HYPERTROPHIC CARDIOMYOPATHY
(Past, Present and Future)

by

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Hypertrophic Cardiomyopathy is a condition or more probably a group of conditions in which all or part of the heart muscle undergoes hypertrophic changes in the absence of any known stimulus for hypertrophy (i.e. no valvular heart disease or hypertension etc).

Historical Background:

The disease entity as we have come to recognise it today was placed in proper perspective to a large extent due to the classification of the disorganized groups of cardiomyopathies into four distinet types by Goodwin et al. (1, 2). However, the condition which comprises by far the most common disorder under the broad category of Hypertrophic Cardionyopathy i.e., the condition named Idiopathic Hypertrophic Subaortic Stenosis (IHSS) in U.S.A. and Hypertrophic Obstructive Cardiomyopathy (HOCM) in U.K. was first accurately recognised by the British Pathologist Donald Teare (3). Teare described described massive hypertrophy of the ventricular septum and adjacent walls, involving from a third to half of the left ventricle, in eight cases.

Prior to Teare's description, the earliest report of what appears to be a description of this condition is that of the German pathologist Schmincke who in 1907 described "hyperplasia" of the muscle mass of the left ventricular outflow area (4). In 1910 Bernheim's description of right ventricular obliteration by left ventricular disease included cases with asymmetric left ventricular hypertrophy with very thickened septum which probably were cases. of Hypertrophic Cardiomyopathy. In 1952, a family with several members who had systolic heart murmurs and died suddenly was described by Davies (5). It appears quite probable that Davies too was describing a family with Hypertrophic Cardiomyopathy. The British Surgeon Lord Brock in 1957 operated on a patient throught to have aortic stenosis only to find a normal aortic valve and massive subaortic muscular hypertrophy (6). A somewhat similar experience was preported from across the Atlantic by Braunwald & Morrow (7). These early descriptions were followed by a barrage of papers from centers all over the world describing in great details various aspects of this disease entity.

Nomenclature:

Right from the earliest descriptions, there has been a great deal of confusion in the nomenclature of this disease entity. A lot of lively debates and pleas have appeared regarding what name to give this disease (8, 9). This disease perhaps has the longest list of synonyms that I am aware of as listed in Table 1. Part of the problem stems from the fact that like the blind men and the elephant, authors have been describing various aspects of the disease and renaming the disease after one particular attribute. The more we are learning of the many facets of this disease, the more reasonable sounds the simple title of "Hypertrophic Cardiomyopathy" which is able to embrace the many clinical sub-types now known to exist.

Patho-Physiology:

As the name cardiomyopathy implies, nothing is known as to the etiology of this condition. The common pathological feature is a thickening of the interventricular septum and the adjacent portions of the left ventricle but initially sparing the free walls. At the cellular level there is present a bizarre arrangement of individual muscle cells as well as muscle bundles which take the appearence of whorls rather than the normal parallel alligned fibres (10, 11). The papillary muscles which are hypertrophied have been noted to have an abnormal alignment vis-a-vis the mitral leaflets (12) and the entire mitral valve apparatus is placed abnormally anterior into the left ventricular outflow.

During the rapid and forceful ejection of this hypertrophied ventricle into a narrow left ventricular outflow, a venturi-like effect (Figure 2) seems to suck the anterior leaflet further into the outflow until it touches the interventricular septum which is already bulging into the outflow. This causes the dynamic obstruction characteristic of this disease. It should not be surprising then that at the time when the mitral leaflet is being pulled anteriorly, a variable degree of mitral incompetence occurs which is seen so commonly in L.V. angiogram.

The obstruction if severe and unrelieved for a significant period of time results in secondary hypertrophy of the left ventricular free wall. This vicious cycle can result in tremendous cardiac hypertrophy unlike that seen in any condition. While asymmetrically thickened septum is an essential feature in the vast majority of the patients, more and more cases are being recognized without this feature. These patients have a concentrically thickened ventricle involving the free wall and the septum equally (13).

Table 1 Synonyms of Hypertrophic Cardiomyopathy (IHSS)

1957 Functional obstruction of the left ventricle.
1958 Asymmetrical Hypertrophy of the heart.
1958 Pseudoaortic Stenosis.
1959 Functional aortic stenosis.
1959 Familial muscular subaortic stenosis.
1960 Obstructive Cardiomyopathy.
1960 Functional subaortic stenosis.
1960 Idiopathic hypertrophic subaortic stenosis.
1961 Muscular stenosis of the left ventricle.
1961 Hereditary Cardiovascular dysplasia.
1961 Familial hypertrophic subaortic stenosis.
1962 Hypertrophic subaortic stenosis.
1962 Idiopathic ventricular septal hypertrophy.
1962 Low subvalvular aortic stenosis.
1963 Idiopathic myocardial hypertrophy.
1964 Hypertrophic obstructive cardiomyopathy.
1964 Idiopathic stenosis of the flushing chamber of the left ventricle.
1964 Muscular subvalvular aortic stenosis.
1964 Subaortic hypertrophic stenosis.
1964 Subaortic musclar stenosis.
1964 Subvalvular aortic stenosis of the muscular type.
1965 Hypertrophic hyperkinetic cardiomyopathy.
1966 Dynamic muscular subaortic stenosis.
1966 Idiopathic hypertrophic obstructive cardiomyopathy.
1966 Idiopathic hypertrophic subvavlular stenosis.
1966 Idiopathic muscular hypertrophic subaortic stenosis.
1966 Muscular hypertrophic stenosis of the left ventricle.
1966 Muscular subaortic stenosis.
1966 Stenosing hypertrophy of the left ventricle.
1966 Stenosis of the ejection chamber of the left ventricle.
1967 Familial myocardial disease.
1967 Obstructive hypertrophic aortic stenosis.
1968 Functional obstructive subvalvular aortic stenosis.
1968 Irregular hypertrophic cardiomyopathy.
1968 Left ventricular muscular stenosis.
1968 Obstructive hypertrophic cardiomyopathy.
1968 Obstructive hypertrophic myocardiopathy.
1968 Obstructive myocardiopathy.
1968 Subaortic idiopathic stenosis.
1969 Functional hypertrophic subaortic stenosis.
1969 Idiopathic muscular stenosis of the left ventricle.
1969 Muscular aortic stenosis.
1970 Hypertrophic Cardiomyopathy.
1971 Dynamic hypertrophic subaortic stenosis.
1971 Hypertrophic infundibular aortic stenosis.
1972 Asymmetrical hypertrophic cardiomyopathy.
1972 Hypertrophic constrictive cardiomyopathy.
1972 Hypertrophic stenosing cardiomyopathy.
1972 Idiopathic hypertrophic cardiomyopathy.
1973 Asymmetrical septal hypertrophy.
1973 Diffuse muscular subaortic stenosis.
1973 Functional obstructive cardiomyopathy.
1974 Non-dilated cardiomyopathy.
1975 Hypertrophic non-obstructive cardiomyopathy.
1975 Nonobstructive hypertrophic cardiomyopathy.
1977 Brock's disease.
1977 Teare's disease.

As the concentric (symmetric) hypertrophy cases are only recently being recognized, it is still not established if this is a separate entity or only a different stage or sub-set of the classical disease. It is possible that some of these cases may represent pronounced secondary hypertrophy of the free wall, as noted earlier, and as such conversion of asymmetric to symmetric hypertrophy. However cases with symmetric hypertrophy are clinically similar (13) and some of them exhibit both left ventricular intracavitary gradient, mitral regurgitation and the systolic anterior movement of the anterior mitral leaflet.

Finally, everyone recognizes a late stage of burnt-out disease where the left ventricle is relatively dilated and the outflow obstruction is lost (15). Besides being older these cases are more symptomatic though now non-obstructive. Most cases still retain their asymmetric septal hypertrophy and while the cavity dilates, it is never enlarged to the extent of the usual Congestive Cardiomyopathy and is easy to recognise as Hypertrophic Cardiomyopathy on angio, Echo or autopsy.

Clinical Presentations:

Hypertrophic Cardiomyopathy is a great masquerader. The clinical presentations are so varied that it is difficult to give an exhaustive review of all possible presentations. Some common presentations are as follows:—

1. Chest pain.
2. Palpitations.
3. Dyspnea.
4. Syncope/sudden death.
5. Congestive heart failure and acute pulmonary edema.
6. Asymptomatic heart murmur.
7. Asymptomatic E.C.G. changes.

Chest pain complained may be typical anginal pain of effort. However, atypical chest pain is common too as is post-exertional pain (15). By history alone it may be difficult, nay, impossible to distinguish from ischemic heart disease.

The complaint of palpitation may be related to repititive supraventricular and ventricular arrythmias these patients are prone to (16). However, it is not uncommon to see patients with complaint of palpitation but no documented arrythmias even on Holter monitoring.

Dyspnea is a frequent and distressing complaint. As a rule the dyspnea is exertional but orthopnea, paroxysmal nocturnal dyspnea and dyspnea with palpitation or angina can all occur. Frank pulmonary edema and congestive heart failure occur in severe cases. If one sees acute pulmonary edema with a normal or slightly enlarged heart on X-ray chest, one of the conditions to consider is hypertrophic cardiomyopathy. Right heart failure which occurs in severe cases is as a rule not due to right ventricular outflow obstruction but usually secondary to high left atrial pressures resulting in pulmonary hypertension (17). The poor cardiac output further aggravates the problem by causing fluid retention as in other cases of heart failure.

In the author's own experience as well as those of others, a number of cases were picked upon routine physical examination by the finding of systolic murmur, left ventricular hypertrophy and a quick rising (jerky) carotid pulse. Cases have also been picked upon screening of families of index cases. Routine or insurance electrocardiograms have also identified pseudo-infarction patterns, pre-excitation or left ventricular

hypertrophy and led to the diagnosis of hypertrophic cardiomyopathy.

A common and potentially life threatening symptom is syncope. Syncope may be related to exertion and not uncommonly occurs following rather than during the exertion. The exact cause of the syncope is not known in the majority of cases (18). It is believed that it may be related to occurrence of an arrythmia or a sudden worsening of the outflow obstruction resulting in a drop in the cardiac output temporarily. Sudden death which occurs in about 2-4% of cases per year (19) may be the first manifestation of the disease in an otherwise asymptomatic individual where autopsy proves the presence of hypertrophic cardiomyopathy.

Unusual presentations may be cases with bacterial endocarditis, systemic emboli, lentiginosis, skelletal muscle and neurological disorders (20).

Cases encountered are both sporadic as well as familial. It has been claimed that asymmetric septal hypertrophy (ASH) can be regarded as a genetic marker and on family screening is seen to be transmitted as an autosomal dominant trait (21). In the author's experience both in western population and in Pakistan this is not invariably so and on screening families of patients with ASH no further cases could be located in the rest of the family members. It seems that ASH while being a genetic marker in most cases may occur sporadically. Also there is recent evidence showing dominance of certain HLA types in cases of hypertrophic cardiomyopathy (22). So while there appears to be a genetic basis for the disease, the picture is far from being totally clear.

Physical Examination:

The peripheral pulses and in particular the carotid pulses are brisk and jerky. If obstruction is present at the time of examination, the carotid is typically bisferience but unlike the large volume bisferience of aortic regurgitation.

The apex beat is forceful and sustained and typically a double or triple impulse may be palpable. The double impulse is due to the midsystolic obstruction causing an interruption in the apical impulse. The triple impulse is felt when the atrial contraction wave (a wave) is palpable. Also rarely one can feel a quadruple apical impulse when the rapid filling wave causes a palpable impulse too. On auscultation a systolic murmur may be audible which may range from a barely audible short ejection murmur to a pan-systolic thrill. The murmur is usually equally well heard at the apex and the base and may have qualities both of the aortic stenosis murmur and the mitral regurgitation murmur as both left ventricular outflow obstruction and mitral regurgitation may be occurring. In fact if in a case the clinican has difficulty deciding whether it is aortic stenosis or mitral incompetence, he should always consider and exclude hypertrophic cardiomyopathy. Ejection clicks and diastolic flow rumble may occasionally be audible. The triad of a jerky carotid pulse, a thrusting apex beat and a systolic murmur which sounds like aortic stenosis or mitral regurgitation or both should arouse suspicion of hypertrophic cardiomyopathy.

Investigations:

Electrocardiogram invariably is abnormal. As a matter of fact in review of over 2000 E.C.G's in approximately 250 proven cases of hyper-

trophic cardiomyopathy by the author, only one case of proven but early case had a normal E.C.G. As such a normal E.C.G. is a strong point against making the diagnosis of hypertrophic cardiomyopathy.

The E.C.G. may show simple left ventricular hypertrophy, pseudoinfarction patterns, right ventricular hypertrophy or only ST and T wave changes (23). Pre-excitation in all its forms is commonly seen in this condition (24).

Plain X-Ray chest is not very helpful and may show mild cardiomegaly and pulmonary venous congestion.

Echocardiography has been a great advance as far as the diagnosis of hypertrophic cardiomyopathy is concerned and has made catheterization and angiography unnecessary in the vast majority of cases. The interventricular septum can be studied in a way not possible by any other mean. The typical features seen (Fig. 2) are the asymmetrically thickened septum (i.e. septum to left ventricular free wall thickness ratio=1.3 or more) not moving much in systole, the abnormal systolic anterior motion of the mitral leaflet in systole and the small left ventricular cavity with the mitral valve placed anteriorly in the cavity (25). The introduction of Real-Time B-Scan Echo has made it possible to study the septum and its orientation in further detail (23).

Cardiac catheterization shows obstruction in the left ventricular outflow below the aortic valve (Fig. 3). Also if a premature beat occurs or is induced during pressure recording, hte stronger post premature beat causes a greater degree of dynamic obstruction where for a higher left ventricular pressure, the aortic pressure further falls, this is the well known Brockenborough phenomenon (Fig. 3). In some cases where there is no resting gradient a gradient can be provoked by inotropic stimulation by Isuprel or by inhalation of Amyl nitrite. Volume infusion and raising afterload (aortic pressure) causes reduction or disapearance of the gradient hence the name dynamic L.V. obstruction.

Left ventricular angiography shows a hypertrophied ventricle and the septal bulge into the narrow left ventricular cavity. It is not uncommon to see some mitral regurgitation usually at the point of mid-systolic abutting of the mitral anterior leaflet against the septum. However, mitral regurgitation may occur in cases without left ventricular obstruction or systolic re-opening of the mitral leaflet.

Management:

Management of hypertrophic cardiomyopathy depends on several factors including symtomatology, presence of obstruction, heart failure, arrythmias and any other associated condition.

In the presence of obstruction drugs like digitalis (inotropic agents) and nitrites (vasodilators) should be avoided as they worsen the obstruction. Inderal or more recently verapamil by their negative inotropic effect decrease the outflow obstruction and perhaps help in the diastolic relaxation of these very stiff non-compliant ventricles whose main problem is diastolic filling and not systolic emplying (26). While acute volume loss is dangerous, uses of judicious amounts of diuretics may help patient in heart failure.

In advanced non-obstructive cases especially those developing artial fibrillation the use of digitalis may be helpful alongwith diuretics. The routine use of other antiarrythmic agents for other atrial and ventricular arrythmias is

not established. Use of Inderal in early cases and for prophylaxis of sudden death is not of proven usefullness (27).

In selected cases with severe resting obstruction (⩾ 60mm Hg) and especially syncopal spells despite beta blockers, surgery is indicated. Presently in experienced centers surgery can be performed with mortality under 5%. Surgery which involves removing a chunk of the bulging septum can result in postoperative bundle branch block or an iatrogenic ventricular septal defect (28). A less well accepted approach has been to remove the other aspect of the obstruction i.e. the mitral valve and perform a prosthetic replacement (29).

Special situations like pregnancy management in patient with this disease should be under-taken in centers experienced in such problem handling. Inderal is continued throughout pregnancy and during delivery special efforts are made to prevent any sudden loss of volume. As the risk of pregnancy in most cases is not high in experienced hands, sterilization is not indicated unless the patient has completed her family or desires no further children. In advanced cases in the later stages of their disease sterilization may be a safer alternative to contraception.

Prognosis:

This author and associates (27) reviewed the prognosis and mortality in 216 patients with proven hypertrophic Cardiomyopathy. There were 119 males and 87 female patients with a mean follow up of 6 years (range 1 year to 23 years). There have been 48 deaths. 8 deaths were non cardiac, 9 were perioperative, 7 with cardiac failure and 24 patients died suddenly. Comparing the survivors with the non-survivors no significant difference was seen in right atrial pressure, pulmonary artery pressures, left ventricular end diastolic pressure and resting or provocable left ventricular outflow gradient. In short, no hemodynamic, or E.C.G. parameter predicted mortality. Beta blockers did not influence mortality. However, certain features did prove to be harbingers of poor prognosis. They were as follows:—

1. Young age at diagnosis.
2. Dizzy/Syncopal episodes.
3. Palpitations.
4. Cardiomegaly on X-Ray Chest.
5. Severe dyspnea.
6. Congestive heart failure.
7. New onset atrial fibrillation.

An overall incidence of 4% sudden cardiac death per year is seen. This figure is higher for children and surgical patients. This progrnosis is about the same as for the overall population with Ischemic Heart Disease.

Changing Concepts and Future Directions:

While hypertrophic cardiomyopathy is not a very common cardiac ailment the interest and literature it has generated have been out of proportion to its prevalence. The reason has been the dynamic and changing nature of clinical findings and the excellent opportunity it provides the student of cardiology to understand hemodynamics and their bedside correlation with physical findings. It provides excellent ground for the theorist and a good topic for the examiner to test students on.

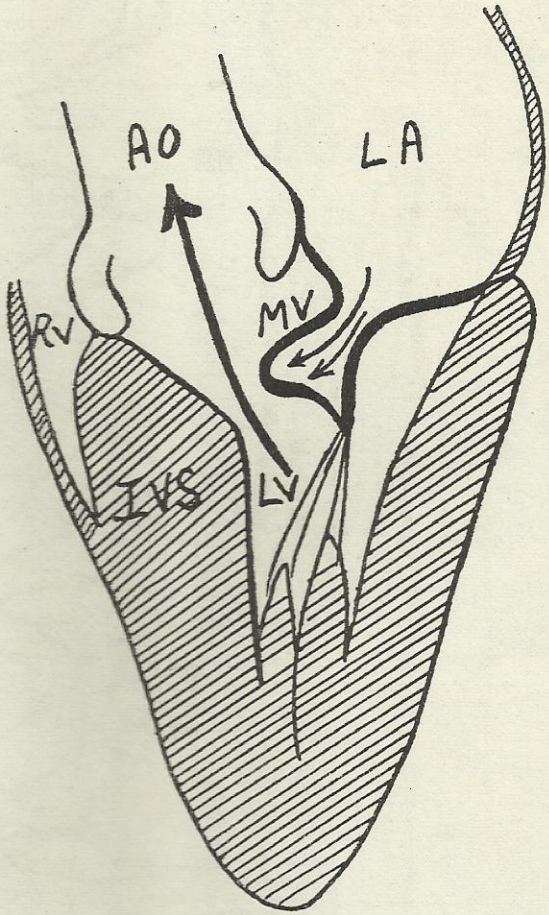

Figure 1:
The Venturi-like effect of rapid ejection through a narrow L.V. outflow thought responsible for the dynamic obstruction in Hypertrophic Cardiomyopathy.

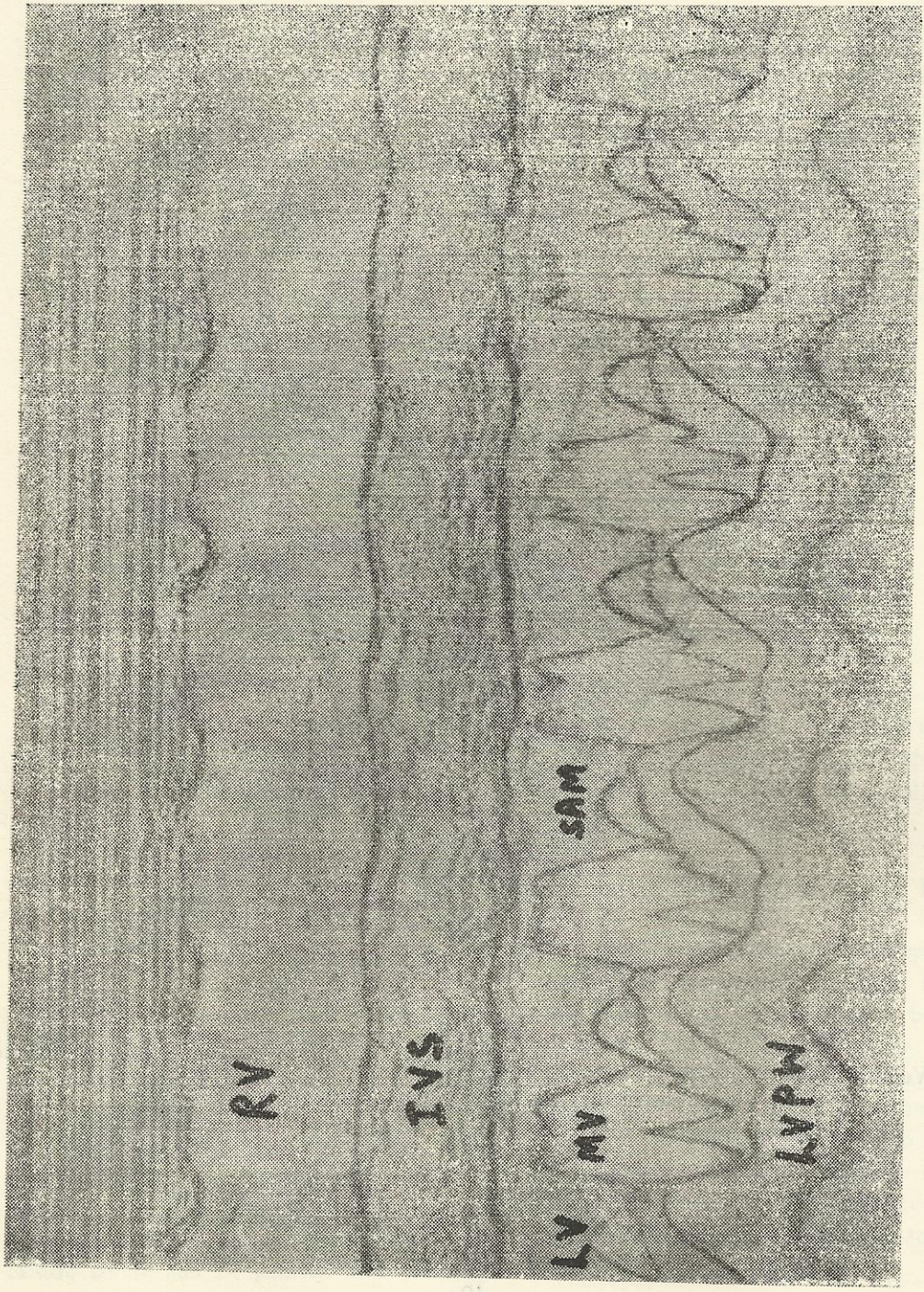

Figure 2: M-Mode Echo in Hypertrophic Cardiomyopathy showing the interventricular Septum (IVS) much thicker than the left ventricular porterior wall (LVPW). The mitral valve shows the systolic anterior motion (SAM).

Figure 3:
Pressure recording showing the gradient between the aorta and the left ventricle cavity. Post PVC worsening of obstruction (Brocken borough Phenomenon) is also shown.

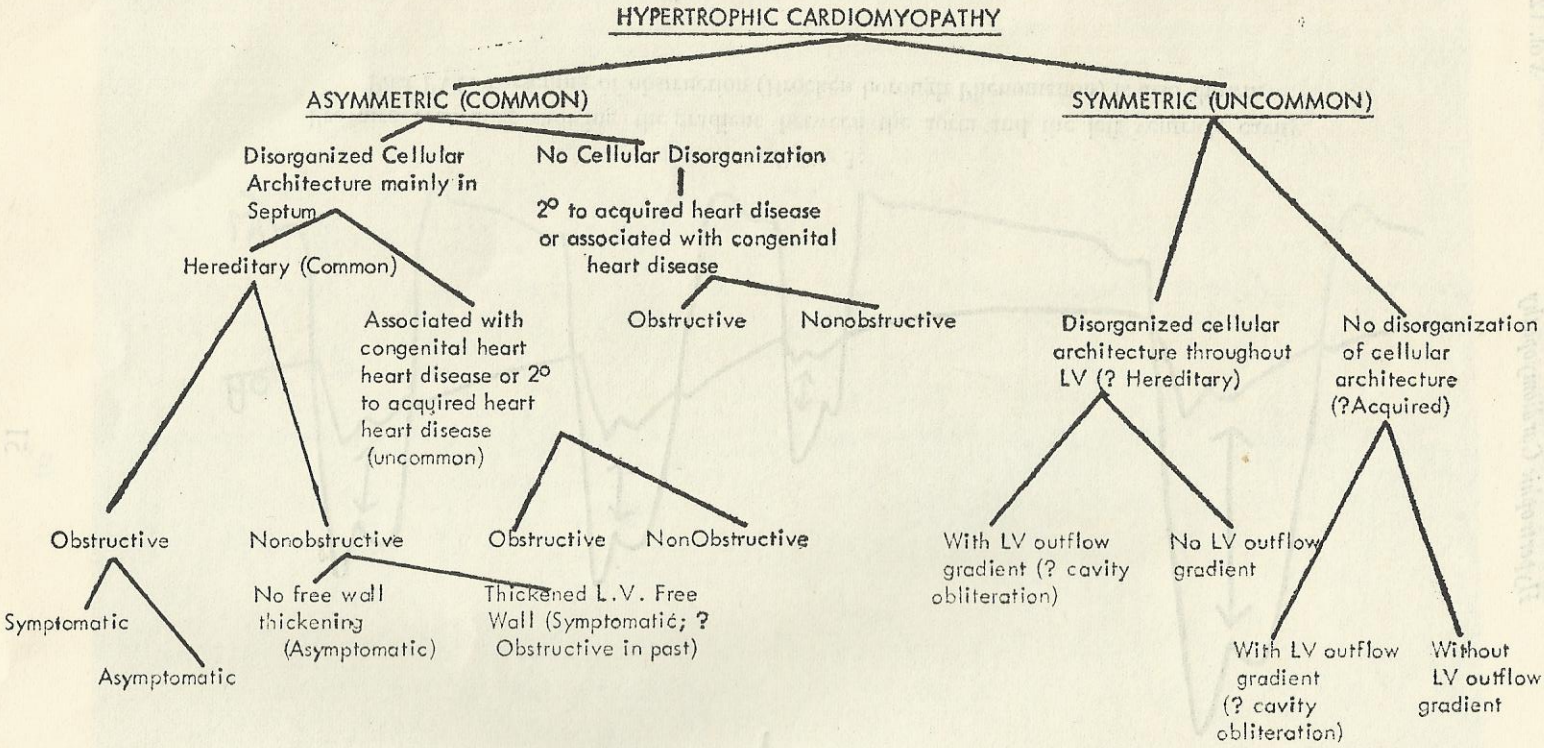

Table 2:

A Schema depicting our present day understanding of the clinico-pathological sub-sets of Hypertrophic Cardiomyopathy.

While today we still speak of hypertrophic cardiomyopathy as if it were a single entity, in reality this is probably not so. Table 2 summarizes the state of art as the author sees it today in our understanding of the various sub-sets that exist.

Looking at the future brings into focus the greatest disappointment about this disease i.e. the proor prognosis despite presently available treatment, while beta blockers cause symptomatic inprovement, there is still no proof that they influence the mortality and the high incidence of sudden death that occurs in this disease. Surgery in severely symptomatic patients has also been disappointing. Trials of surgery early in the course of the disease as are being conducted at the NIH, USA, and elsewhere are being watched. Newer drug approaches with calcium antogonists like verapamil are being tried. Holter monitoring and exercise testing are helping document arrythmias and effectiveness or otherwise of anti-arrythmic treatment (30). It is hoped that over the coming years not only will we be able to better understand the pathogenesis of this disorder but also come up with effective means of altering the serious prognosis of this disorder.

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