impressive to the individual investigators. Second, as additional information accumulated, concepts of the disease changed, with important new insights often leading to new names.

Characteristic Features of Hypertrophic Cardiomyopathy

Initially, this disease was viewed primarily as one characterized by obstruction to left ventricular outflow; hence, the disease acquired such names as "idiopathic hypertrophic subaortic stenosis", or IHSS, [2] "muscular subaortic stenosis" [3], and "hypertrophic obstructive cardiomyopathy", or HOCM [4].

The widespread application of M-mode echocardiography to cardiac diagnosis in the early 1970s confirmed the hypertrophic nature of the disease [5–8]. Echocardiographic studies also demonstrated that outflow obstruction was absent in a large proportion of patients with hypertrophic cardiomyopathy [9], that it was often transmitted as an autosomal dominant trait [9, 10], and that an hypertrophied ventricular septum, measuring at least 1.3 times the thickness of the left ventricular free wall, was invariable. These echocardiographic observations led to the introduction of the term "asymmetric septal hypertrophy" and its acronym "ASH" to describe the *disease* hypertrophic cardiomyopathy [5]. However, recent observations have indicated the inadequacy of this concept of the disease [11]. In particular, extensive two-dimensional echocardiographic studies [11a, 12], demonstrated that while most of the patients have septal hypertrophy, the majority also have considerable thickening of the left ventricular free wall, which not infrequently is equal to or

* This paper is revised and updated from that published in Clinical and Investigative Medicine 3:185–193, 1980

Table 1. Terms used to describe hypertrophic cardiomyopathy

Asymmetrical hypertrophic cardiomyopathy	1972
Asymmetrical hypertrophy of the heart	1958
Asymmetrical septal hypertrophy	1973
Brock's disease	1977
Diffuse muscular subaortic stenosis	1973
Diffuse subvalvular aortic stenosis	1961
Dynamic hypertrophic subaortic stenosis	1971
Dynamic muscular subaortic stenosis	1966
Familial hypertrophic subaortic stenosis	1961
Familial muscular subaortic stenosis	1959
Familial myocardial disease	1967
Functional aortic stenosis	1959
Functional hypertrophic subaortic stenosis	1969
Functional obstructive cardiomyopathy	1973
Functional obstruction of the left ventricle	1957
Functional obstructive subvalvular aortic stenosis	1968
Functional subaortic stenosis	1960
Hereditary cardiovascular dysplasia	1961
Hypertrophic cardiomyopathy	1970
Hypertrophic constrictive cardiomyopathy	1972
Hypertrophic hyperkinetic cardiomyopathy	1965
Hypertrophic infundibular aortic stenosis	1971
Hypertrophic nonobstructive cardiomyopathy	1975
Hypertrophic obstructive cardiomyopathy	1964
Hypertrophic stenosing cardiomyopathy	1972
Hypertrophic subaortic stenosis	1962
Idiopathic hypertrophic cardiomyopathy	1972
Idiopathic hypertrophic obstructive cardiomyopathy	1966
Idiopathic hypertrophic subaortic stenosis	1960
Idiopathic hypertrophic subvalvular stenosis	1966
Idiopathic muscular hypertrophic subaortic stenosis	1966
Idiopathic muscular stenosis of the left ventricle	1969
Idiopathic myocardial hypertrophy	1963
Idiopathic stenosis of the flushing chamber of the left ventricle	1964
Idiopathic ventricular septal hypertrophy	1962
Irregular hypertrophic cardiomyopathy	1968
Left ventricular muscular stenosis	1968
Low subvalvular aortic stenosis	1962
Muscular aortic stenosis	1969
Muscular hypertrophic stenosis of the left ventricle	1966
Muscular stenosis of the left ventricle	1961
Muscular subaortic stenosis	1966
Muscular subvalvular aortic stenosis	1964
Non-dilated cardiomyopathy	1974
Nonobstructive hypertrophic cardiomyopathy	1975
Obstructive cardiomyopathy	1960
Obstructive hypertrophic aortic stenosis	1967
Obstructive hypertrophic cardiomyopathy	1968
Obstructive hypertrophic myocardiopathy	1968