Review Article

Why Look for Myocardial Disarray

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ABSTRACT

Myocardial disarray is the screening tool for HCM (hypertrophy cardiomyopathy). It is also found in hypertension, congenital heart disease, corpulmonale, etc. Many patients died from heart failure due to myocardial disarray. The risk of premature death may be determined by the degree of myocyte disarray. This article reviews the anatomical explanation of myocardial disarray. It also discusses the pathogenesis of the myocardial disorganization that causes heart failure. How to measure myocardial disarray has also been assessed. Therefore, early detection of myocardial disarray is advised to prevent heart failure.

KEY WORDS : *Myocardial disarray, Cardiac muscle, HCM, Heart failure*

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INTRODUCTION

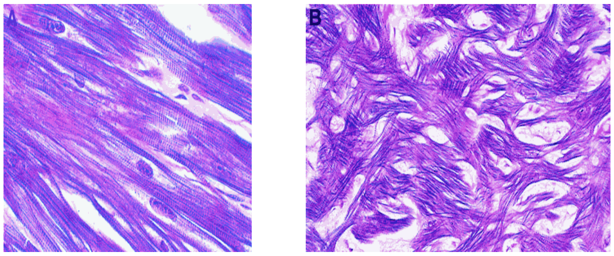
Myocardial disarray is defined as an area of the myocardium where adjacent myocardial cells are aligned perpendicularly or obliquely to each other rather than their normal parallel alignment (Figure 1).[1] Myocardial disarray is a definitive pathological feature of hypertrophic cardiomyopathy HCM.[2] This lesion is also observed in coronary heart disease, cor pulmonale[3], congenital heart disease[1,4], myocardial infarction, and hypertension[5]. It is usually found abundantly in the interventricular septum and also found in the ventricular free wall[6,7]. Males are more predisposed to disarray than females.[8] The disarray has no relation with heart weight.[1,9]

Classification of myocardial disarray:

Myocardial disarray is classified into four types[6] (Figures 2 & 3). This classification has been accepted worldwide.[10, 11,12]

Types I-A : When cardiac muscle cells are oriented obliquely or perpendicularly to each other in the form of tangled masses or "pinwheel" configuration. This is the most common form of cellular disorganization.

Type I-B : When bundles of muscle cells are oriented obliquely or perpendicularly to each other in the form of “windmill” configurations.[11] This type is relatively uncommon. However, cells within this bundle are normally arranged.



A. Normal heart muscle B. Myocardial disarray

Fig. 1 : Photomicrograph showing the (A) normal and (B) myocardial disarrayed [13]

Type II-A : This type of disorganization consists of relatively narrow batches of cells usually one or two cells wide. Cells are arranged in various directions in the form of a "swirled appearance".

Type II-B : It is similar to type II-A disorganization except that the narrow, longitudinal cut bundle of cells is more linear.

Type II-C : It is a rare form of myocardial disarray. In this type, cardiac muscle cells showed a relatively small "island" of disorganization.

Type I-A and I-B are exclusively found in the septum and muscle cells are arranged rectangular in longitudinal sections. Type II-A, II-B, and II-C disorganization are placed in a longitudinal direction within the large transverse section. Septal myocardial disarray is well found in transverse sections in HCM.[6] Interestingly, disarray varies in terms of the plan of the section. It may present in one plane, however, cannot be discernible in another plane. [16]

Electron Microscopic feature of myocardial disarray : Under an electron microscope, a variable amount of collagen fibres is present that separate the bundle of muscle cells. Cells are wider and shorter. The transverse diameter of cells is up to 80 µm (normal 10-15µm). Some areas of cells are rectangular in shape. Several intercellular branching in various directions has also been found. Myofibrils within the cells are extremely disorganized, oriented obliquely or perpendicular to the longitudinal axes of the cells, rather than in a parallel arrangement. Z bands were widened and split with the formation of new sarcomeres. (Figure 3). The nuclei are markedly enlarged and the nuclear membrane are showed bizarre convolutions. The degrees of convolution of the nuclear membrane appear greater. (Figure 4 above picture).

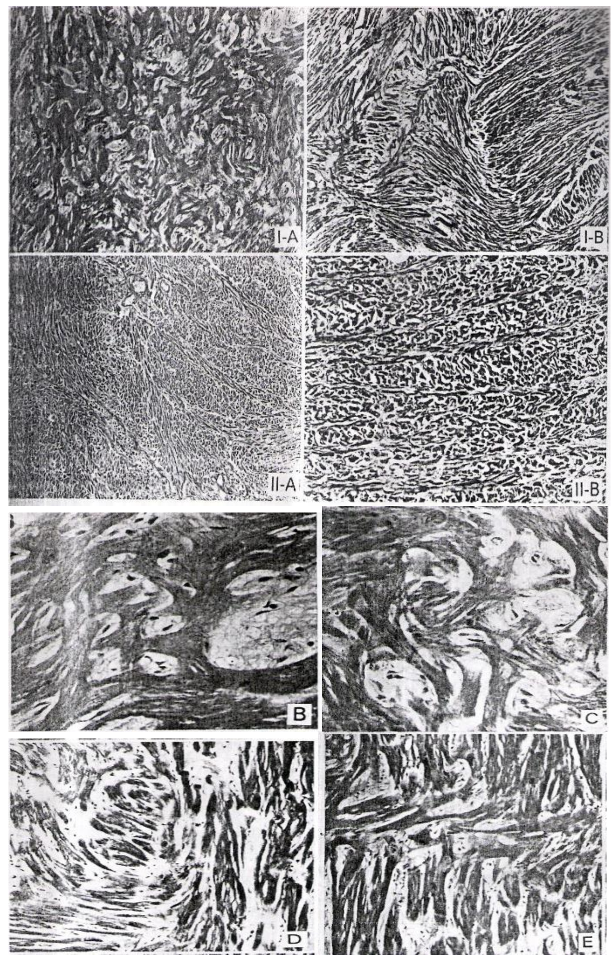


Fig. 2 : Photomicrograph shows the different types of I-A, I-B, II-A, and II-B of myocardial disarray. B Swiss cheese appearance C. Tangled arrangement of cardiac muscle cells in form of whorled configuration. D. Some cells are oriented circumferentially to other cells. E Small group of the cells are oriented at an extremely acute angle to large groups of cells (II C).[6]

There are extensive intracellular junctions, arranged in a side to side instead of end to end apposition that demonstrated the loss of their normal parallel arrangement (Figure 4 middle picture). Mitochondrial damage (swelling of mitochondria and disruption of cristae) was profound. Lysosome, ribosome, glycogen, and lipofuscin granules were abundant. Ribosomes are occurred in free and in perinuclear areas. The transverse tubule system is dilated (Figure 4 below). [6,14,15]

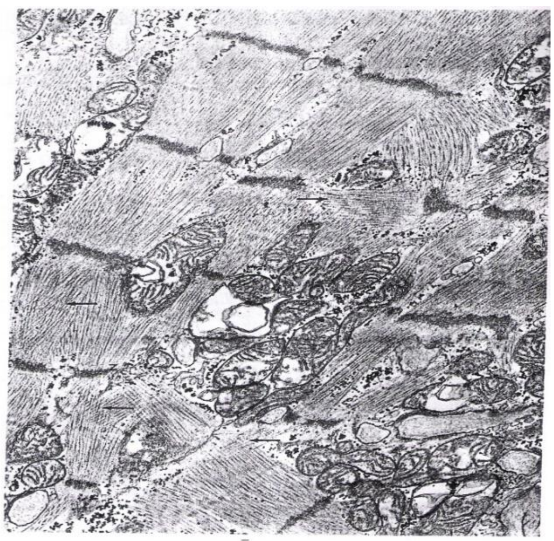


Fig. 3 : Photomicrograph shows myofilaments that originate from single Z bands inserted into several different myofibrils indicating marked disorganization of myofibrils and myofilaments (arrow) [15]

Myocardial disarray and HCM: Myocyte disarray was first reported by Terea in 1958. He found that sudden death and unexpected death toll his eight out of nine patients with asymmetric septal hypertrophy (ASH) had myocardial disarray.[11] Several investigators on analysis of tissue at necropsy, operation, or biopsy have confirmed the observation of Teara and proposed that disorganized cardiac muscle is a pathognomonic feature of HCM.[1,12] Electron microscopic and echocardiographic analysis have also confirmed this observation. [6; 13,15 16]

Myocardial disarrangement is also found in both obstructive[17] and non-obstructive idiopathic hypertrophic cardiomyopathy[11,16], dilated cardiomyopathy[7,9,] and constrictive cardiomyopathy[16]. Vernava and colleagues added that patients with dilated cardiomyopathy had a greater amount of disarray in the early stage of the disease but diminished with time as a result of myocyte loss later is replaced by fibrosis.[9]

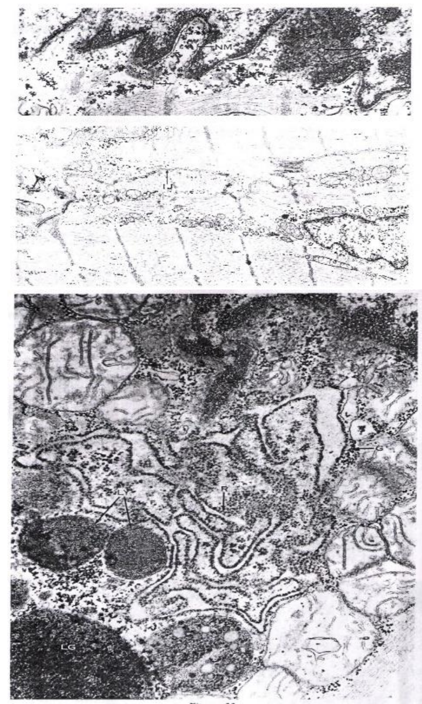


Fig. 4: Top picture shows a bizarre nuclear membrane NM (arrow). Extensive side-to-side intercellular junction (IJ) between the muscle cells (middle). A large number of the ribosome (R), Glycogen particles (G), and lysosome (LY) contain lipid droplets, and lipofuscin granule(LG) [15].

Myocardial disarray, HCM, and sudden death: Myocardial disarray is associated with sudden death. A young adult with sudden premature death had myocardial disarray. Extensive myocardial disorganization had been reported in the left ventricular wall at necropsy of a 25-year-old patient with HCM who died suddenly.[6] The animal study confirmed that four of the seven cats died suddenly and unexpectedly of those with marked cardiac muscle cell disorganization in the ventricular septum associated with HCM.[12] Similar results have also been found by Varnava who reported that eight out of nine young patients with greater myocardial disarray died suddenly from HCM.[9]

Myocardial disarray and hypertension: Myocardial disarray has been found in hypertensive heart.[1,3,5] However, Bel- Kahn reported that hypertensive patients have less than five percent involvement of myocyte disarray.[3]

Myocardial disarray and diabetes: Available literature shows that there is no direct relationship between myocardial disarray and diabetes. The literature indicates that one out of 70 diabetic patients with HCM died suddenly. At necropsy, the heart showed myocyte hypertrophy and myocardial disorganization.[18] Another study revealed that a macrosomic male fetus of a diabetic mother had HCM. Death of the fetus was considered from HCM though fetal cardiac function was not determined.[19] However, in diabase, diastolic function impairs due to abnormal stiffness, and prolonged relaxation phase.[20] The total velocity-time, early passive period of ventricular filling, and late active period of atrial emptying are also depressed in diabetic patients compared to nondiabetic patients [20]. This passive compliance dysfunction may have a relation to the o development of myofibre disarray in diabetes HCM.[21]

Pathogenesis of disarray: Bulklet et al. proposed that physiologically the myocardial disorganization may be produced by hemodynamic derangement in the early developmental stages of the heart. During the formation of the normal pattern of bone and cartilage, linear stress is needed. Similarly, the contraction-induced linear stresses are probably important to proper muscle fiber alignment during the development of the ventricular myocardium. Abnormal muscular contractions in middle and late systole, particularly when present early in life, may lead to the development of disorganization of muscle fiber in idiopathic hypertrophy subaortic stenosis (IHSS).[4] It is also suggested that the myocyte asynergy is important in the pathogenesis of severe congestive heart failure in HCM.[22.] Abnormally arranged cardiac muscle cells do not produce an efficient pattern of contractility and may be responsible for marked functional limitation, and may cause premature sudden death in HCM.[6] It cannot produce an orderly pattern of electrical depolarization and repolarization, which impairs the transmission of normal electrophysiological impulses. This causes ventricular arrhythmia that develops into heart failure from HCM.[1] Three-dimensional finite element models also explained the same notion.[23] Therefore, mechanical stress is important in the histogenesis of fiber disarray that creates myofibre dispersion and reduces sarcomere length.[23]

Cellular biology recommends that; the transverse diameter of cells is increased in HCM. To maintain the intercellular connection with several adjacent cells they are disorganized at oblique or perpendicular angles to each other. Therefore, an area of normal or only slightly increased left ventricular wall thickness may also show evidence of the myocardiopathy process in the form of cellular disarray. Nevertheless, there is little correlation between wall thickness and amount of disorganized myocyte.

However, molecular genetics proposed that mutation of the structure of myofibrils might be responsible for the myocyte and myofibrillar disarray. It is estimated that about 30 percent of familial HCM are due to mutation of the myosin heavy chain (MHC) gene, fifteen percent are due to Troponin T and less than three percent are due to tropomyosin mutation (and remaining are due to another gene gene).[24] Some suggested that random methylation of the diseased gene or mitochondrial DNA heteroplasmy may play a role in the pathogenesis of disarray.[9]

In a transgenic animal model, mutation of MHC is directly caused by non-uniformity of ventricular relaxation or increased chamber stiffness that leads to reduced cardiac output. Thus the myocyte disarray is developed secondary to hemodynamic abnormalities that in turn developed myocyte hypertrophy. Injured myocyte fibres are later replaced by fibrosis.[8] Troponin T mutations cause severe disarray with mild hypertrophy and fibrosis. Thus the risk of premature death may be determined by the level of myocyte disarray and is independent of the degree of cardiac hypertrophy.[25]

Other said that the pharmacologically, pathogenesis of myocardial disorder has a link to norepinephrine stimulation. Faulty interaction between the adrenergic stimulus (norepinephrine) and myocardial adrenergic receptors may play a fundamental role in initiating myocardial cellular disarray. The timing of autonomic derangement may prove crucial, with the highest yield in immature hearts that still harbor disproportionate septal thickness and are susceptible to the development of marked cellular disorganization. Thus the presence of abnormal septal cellular disarray may be responsible for the failure of regression of embryonic and fetal disproportionate septal thickness, setting the stage for subsequent progression to the clinically overt disease.[26]This might be the answer the researchers to find out disarray in fetal and infant hearts.[4,27]

Moreover, Fineschi et al. also proposed that the risk of premature death is determined mainly by myocyte disarray but has little relationship with HCM. A study was done on 340 hearts indicating a link between adrenergic overactivity and myocardial disarray.[28] These authors divided the patients into seven groups such as (1) sudden/ unexpected coronary death, (2) sudden/ unexpected death in silent Chagas disease, (3) brain hemorrhage, (4) transplanted heart, (5) congestive heart failure, (6) acquired immune deficiency syndrome(AIDS) cocaine abuse and (7) control heart and correlated to heart weight, myocardial disarray, extend of fibrosis and contraction band necrosis. Myocardial disarray has found an association with an increased sympathetic tone, especially in sudden/unexpected death. Fineschi et al. concluded that the histogenesis of disarray may be due to over activity of the sympathetic nervous system.[28]

Myocardial disarray and fibrosis: Interstitial collagen content is increased in HCM, hypertension, and diabetes. Extracellular fibrosis is eight times greater in HCM and three times greater in hypertension than control.[29] Expansion of matrix collagen independently produces segmental wall thickness, degree of regional myocyte disorganization, left ventricular diastolic dysfunction, small vessels disease, myocardial ischemia and sudden death in HCM.[29]

Usually, collagen type I and III is important for maintain of left ventricular geometry and myocyte alignment.[30] Collagen synthesis is degraded by matrix metalloproteinase (MMPs) and this degradation is regulated by tissue inhibitor matrix metalloproteinase (TIMPs). In dilated cardiomyopathy and ischemic cardiomyopathy TIMPs are increase causes excessive collagenolysis leads to myocyte rearrangement (slippage) that account for wall thinning and dilatation which characterizes end stage heart failure.[30,31] In addition, angiotensin II, endothelin and aldosterone are sufficient to trigger excessive fibrosis in myocardium.[32] Angiotensin II can also influence MMP-I. [33]

How to measure disarray: Many techniques has been deployed to measure disarray. Manually, percentage of disarray involvement can be estimated from histological tissue sections using planimeter from microphotographs.[6] Myocardial disarray can also be measured by computer-assisted morphometry. Myocyte outlines are traced from scanned microphotographs and can record. The average area of disarray is determined using quantitative image analysis software. Mean myofibre disarray is expressed in square pixels.[34]

An accurate angulation of myofibre organization is required for predicting regional cardiac function. Deviation greater than 20^0 are normally considered as disarray[35]. Three dimensional finite element models has been proposed to measure the angulations. Myocyte angulation greater than 20^0 can reduce systolic shortening, torsional systolic shear as well as sarcomere length. Thus the angular deviation can be used as a sensitive indicator of the presence of disarray[23].

However, mean orientation and standard deviation of disarray can be measured accurately by both manual and computer based methods. The human estimation of the angle is error-prone and subject dependent [35]. Thus, the differing angulation dispersion, as well as differing mean orientation is used to estimate myocardial disarray by automated methods (this method is used in assessing the orientation of textural patterns, such as herringbone weave in cloth (Figure 5). By this method, a large number of areas in any given tissue section can measure faster and more objectively than the manual or any other computer based-techniques.

High-resolution episcopacy microscopy (HREM) can visualize the hearts and morphological features in three dimensions (3D) even a few microns from pos- mortem heart. The orientation of cardio myocytes is assessed by computation of helical structure and angles can be measure by structure tensor method through MATLAB.[36]

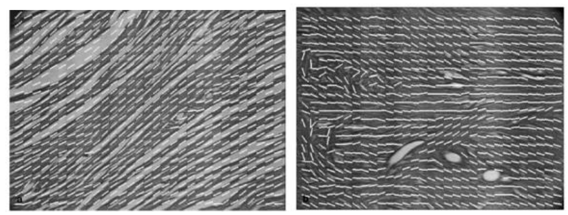


Fig. 5 : shows sample images of normal (left) and disarrayed (right) tissue section by automated method [35]

Currently, myocardial disarray can be mapped using diffusion tensor cardiac magnetic resonance (DT-CMR) image that is noninvasive and feasible in humans in vivo. Fractional anisotropy (FA) is reduced in HCM due to disarray and fibrosis that may cause ventricular arrhythmia. In diastole, cine, late gadolinium enhancement (LGE), and extracellular volume (ECV) are significantly low FA.[38] A single mid-ventricular short-axis slice at the diastole is sufficient for detection of myocardial disarray by holding breath for 18-heartbeat at a heart rate of 60 beats/min.[37]

CONCLUSION

From the above literature, it has been seen that myocardial disarray is the pathognomy feature for HCM. Myocardial disarray is also found in hypertension, congenital heart disease, corpulmonale etc. Many patients died suddenly and unacceptably from myocardial disarray. The risk of premature death may be determined by the degree of myocyte disarray. Expansion of matrix collagen independently produces segmental wall thickness, degree of regional myocyte disorganization, left ventricular diastolic dysfunction, small vessels disease, myocardial ischemia, and sudden death in HCM. Therefore, early detection of myocardial disarray is advised to prevent heart failure. Recently DT-CMR imaging, a noninvasive procedure for detection of myocardial disarray is possible in humans in vivo.

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Author Contribution: 1st author Shamima Parvin Lasker conceived the idea, did the literature review and wrote the article. 2nd and 3rd authors Craig McLachlan and Laxin Wang reviewed the manuscript. 4th author Harbert Jelinek meticulously guided to write in manuscript.

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