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THE PATHOLOGY OF CARDIOMYOPATHY. PRESENT STATE OF KNOWLEDGE

The definition and classification of myocardiopathies is presented, based on clinical, hemodynamic and pathological bases. It is important to make an early diagnosis, such as from a biopsy of endomyocardial tissue.

This article treats especifically of congestive myocardiopathy (cardiac enlargement without definite etiology) and hypertrophic myocardiopathies .The more recent knowledge on restrictive myocardiopathies (endomyocardial fibrosis) is reported in another article of this issue.

Much confusion had existed as to what diseases constituted cardiomyopathies. Recently, the World Health Organization/ ISFC Task Force meeting published a definition and classification based on Goodwin's original concept[1,2]. This definition and classification will be used in this article.

Cardiomyopathies are defined as "heart muscle diseases of unknown cause" and are classified into three major groups: dilated cardiomyopathy, hypertrophic cardiomyopathy and restrictive cardiomyopathy.

Dilated cardiomyopathy

This condition is recognized by dilatation of left or right or both ventricles. Congestive heart failure may or may not supervene. The patients may present with abnormal ventricular or atrial rhythms and death may occur at any stage.

Pathology - When patients die of this condition the hearts are usually overweight and weights of 700 g (almost double the normal for a male patient of 191 cm in height) are not unusual. Usually severe dilatation of all cardiac chambers is present (fig. 1). The myocardium is pale and flabby[3,4]. Although hypertrophy is present ventricular wall measurements may be normal (right ventricular measurement up to 3 mm and left ventricular measurement up to 14 mm), despite the hypertrophy. This is due to stretching of muscle as a result of dilatation, which masks the degree of hypertrophy that may be present. Non-specific endocardial thickening is present and thrombus may or may not be superimposed which can be located anywhere but is most frequently found in the apical region[5]. This is the consequence of poor pumping function of the heart. Foci of fibrous tissue may be found in the myocardium but this is usually limited to the inner third of the myocardium. With rare exception the coronary arteries are normal.

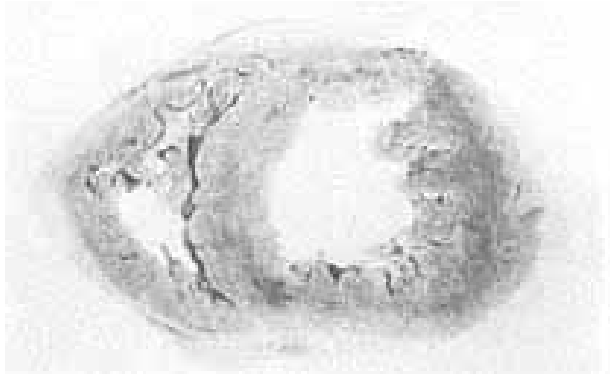

Fig 1 - Cross section of the ventricles showing dilatation of right and left ventricles from a patient with dilated (congestive) cardiomyopathy.

Histology - The myocardial fibres, as in the normal heart, are regularly arranged. Nuclear changes of hypertrophy, either in the form of vesicular changes or pyknosis, are evident but the diameter of myocardial fibres is frequently normal (fig. 2a). (Average diameter 12 μm)[6]. This is due to stretching of myocardial fibres[3,7]. As noted macroscopically the endocar-

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dium is thickened and particularly the smooth muscle component is prominent (fig. 2b). This is a non specific change and implies that dilatation had been present for some time. The intramyocardial vessels are usually normal. Occasionally, particularly in the inner third of the myocardial wall, foci of fibrous tissue, as already noted macroscopically, are frequently present. This explains the chest pain from which some of the patients may suffer. The fibrous tissue is secondary to dilatation. Mild intimal chages in the form of fibro elastic thickening may occur in some small vessels but these are considered secondary and not a primary event, had been suggested by James in 1964[5,8]. Occasionally, small accumulations of lymphocytes can be found. In view of the fact that contours of adjacent myocardial fibres are smooth, myocarditis can be ruled out.

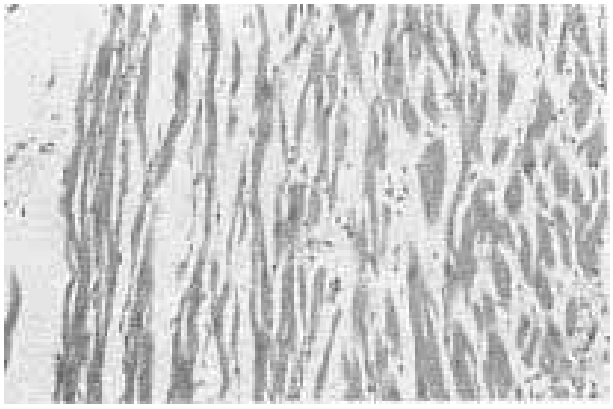

Fig 2 - Photomicrograph from a patient with dilated (congestive) cardiomyopathy showing regulary arranged, hypertrophy myocardial fibres with attenuation. Despite the hypertropy (nuclear changes) the diameter of myocardial fibres is normal This is due to stretching. Haematoxylin and Eosin x 250.

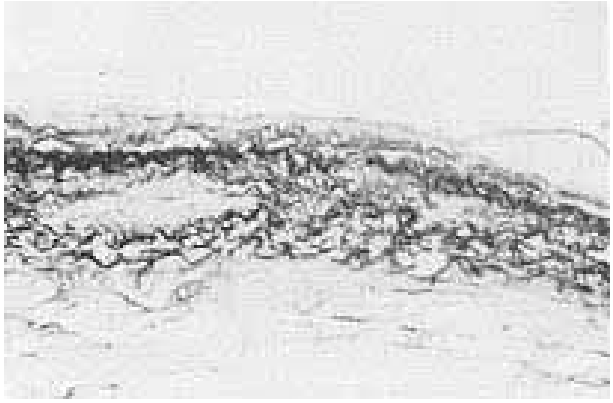

Fig 2B - Photomicrograph of the same case showing endocardial thickening with great focal prominence of the endocardial smooth muscle, located between the elastic fibres. Miller‘s elastic van Gieson x 350.

Histochemistry - These show often patchy depletion of enzyme systems, particularly succinic dehydrogenase and glycogen. At one time it had been thought that decrease is succinic dehydrogenase was a primary cause of dilated cardiomyopathy[9] . It has subsequently been found that if dilatation has been present for some time focal depletion of succinic dehydrogenase is consequent upon the dilatation of the myocardium. Similar changes of patchy depletion are also found in glycogen distribution[10].

Electron microscopy - As in the normal heart the myocardial fibrils are regularly arranged but evidence of hypertrophy, such as an increase in mitochondria, showing variation of size and shape, of more than 2 per 2 sarcomeres, cremation of nuclear membranes and Z band changes are evident. An increased number of ribosomes is found. Varying degrees of degeneration may be seen at this level of examination[10,11]. Not infrequently foci of irregularly arranged myocardial fibrils are present. These are nom specific and are found as am accompaniment of hypertrophy including those cases where the cause is determined[12,l3].

Comment - Clinically, as well as pathologically, the diagnosis of dilated (congestive) cardiomyopathy can only be made by excluding such cardiac or extra - cardiac conditions that may give rise to heart failure. Morphologically, conditions such as infiltrations of the heart or myocarditis must be excluded before a firm diagnosis of dilated cardiomyopathy can be made. To this end examination of fresh endomyocardial biopsy tissue obtained by bioptome is indicated[14]. From a pathological point of view distinction between heart failure due to alcoholic abuse and that occurring following child birth are indistinguishable from dilated cardiomyopathy at morphological level.

Extensive morphometric analyses have been made at histological and at electron microscopic levels on biopsy material and a correlation with haemodynamic parameters such as ejection fraction or LEVDP have not been confirmed[15 17]. Using a scoring system[18] degenerative changes have been analysed. It has been suggested that patients with a score of 4 points or more had a worse prognosis than those with a lower score. In our experience [17] a trend of patients showing a higher score was certainly confirmed but this unfortunately did not apply to individual patients. In order to assess prognosis great caution should therefore be exercised.

As far as the aetiological background is concerned, this is by definition unknown. The various suggested possibilities have been reviewed cardiomyopathy had been made, titres to Coxhighly suggestive of probable association with dilated cardiomyopathy[19] has shown that in15 out of 50 patients in whom a diagnosis of dilated cardiomyopathy had been made, titres to Coxsackie B viruses, of 1.024 or more were found (compared to 1 normal of 50, age and sex matched individuals). Further analysis of data has shown that most of these patients had an infection within one year preceeding the symptoms. In 11 of these 15 patients biopsy examination had been undertaken but these showed, apart from hypertrophy, and some dilatation, no evidence whatever of present or past myocarditis. Furthermore it has been shown that IgG is preferentially absorbed into tissue samples of patients with dilated (congestive) cardiomyopathy[2O]. It is therefore likely that congestive cardiomyopathy has a multifactorial aetiology[21]. It is tempting to speculate that due to sensitisation by virus and consequent immunological idiosyncrasy, with addition of other possible

factors, as yet not identified, may result in the condition we designate dilated cardiomyopathy.

As already mentioned morphological distinction between dilated (congestive) cardiomyopathy and heart failure as a results of alcohol abuse is not possible. Tissue samples obtained by bioptome, analysed for lactic dehydrogenase have shown that in haemodynamically similar patients LDH 1 (H sub units) are more numerous in alcoholic heart disease[22]. Distinction in other enzyme systems have also been shown to distinguish dilated (congestive) cardiomyopathy from alcoholic heart muscle disease[23].

Though morphology is non specific the additional investigations that are now being carried out on the biopsy material, are beginning to throw light on the problem of dilated (congestive) cardiomyopathy[14].

Hypertrophic cardiomyopathy

In the older nomenclature "with or without obstruction" was a sub-division used in the classification of this condition. It has been found that the obstructive element is incidental[24] and that the basic problem in these patients haemodynamically is failure of diastolic compliance[25].

By contrast to congestive cardiomyopathy hypertrophic cardiomyopathy can be distinguished in the majority of cases clinically together with noninvasive techniques and is characterised by disproportionate hypertrophy of the inter ventricular septum affecting the left ventricle and occasionally also the right.

The left ventricular volume is either normal or reduced. Systolic gradiants are common[1] but they may be absent

A familial incidence has been found and inheritance is usually by an autosomal dominant gene with incomplete penetrance[1].

Macroscopically very severe asymmetric hypertrophy of the interventricular septum, when compared with the already hypertrophied free wall of the left ventricle is a highly characteristic finding (fig. 3). This asymmetric hypertrophy may either be diffuse or localised and very occasionally concentric hypertrophy of the left ventricle may be found[26]. As a result of this bulge of the septum the anterior papillary muscle is displaced and interferes with the normal function of the mitral valve apparatus. Frequently as a result of mitral valve dysfunction and disproportionate thickening of the interventricular septum the anterior mitral valve leaflet leaves an imprint in the form of endocardial thickening on the outflow tract of the left ventricle, the so called "mirror image of the anterior leaflet[27] (fig. 3). Coronary arteries as usually, are normal.

Histologically, five characteristic features are noted. Theses are: short runs of myocardial fibres interrupted by connective tissue; large bizarre shaped nuclei; fibrosis; degenerating muscle fibres with disappearing myofibrils resulting in a clear zone, the so called perinuclear halo; disorganised "whorling" muscle (fig. 4).

The five characteristic features formed the basis of the histological HOCM Index[12].

Fig 3. - Left ventricular outflow tract from a patient with hypertrophic cardiomyopathy. The bulge of the interventricular septum is central and indicated by the light reflection is this photograph. Note also the mirror image of the anterior leaflet.

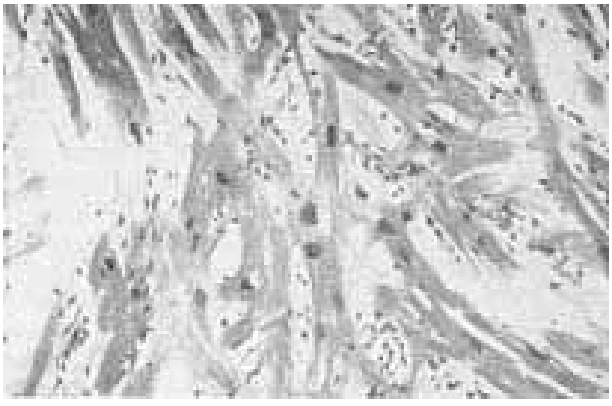

Fig 4. - Photomicrograph from the same patient showing irregularly arranged severely hypertrophied myocardial fibres together with attempts to whorl formation. Haematoxylin and Eosin x 250.

Histochemistry - Great accumulations of glycogen, particularly in the area of the perinuclear halo, have also diagnostic significance. Other enzyme systems assessed histochemically showed frequently an increase but they do not substantially contribute to the diagnosis of this condition[26].

Electron microscopy - Shows disarray of myocardial fibrils coursing in all directions, myofilaments abnormally arranged and frequent abnormal intercellular junctions[12,28]. In addition fibrillar degeneration, focal mitochondrial accummulations, often severe with varying degrees of damage, and an increased number of lysosomes as well as the swelling of the sarcotubular system and Z band changes complete the characteristic changes at this level of investigation.

Comment - Doubt had been cast in recent years regarding the morphological characteristic features of this condition. It is certainly true that some asymmetric hypertrophy of the interventricular septum may occur in congenital heart disease and other cardiac conditions[29 31]. If the ratio of the ventricular septum to the posterior left ventricular free wall exceeds 1.3 this is suggestive of hypertrophic cardiomyopathy. In my experience, the ratio is frequently well above 1.3 and values of 2.5 3 are not unusual. If values of this magnitude are obtained such findings are highly characteristic of hypertrophic cardiomyopathy at macroscopic examination.

Histological confirmation is however desirable and necessary, particularly if the ratio values are low. Regarding histological evaluation, if the criteria mentioned above are present in combination then the diagnosis is not in doubt, particularly if accompanied by an increase of glycogen in the region of the perinuclear halos. The disarray at histological level[32] and changes at electron microscopic level are also confirmatory of the condition. Diagnosis by electron microscopic examination alone must however, be interpreted with caution because the features described above may be found in conditions of secondary cardiac hypertrophy[12].

There is therefore no doubt that apart from clinical and echocardiographical examination morphological changes are sufficiently characteristic to permit a firm diagnosis of hypertrophic cardiomyopathy.

It must be remembered that hyperthrophic cardiomyopathy may occur in a variety of other cardiovascular diseases such as hyperthyroidisn[33], Friedreich's ataxia[34] and lentigenosis[35]. The subject has recently been critically analysed[26].

Regarding the association of hyperthyroidism, experimental work has suggested that in some patients endogenous hormone production could be causally related to hyperthrophic cardiomyopathy[36,37]. Regarding other aetiological suggestions that have been made, these have been summarised by Olsen, 1980[38].

Restrictive cardiomyopathy

Under this category diseases considered for a long time to be separate entities are included. They are: endomyocardial fibrosis and Löffler's endomyocardial disease. It had been considered that the first mentioned condition was limited to the tropical zones, while Löffler's endomyocardial disease to the temperate zones. In another article this subject will be discussed in greater detail and evidence will be presented that these two, hitherto considered separate entities, belong in fact to the same disease process (see "The pathophysiology of endomyocardial fibrosis").

To sum it up in this chapter the definition and classification of cardiomyopathy are included: dilated, hypertrophic and restrictive.

Distinction between the three groups can be made on clinical, haemodynamic and pathological features. Dilated and hypertrophic cardiomyopathy are discussed in detail in this chapter and some comments regarding recent views expressed in the literature, as well as aetiological suggestions are discussed. Restrictive cardiomyopathy (endomyocardial fibrosis and Löffler's endomyocardial disease) will be discussed in another article in this special edition of *Arquivos Brasileiros de Cardiologia*.

The use of the bioptome permits now the examination of fresh endomyocardial tissue to be evaluated and this procedure has proved useful as an adjunct to the diagnosis of cardiomyopathy and permits recognition of early cases. By additional examinations that have been carried out, such as virological, biochemical and enzyme analyses, as well as immunological studies, these are now beginning to throw light on the problems of cardiomyopathy.

RESUMO

O autor apresenta a definição e classificação de cardiomiopatias, destacando a diferenciação com base em elementos de ordem clínica, hemodinâmica e patológica. Também chama atenção para a importância do reconhecimento precoce dessas entidades clínicas, o que pode ser feito mediante a análise de tecido endomiocárdico recolhido por biopsia cardíaca. O autor ocupa-se particularmente da cardiomiopatia congestiva (aumento do coração sem causa determinada) e da cardiomiopatia hipertrófica. Os mais recentes conhecimentos sobre o tipo restritivo de cardiomiopatia (endomiocardiofibrose) são tratados em outro artigo deste número especial da revista.

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