INTRODUCTION

Hypertrophic Cardiomyopathy

For over 50 years, hypertrophic cardiomyopathy (HCM) has been recognized as a familial cardiac disease with highly visible risk for sudden death and disease progression, characterized by heterogeneous phenotypic expression, natural history, and genetic profile. [1–6]

Although HCM is the preferred nomenclature to describe this disease,[7] confusion over the names used to characterize the entity of HCM has arisen over the years. At last count > 80 individual names, terms, and acronyms have been used (most by early investigators) to describe HCM.[7] Furthermore, nomenclature that was popular in the 1960s and 1970s, such as IHSS (idiopathic hypertrophic subaortic stenosis) or HOCM (hypertrophic obstructive cardiomyopathy), is potentially confusing by virtue of the inference that LVOT is an invariable and obligatory component of the disease. In fact, fully one third of patients have no obstruction either at rest or with physiologic provocation.[8] Although terms such as IHSS and HOCM persist occasionally in informal usage, they now rarely appear in the literature, whereas HCM, initially used in 1979, allows for both the obstructive and nonobstructive hemodynamic forms and has become the predominant formal term used to designate this disease.[7]

Definition:

Disease state characterized by unexplained LV hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy evident in a given patient,[3,4,7,9-11] with the caveat that patients

who are genotype positive may be phenotypically negative without overt hypertrophy.[12,13]

Clinically, HCM is usually recognized by maximal LV wall thickness ≥15 mm, with wall thickness of 13 to 14 mm considered borderline, particularly in the presence of other compelling information (e.g., family history of HCM), based on echocardiography.

In the case of children, increased LV wall thickness is defined as wall thickness ≥ 2 standard deviations above the mean (z score ≥2) for age, sex, or body size.[12,13]

Prevalence:

HCM is a common genetic cardiovascular disease. In addition, HCM is a global disease [14], with epidemiological studies from several parts of the world [15] reporting a similar prevalence of left ventricular (LV) hypertrophy, the quintessential phenotype of HCM, to be about 0.2% (ie, 1:500) in the general population, which is equivalent to at least 600 000 people affected in the United States.[9]

This estimated frequency in the general population appears to exceed the relatively uncommon occurrence of HCM in cardiology practices, implying that most affected individuals remain unidentified, probably in most cases without symptoms or shortened life expectancy.

Genetic basis:

HCM is caused by an autosomal dominant mutation in genes that encode sarcomere proteins or sarcomere associated proteins as in figure (1). The most vigorous evidence indicates that 8 genes are known to definitively cause

HCM*: beta myosin heavy chain, myosin binding protein C, troponin T, troponin I, alpha tropomyosin, actin, regulatory light chain, and essential light chain* .[10,11,16–19] ,in addition, *actinin and myozenin* are associated with less definitive evidence for causing HCM as in table (1) .

At this time there is inconclusive evidence to support other genes causing HCM [20-23], but research is ongoing and other genetic causes may be identified [24,25].

A single mutation in 1 of the 2 alleles (or copies) of a gene is sufficient to cause HCM; however, 5% of patients with HCM have ≥2 mutations in the same gene or different genes [26,27].

Table (1): Cardiac Hypertrophy Disease Genes.[28]

LOCUS	SYMBOL	NAME	FUNCTION	DISEASE
1q32	*TNNT2*	Cardiac troponin T	Sarcomere	HCM
2q31	*TTN*	Titin	Sarcomere	HCM
3p21	*MYL3*	Essential myosin light chain	Sarcomere	HCM
3p21-p14	*TNNC1*	Cardiac troponin C	Sarcomere	HCM
11p11.2	*MYBPC3*	Cardiac myosin binding protein C	Sarcomere	HCM
12q23-q24	*MYL2*	Regulatory myosin light chain	Sarcomere	HCM
14q12	*MYH7*	Beta-myosin heavy chain	Sarcomere	HCM
14q12	*MYH6*	Alpha-myosin heavy chain	Sarcomere	HCM
15q14	*ACTC*	Cardiac actin	Sarcomere	HCM
15q22	*TPM1*	Alpha-tropomyosin	Sarcomere	HCM
19p13.2	*TNNI3*	Cardiac troponin I	Sarcomere	HCM
7q36	*PRKAG2*	Protein kinase, AMP-activated, noncatalytic, gamma$_2$	Metabolism	PRKAG2 cardiomyopathy
Xq22	*GLA*	Alpha-galactosidase A	Lysosome, metabolism	Fabry disease
Xq24	*LAMP2*	Lysosome-associated membrane protein B	Lysosome, metabolism	Danon disease

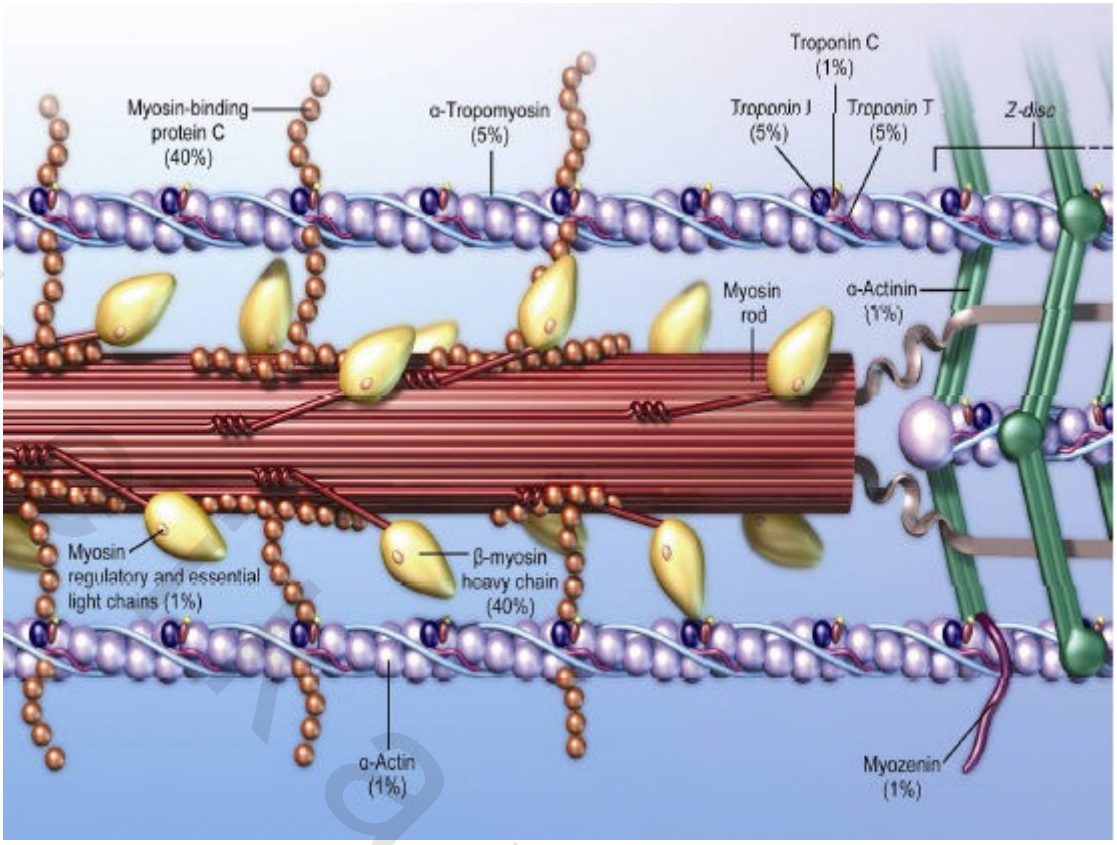

Figure (1): **Cardiac sarcomere**; showing the location of known disease-causing genes for HCM. [29]

Sporadic HCM can reflect an inaccurate family history, incomplete penetrance (absence of clinical expression despite the presence of a mutation) in family members, or a de novo (new) mutation that can initiate new familial disease [24,25].

Non-sarcomeric protein mutations cause storage diseases that are **phenocopies of sarcomeric HCM** and require molecular diagnosis, namely, Fabry disease, γ_2 regulatory subunit of adenosine monophosphate–activated protein kinase (*PRKAG2*), and lysosome-associated membrane protein 2 (*LAMP2;* Danon disease).[30,31] Clinical presentation is often indistinguishable from sarcomeric HCM, although *PRKAG2* and *LAMP2* are frequently associated with ventricular preexcitation. *LAMP2* cardiomyopathy, which is

characterized by massive LV hypertrophy and profound clinical course refractory to defibrillator therapy (with survival beyond 25 years unusual), necessitates consideration for early heart transplantation.[31]

Histopathology:

In HCM, cardiac muscle cells (myocytes) in both ventricular septum and LV free wall show increased transverse diameter and bizarre shapes, often maintaining intercellular connections with several adjacent cells.[3] Many myocytes (and myofilaments) are arranged in chaotic, disorganized patterns at oblique and perpendicular angles. Areas of disorganized architecture are evident in 95% of HCM patients at autopsy, usually occupying substantial portions of hypertrophied (as well as nonhypertrophied) LV myocardium (33% of septum and 25% of free wall).[3]

Abnormal intramural coronary arteries with thickened walls (composed of increased intimal and medial components) and narrowed lumen are present in 80% of patients at necropsy, most frequently within or close to areas of replacement fibrosis.[3,4,32] This microvascular small-vessel disease[32] is responsible for clinically silent myocardial ischemia[32] and myocyte death, leading to a repair process in the form of replacement (often transmural) with fibrosis[3,32-34]. Also, the volume of the interstitial (matrix) collagen compartment, constituting the structural LV framework, is greatly expanded.

It is likely that the disorganized cellular architecture and replacement fibrosis evident in HCM impair transmission of electrophysiologic impulses and predispose to disordered patterns and increased dispersion of electrical depolarization and repolarization, in turn serving as an electrically unstable substrate and nidus for reentry ventricular tachyarrhythmias and sudden death as in figure (2).

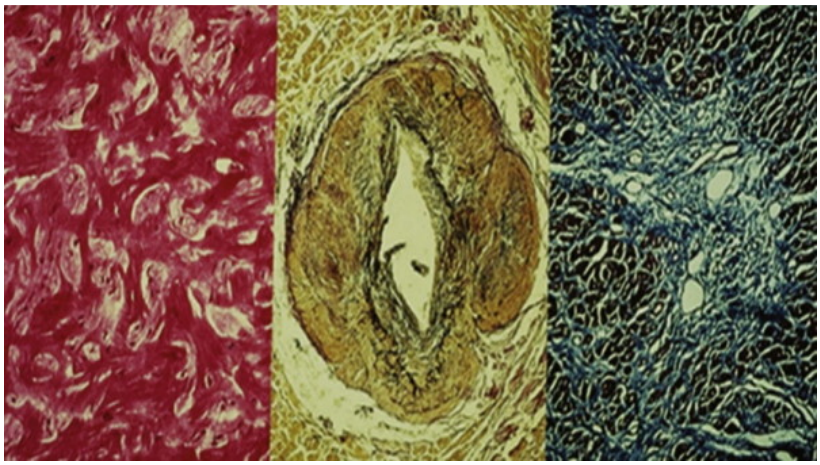

Figure (2): Arrhythmogenic myocardial substrate[35]. **Left,** Disorganized LV architecture with myocyte disarray. **Center,** Small-vessel disease; remodeled intramural coronary arteriole with thickened media and narrowed lumen. **Right,** Repair process with replacement fibrosis, the consequence of silent myocardial ischemia and myocyte death.

Morphology:

1-LVH

Diverse patterns of asymmetric LV hypertrophy are characteristic of HCM, including dissimilar phenotypes in relatives (with the exception of identical twins). Typically, one or more regions of the LV wall are of greater thickness than other areas, frequently with sharp transitions in thickness between adjacent areas or noncontiguous patterns of segmental hypertrophy, as well as extension into the right ventricle.[36] However, there is not a single "classic" morphologic form, and virtually all possible patterns of LV hypertrophy have been reported in HCM, including genetically affected children and adults with normal LV wall thicknesses.[3,4,6] There is no evidence that specific patterns of LV hypertrophy are consistently related to outcome.[3,4]

Hypertrophy is frequently diffuse, involving portions of both ventricular septum and LV free wall, including some patients with the greatest magnitude of LV hypertrophy observed in any cardiac disease with wall thicknesses ranging to 50 to 60 mm.[6] However, in about 50% of patients, LV hypertrophy is nondiffuse, including a sizeable minority with wall thickening confined to segmental areas of the LV chamber.

Wall thickening limited to the most distal portion of the LV chamber (apical HCM) represents a morphologic form characterized by a "spade" deformity of the distal left ventricle and marked T wave negativity on electrocardiography that may be due to mutations in proteins of the cardiac sarcomere.

LV hypertrophy commonly develops dynamically after a variable period of latency. Typically, the HCM phenotype is incomplete until adolescence, when accelerated growth and maturation are often accompanied by spontaneous and striking increases in LV wall thickness (i.e., average 100% change) and more extensive distribution of hypertrophy.[3,4] These structural changes, which occasionally may be delayed until later in midlife, are part of a genetically predetermined remodeling process not usually associated with development of symptoms or arrhythmia-related events.

2-Mitral Valve Apparatus

Structural abnormalities of the mitral valve apparatus that are responsible for LV outflow obstruction include diverse alterations in valvular size and shape and represent a primary morphologic abnormality in HCM, most frequently evident in younger patients.[3,4] The mitral valve may be as much as twice normal size from elongation of both leaflets or segmental enlargement of only the anterior leaflet or the midportion of the posterior leaflet. In a small

subset of patients, congenital and anomalous anterolateral papillary muscle insertion into the anterior mitral leaflet (without the interposition of chordae tendineae) produces muscular midcavity outflow obstruction.[3]

Pathophysiology:

1-Left Ventricular Outflow Obstruction

Left ventricular outflow tract obstruction was defined as a peak instantaneous outflow gradient of ≥30 mmHg by continuous-wave Doppler under basal conditions.[37-39]

Longstanding LV outflow tract obstruction (basal gradient, ≥30 mm Hg) is a strong determinant of HCM-related progressive heart failure symptoms and cardiovascular death.[38,40] However, only a weak relationship is evident between outflow obstruction and specifically the risk for sudden cardiac death (usually in patients without significant heart failure symptoms).[38,40]

Subaortic obstruction in HCM represents true mechanical impedance to LV outflow, producing markedly increased intraventricular pressures that may be detrimental to LV function, probably by increasing myocardial wall stress and oxygen demand.[38,40] In most patients, obstruction is produced in the proximal left ventricle by systolic anterior motion (SAM) of mitral valve and midsystolic ventricular septal contact. Characteristic of SAM, particularly in young patients, is abrupt anterior motion of the mitral valve in which elongated leaflets move toward the septum with a sharp-angled 90-degree bend. SAM appears to be generated largely by a drag effect, that is, hydrodynamic pushing force of flow directly on the leaflets.

Magnitude of the outflow gradient, reliably estimated with continuous-wave Doppler, is directly related to duration of mitral valve–septal contact. Mitral regurgitation is a secondary consequence of SAM, with the jet (usually mild to moderate in degree) directed posteriorly.[4]

Subaortic gradients (and systolic ejection murmurs) in HCM are often dynamic (see table 2), with spontaneous variability,[4] or reduced or abolished by interventions that decrease myocardial contractility (e.g., beta-adrenergic blocking drugs) or increase ventricular volume or arterial pressure (e.g., squatting, isometric handgrip, phenylephrine).[1] Alternatively, gradients can be augmented by circumstances in which arterial pressure or ventricular volume is reduced (e.g., Valsalva maneuver, nitroglycerin or amyl nitrite administration, blood loss, dehydration) or contractility is increased, such as with premature ventricular contractions, infusion of isoproterenol or dobutamine, or exercise.[1]

Consumption of a heavy meal or small amounts of alcohol can also transiently increase subaortic gradient and produce dyspnea. Furthermore, a large proportion of HCM patients without outflow obstruction (or SAM) at rest may generate outflow gradients with physiologic exercise, sometimes associated with severe heart failure symptoms.[8] Fully 70% of a hospital-based HCM cohort have the propensity to develop an outflow gradient ≥30 mmHg, either at rest or during exercise.[8]

Table (2): Definitions of Dynamic Left Ventricular Outflow Tract Obstruction [41-43]

Hemodynamic State	Conditions	Outflow Gradient*
Basal obstruction	Rest	≥30 mm Hg†
Nonobstructive	Rest	<30 mm Hg
	Physiologically provoked	<30 mm Hg
Labile obstruction	Rest	<30 mm Hg†
	Physiologically provoked	≥30 mm Hg†

*Either the peak instantaneous continuous wave Doppler gradient or the peak-to-peak cardiac catheterization gradient, which are equivalent in hypertrophic cardiomyopathy.
†Gradients ≥50 mm Hg either at rest or with provocation are considered the threshold for septal reduction therapy in severely symptomatic patients.

2-Microvascular

Severe myocardial ischemia and even infarction may occur in HCM.[32,44]

The myocardial ischemia is frequently unrelated to the atherosclerotic epicardial coronary artery disease (CAD) but is caused by supply–demand mismatch. Patients with HCM of any age have increased oxygen demand caused by the hypertrophy and adverse loading conditions. They also have compromised coronary blood flow to the LV myocardium because of intramural arterioles with thickened walls attributable to medial hypertrophy associated with luminal narrowing [45].

Myocardial ischemia due to microvascular dysfunction occurs in HCM and is an important pathophysiologic component of the disease process, promoting LV myocardial scarring and remodeling and affecting clinical course.[32] Active ischemia, demonstrable with positron emission tomography, is a determinant of progressive heart failure and cardiovascular mortality.[32]

However, the relationship between chest pain commonly encountered in HCM and active myocardial ischemia is unresolved.

3-Diastolic Dysfunction

Evidence of impaired LV relaxation and filling, by mitral inflow pulsed Doppler and tissue Doppler imaging , is present in as many as 80% of HCM patients, probably contributing to heart failure symptoms of exertional dyspnea, although not directly related to severity of LV hypertrophy.[4] The rapid filling phase is usually prolonged, associated with decreased rate and volume of LV filling and (in sinus rhythm) a compensatory increase in the contribution of atrial systole to overall filling.[4,46] Parameters of diastolic function have limited applicability to patient management and do not accurately predict prognosis, symptoms, or filling pressures, although restrictive LV filling patterns may be linked to adverse outcome in some HCM patients.

Reduced ventricular compliance in HCM probably results largely from those factors determining passive elastic properties of the LV chamber, such as hypertrophy, replacement scarring and interstitial fibrosis, and disorganized cellular architecture. Diastolic dysfunction is likely to be the fundamental mechanism by which heart failure occurs in nonobstructive HCM with preserved LV systolic function.

4-Autonomic Dysfunction

During exercise, approximately 25% of patients with HCM have an abnormal blood pressure response defined by either a failure of systolic blood pressure to rise (≥20) mmHg or a fall in systolic blood pressure [47,48]. The presence of this finding is associated with a poorer prognosis[48,49]. This inability to augment and sustain systolic blood pressure during exercise is

caused by either the dynamic LVOT obstruction or systemic vasodilatation during exercise. It is speculated that autonomic dysregulation [47] is present in patients with HCM and that the fall in blood pressure associated with bradycardia may be an abnormal reflex response to obstruction.

5-Mitral Regurgitation

Mitral regurgitation is common in patients with LVOT obstruction and may play a primary role in producing symptoms of dyspnea. The temporal sequence of events of eject-obstruct-leak supports the concept that the mitral regurgitation in most patients is a secondary phenomenon [50-52]. The mitral regurgitation is usually caused by the distortion of the mitral valve apparatus from the SAM secondary to the LVOT obstruction. The jet of mitral regurgitation is directed laterally and posteriorly and predominates during mid and late systole. An anteriorly directed jet should suggest an intrinsic abnormality of the mitral valve. If the mitral regurgitation is caused by distortion of leaflet motion by SAM of the mitral valve, the severity of the mitral regurgitation may be proportional to the LVOT obstruction in some patients.

Changes in ventricular load and contractility that affect the severity of outflow tract obstruction similarly affect the degree of mitral regurgitation. It is important to identify patients with additional intrinsic disease of the mitral valve apparatus (prolapse or flail), because this finding influences subsequent treatment options. [53]

Clinical course:

Although clinical course is typically variable, patients with HCM may remain stable during long periods.[3,4,54] Notably, HCM is compatible with

normal life expectancy with little or no disability and without the necessity for major therapeutic interventions to achieve this outcome.[3,4,54,55]

Nevertheless, subgroups at higher risk for important disease complications and premature death reside within an HCM population. Such patients proceed along specific adverse pathways, punctuated by clinical events that ultimately dictate targeted treatment strategies[3,4,33,37,38,54,56-60] : (1) sudden and unexpected death; (2) progressive heart failure with exertional dyspnea and functional limitation (often accompanied by chest pain) in the presence of preserved LV systolic function; and (3) atrial fibrillation (AF), with the risk for embolic stroke and heart failure. However, prediction of clinical course and outcome for individual patients with HCM remains encumbered by the markedly diverse disease expression and the long period of potential risk for young patients.[3,4,59,60]

Heart Failure

Whereas some degree of heart failure with exertional dyspnea is common in HCM, progression to severe functional limitation with preserved LV systolic function (i.e., New York Heart Association [NYHA] Class III or IV) is infrequent, occurring in probably 10% to 15% of the overall patient population.[3,4]

The principal determinants of progressive heart failure and heart failure–related death appear to be LV outflow obstruction, AF, and diastolic dysfunction.[8,32,36,38,40,46,54] Also, microvascular dysfunction[32] has been advanced as a predictor of long-term outcome and heart failure death. In contrast to the risk specifically for sudden death (which bears a linear relationship to magnitude of LV hypertrophy) greater degrees of LV wall thickness are not associated with higher likelihood for development of

progressive heart failure symptoms.[56] HCM is a rare cause of heart failure in infants and young children, and this presentation is regarded as an unfavorable prognostic sign.[4,12]

About 3% of HCM patients manifest the end stage characterized by systolic dysfunction (ejection fraction <50%).[33] This profound form of progressive heart failure (often associated with AF) may be expressed by various patterns of LV remodeling, including wall thinning and cavity dilation, associated with diffuse transmural scarring that can be identified in vivo by CMR[33,34] (the consequence of small-vessel mediated myocardial ischemia). Clinical course is unpredictable, but progression to refractory heart failure or sudden death is frequent (10%/year). The most reliable risk marker for evolution to the end stage is a family history of the end stage.[33]

Sudden Death

Sudden death in HCM may occur at a wide range of ages but most commonly in adolescents and young adults < 30 to 35 years of age.[3,4,37,57,59,61] These events are arrhythmia based, caused by primary ventricular tachycardia and ventricular fibrillation.[59,60]

The estimated annualized rate of SCD is about 1% in the overall HCM population but substantially higher in those at greatest risk.[41]

Whereas most sudden deaths occur while sedentary or during modest physical activity, such events are also frequently associated with vigorous exertion, consistent with the observation that HCM is the most common cardiovascular cause of athletic field deaths.[57]

Several risk factors for sudden death have been identified.[62,63] The generally accepted major risk factors include: family history of sudden death;

unexplained syncope; non-sustained ventricular tachycardia (NSVT) on ambulatory monitoring; severe hypertrophy (≥30 mm); and abnormal blood pressure response to exercise (although this risk may be relevant only in those under the age of 40 years).[41,64] Additional 'risk modifiers' have also been reported and include the presence of significant left ventricular outflow tract obstruction (LVOTO), significant late gadolinium enhancement (LGE) on cardiac MRI scanning and 'high risk' genotype, as well as other less commonly seen complications, such as exercise-induced ventricular tachy-arrhythmias, the presence of a left ventricular aneurysm and late systolic dysfunction.[62,63]

Clinical Features:

Gender and Race

HCM occurs with equal frequency in men and women.[16] The predominance of men in the literature reflects underdiagnosis in women, who achieve clinical recognition less frequently, at older ages, and with more pronounced symptoms than in men.[65] Furthermore, women have greater risk than men do for progression to advanced heart failure (usually associated with outflow obstruction), although there is no relation between gender and sudden death or overall mortality.[65]

HCM has been reported in many races[4] but is underrecognized in African Americans, with most competitive athletes who die suddenly of HCM previously undiagnosed black men.[61] Phenotypic expression of HCM is similar throughout the world, with the possible exception of the morphologic form characterized by hypertrophy confined to the LV apex, most common in Japan.[3,14]

Symptoms

Symptoms of heart failure (with preserved LV function) may develop unpredictably at any age, with functional limitation due to exertional dyspnea or fatigue, and in advanced stages by orthopnea or paroxysmal nocturnal dyspnea.[3,31]

Disability is frequently accompanied by chest pain, either typical angina pectoris or atypical in character, possibly resulting from structural microvasculature abnormalities responsible for silent myocardial ischemia.

HCM patients may also experience impaired consciousness with syncope (or near-syncope) and lightheadedness potentially explained by several mechanisms, including arrhythmias and outflow obstruction.

Severity of symptoms in HCM may be similar, independent of whether obstruction to LV outflow is present.[4]

Physical Examination

Physical examination findings in patients with HCM are variable and related in large measure to hemodynamic state . Initial clinical suspicion of HCM may be triggered by recognition of a heart murmur on routine examination or before sports participation, although the majority of patients are still identified by virtue of clinically overt symptom onset or cardiac events.[66] Patients with outflow obstruction characteristically have a medium-pitch systolic ejection murmur at the lower left sternal border and apex that varies in intensity with the magnitude of the subaortic gradient, increasing with the Valsalva maneuver, during or immediately after exercise, or on standing. Most patients with loud murmurs of at least grade 3/6 are likely to have LV outflow gradients >30 mmHg; arterial pulses usually rise rapidly with bisferiens contour, and double or triple apical impulses may be palpable,

reflecting outward systolic thrust caused by ventricular contraction and presystolic accentuated atrial contraction.

Conversely, physical findings in patients without subaortic gradients are more subtle, with no or soft systolic murmur, although a forceful apical impulse may arouse suspicion of HCM.

Investigations:

Electrocardiography

The 12-lead ECG is useful largely for raising the suspicion of HCM in family members without LV hypertrophy and in identifying patterns such as Wolff-Parkinson-White syndrome, which may suggest certain phenocopies of HCM. [3,67-69]

In addition, patterns mimicking myocardial infarction may provide evidence of the diagnosis and may be present in young individuals before there is manifest evidence of wall thickening on echocardiography [4,69,70].

The 12-lead ECG is abnormal in 75% to 95% of patients with HCM[3,68,69]. These abnormalities do not correlate with severity or pattern of hypertrophy as determined by echocardiography.

Ambulatory electrocardiographic monitoring for detection of ventricular tachy-arrhythmias plays an important role in risk stratification of asymptomatic or symptomatic patients with HCM because episodes of non-sustained ventricular tachycardia (NSVT) identify patients at significantly higher risk of subsequent SCD [3,4,69-71].

Echocardiography

Two-dimensional and Doppler echocardiography have become the gold standard for the diagnosis of HCM.[50,51] The finding of increased wall thickness in the absence of another etiology is the basis for the diagnosis of HCM .

The hypertrophy can be distributed throughout the myocardium in any pattern but commonly involves the entire ventricular septum see figure (3). No phenotypic expression can be considered classic or particularly typical of this disease. The average maximal left ventricular wall thickness in a population of HCM patients is usually 20 to 22 mm; however, 5 to 10 percent of patients have maximal wall thickness in excess of 30 mm.

Two-dimensional echocardiography is also the primary tool for defining the presence and severity of LVO tract obstruction.[72,73] If true dynamic obstruction is present, there is systolic anterior motion (SAM) of the mitral valve apparatus. Most patients have SAM of the anterior leaflet, but this may also occur with the posterior leaflet.

There are frequently additional abnormalities of the mitral valve supporting structures.[72,74]

The exact site of the obstruction may be determined by visualizing the region of the SAM-septal contact.[75] In the classic form of obstructive HCM, the obstruction occurs at the most basal portion of the septum as it projects into the LVO tract. However, the obstruction may also extend into the LV from SAM of the chordal apparatus. There may be patients with midventricular obstruction in whom a hypertrophied papillary muscle abuts against the ventricular septum.[76]

Two-dimensional echocardiography is useful for ruling out other causes of LVO tract obstruction such as discrete subaortic stenosis or tunnel subaortic stenosis.(77)

Doppler echocardiography can be used to define the pathophysiologic processes that are present in HCM. In the presence of a dynamic LVO tract obstruction, there is a high velocity *dagger-shaped* signal on continuous wave Doppler interrogation of the LVO tract(43) . In patients with low outflow tract velocities (<3 m/sec), provocation with the Valsalva maneuver, inhalation of amyl nitrite, or exercise should be performed during the Doppler study to determine if there is a labile or latent obstruction.

Doppler color flow imaging can be used to determine the presence and severity of mitral regurgitation.(78)

Diastolic function can be assessed noninvasively by Doppler echocardiography. The transmitral flow velocity curves can not be used alone because of the complex interplay of relaxation and compliance abnormalities present in HCM.(79) However, pulmonary vein flows and Doppler tissue imaging together with the transmitral flow velocity curves can improve the accuracy of estimates of left ventricular filling pressures.(80)

Doppler tissue imaging of the mitral annular motion helps evaluate longitudinal contraction of the myocardium, which is abnormal in HCM patients despite normal or supranormal ejection fraction. Abnormally low annular velocities may help detect subclinical disease, for example patients who carry an HCM-associated genetic abnormality but may not yet have developed the phenotypic expression of increased wall thickness.(81-83) It may also help distinguish HCM from the physiologic increase in wall thickness observed in some athletes, who would have preserved or enhanced annular velocities.(84)

Transesophageal echocardiography is usually unnecessary in the evaluation of the patient with HCM. In most patients the clinically necessary anatomic and hemodynamic information can be obtained by transthoracic echocardiography. However, patients in whom discrete subvalvular stenosis or a primary abnormality of the mitral valve is suspected may benefit from transesophageal echocardiography.

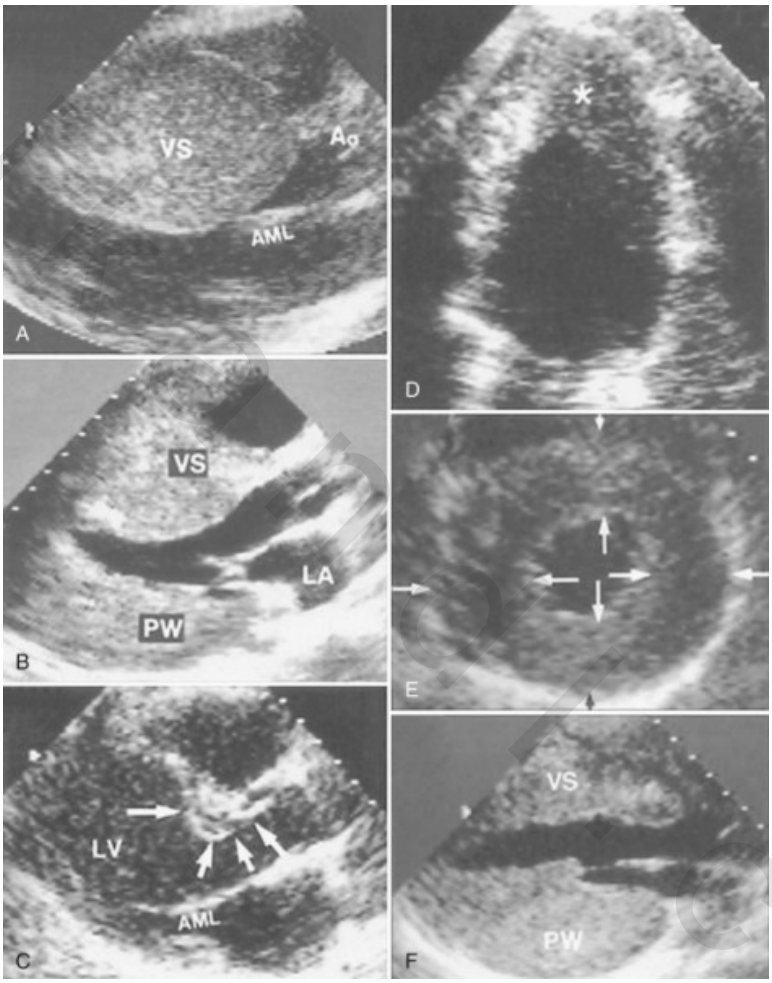

Figure (3): **Patterns of LV hypertrophy in HCM** [85]. Heterogeneous distribution and extent of LV wall thickening by echocardiography. **A,** Massive asymmetric hypertrophy of ventricular septum (VS) with thickness >50 mm. **B,** Septal hypertrophy with distal portion considerably thicker than proximal region. **C,** Hypertrophy confined to proximal septum just below aortic valve (arrows). **D,** Hypertrophy localized to LV apex (asterisk), that is, apical HCM. **E,** Relatively mild hypertrophy in symmetric pattern showing similar or identical thicknesses within each segment (paired arrows). **F,** Inverted pattern with posterior free wall (PW) thicker (40 mm) than anterior VS. Calibration marks = 1 cm. Ao = aorta; AML = anterior mitral leaflet; LA = left atrium.

Cardiac Catheterization

Cardiac catheterization is not required in most HCM patients, because the diagnosis and determination of outflow tract obstruction can usually be made by echocardiography. In uncommon circumstances in which there is a discrepancy between the echocardiogram and the clinical presentation, cardiac catheterization may be of benefit in demonstrating the presence and severity of a LVO tract obstruction.

The outflow tract obstruction has been assessed by a *pull-back* pressure tracing, placing an end-hole catheter at the left ventricular apex, pulling back to the base and then into the Ao. The systolic gradient will be between the apex and base. However, because of the small left ventricular cavity with hyperdynamic systolic function, cavity obliteration and catheter *entrapment* may occur, resulting in a falsely increased left ventricular systolic pressure. The gradient is ideally assessed by a simultaneous left ventricular inflow and LVO (or aortic) pressure.[1,2] The left ventricular inflow position avoids the problem of catheter entrapment and is best obtained by a transseptal approach.

Coronary angiography may be indicated if there are symptoms of angina out of proportion to the degree of obstruction or other symptoms. Epicardial coronary disease is seen in up to 25 percent of older patients. The combination of the epicardial disease and the high myocardial oxygen demand from the hypertrophied muscle may result in significant symptoms of angina and may alter outcome.[3,4] Myocardial bridging is frequent, particularly in younger patients with severe hypertrophy; however, the impact of bridging on outcome is controversial.

CMRI

CMR is complementary to echocardiography by clarifying technically ambiguous LV wall thicknesses, by visualizing abnormalities often not

identifiable with echocardiography (e.g., areas of segmental hypertrophy in the anterolateral free wall[6,86], or by depicting pathologic changes in the apical region including hypertrophy[6] and aneurysm formation[87] that may clarify diagnosis or in some patients alter management strategies .

Increased LV mass (calculated by CMR) is not invariable in HCM and is normal or nearly normal in 20% of patients when hypertrophy is localized and segmental.[88]

Rickers[86] has reported that CMR detects hypertrophic segments in 6% of patients in whom it was undetected by two-dimensional echocardiography. In addition, echocardiography underestimated the magnitude of hypertrophy determined by CMR in the basal anterolateral wall by 20% and the presence of extreme hypertrophy (> 30 mm wall thickness) by 10%. Both findings have important prognostic implications.

Also presence of significant late gadolinium enhancement (LGE) as in figure (4) one of the risk modifiers for sudden cardiac death.

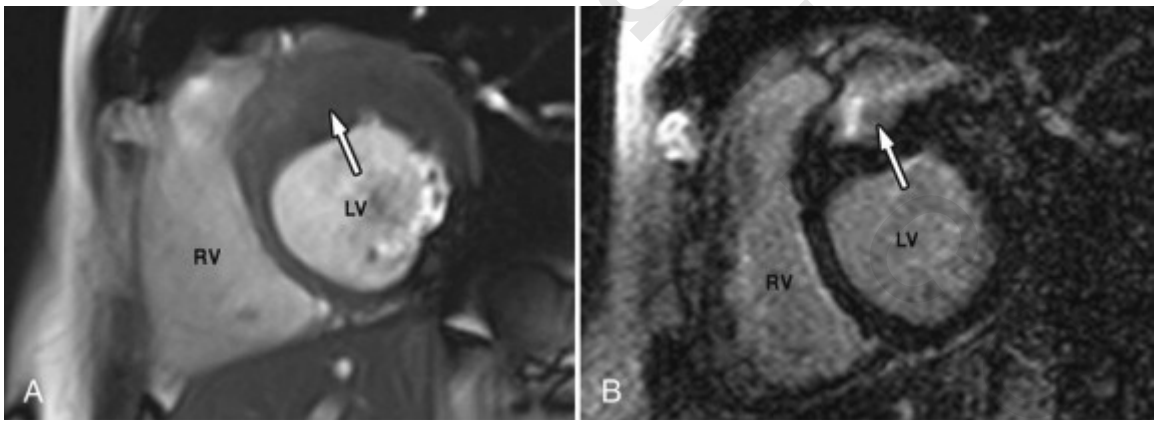

Figure (4): LGE in Patient with hypertrophic cardiomyopathy.[89] A,severe panseptal hypertrophy (arrow). B, The septum demonstrates dense LGE (arrow) consistent with fibrosis.

Stress Testing

Exercise testing with monitoring of ECG and cuff blood pressure is helpful in risk assessment of patients with HCM, because abnormal blood pressure responses to exercise (defined as either a failure to increase by at least 20 mmHg or a drop of at least 20 mmHg during effort) has been demonstrated to be 1 factor associated with risk of SCD [3,4,48,71,90]. A hypotensive blood pressure response was defined as either an initial increase in systolic blood pressure with a subsequent fall by peak exercise of >20 mmHg compared with peak blood pressure value [8,49] or a continuous decrease in systolic blood pressure of >20 mm Hg throughout the exercise test when compared with baseline. A flat response was defined by a change in systolic blood pressure during the whole exercise period of < 20 mmHg compared with the resting systolic blood pressure.

Combining exercise testing with Doppler echocardiography is also useful for determining the presence of physiologically provocable LVOT obstruction and is particularly helpful in patients with symptoms during routine physical activities who do not manifest outflow obstruction at rest [8].

The role of metabolic stress testing (i.e, determination of maximum oxygen consumption) in the routine evaluation of patients with HCM remains to be decided, particularly with regard to clinical outcome, but in individual patients this test may be helpful in providing a more precise assessment of functional capacity. [91]

Genetic Testing

Genetic counseling before genetic testing will increase understanding of the medical and familial implications of test results, enabling informed decision making about potential risks and benefits. [92,93] Genetic counseling

can also reduce potential psychologic responses to learning one's mutation status. [14,94]

Even when genetic testing is not undertaken,genetic counseling about the potential for familial transmission of HCM is medically important.

Genetic and/or clinical screening of all first-degree family members of patients with HCM is important to identify those with unrecognized disease. On the basis of family history, clinical screening, and pedigree analyses, the pattern of inheritance is ascertained to identify and counsel relatives at risk.[94]

Genetic testing may identify a pathogenic mutation (e.g., analysis defines a sequence variant known to cause HCM or a "likely pathogenic" mutation, a DNA variant that was previously *unknown* as a cause of HCM but has molecular characteristics that are similar to recognized HCM mutations.

Adult patients with HCM and an established pathogenic mutation have increased risk for the combined end points of cardiovascular death, nonfatal stroke, or progression to New York Heart Association (NYHA) functional class III or IV compared with patients with HCM in whom no mutation is identified. [95]

Studies suggest that the presence of ≥ 1 HCM-associated sarcomere mutation is associated with greater severity of disease. [26,96-98]

When genetic testing reveals a mutation in the index patient, ascertainment of genetic status in first-degree relatives can be predictive of risk for developing HCM. [99]

These mutation carriers should be evaluated by physical examination, electrocardiography, and 2-dimensional echocardiography, and if HCM is identified,these individuals should undergo risk stratification.

Clinical Management:

Preclinical diagnosis

Genetic and/or clinical screening of all first-degree family members of patients with HCM is important to identify those with unrecognized disease.

Although genetic testing may become the ultimate tool for assessing the risk of disease development, several issues complicate its use as a screening tool.

Preclinical diagnosis of HCM has many medical and social implications. At present, there is no evidence that early detection will change the course of the disease; however, early application of therapy may improve the lifelong management of these subjects.

Prevention of Sudden Death

Patients with HCM are at increased risk for ventricular tachyarrhythmias and SCD , so risk stratification for SCD should also be performed in all patients, irrespective of whether symptoms are present [3,4].

Although the overall rate of SCD in HCM is approximately 1% per year, clearly there are individuals at higher risk for whom prophylactic therapy may be indicated. Pharmacologic therapy has not been demonstrated to provide protection from SCD.

An ICD has been shown to be effective at aborting SCD in patients with HCM.[59] Indications of ICD placement in HCM are summarized in figure (5).

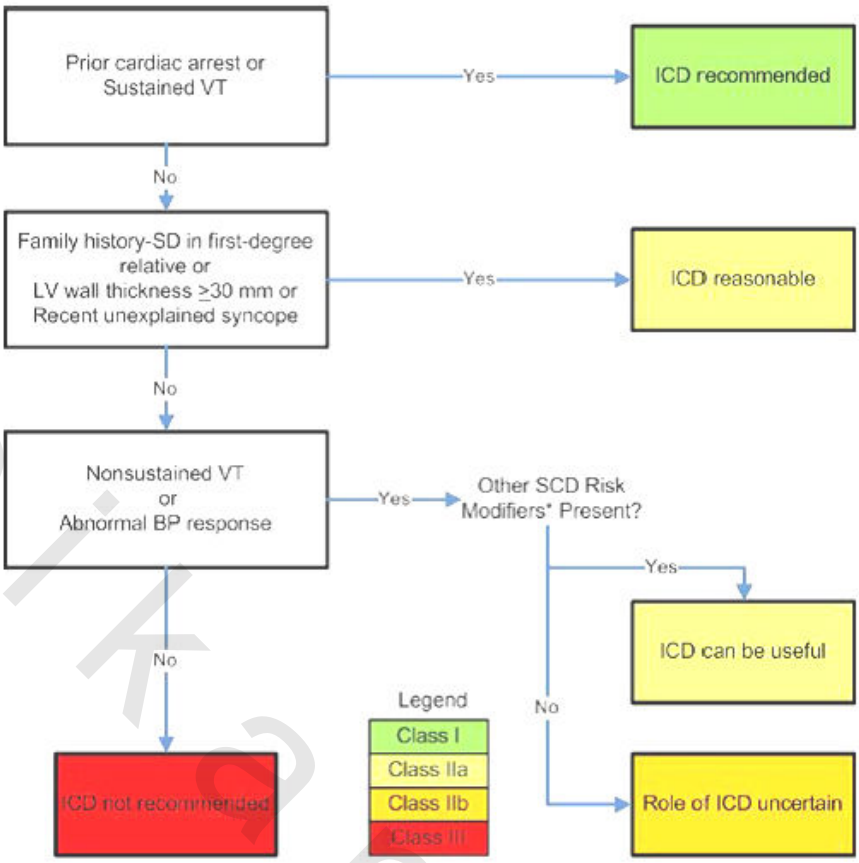

Figure (5): Indications for ICDs in HCM. [41] SCD, sudden cardiac death; SD, sudden death; and VT, ventricular tachycardia.

Asymptomatic patient

Because concomitant CAD has a significant impact on survival in patients with HCM [100], it is recommended that other risk factors that may contribute to atherosclerotic cardiovascular disease be treated aggressively in concordance with existing guidelines.[4,101] This includes aggressive modification of risk factors such as hypertension, diabetes, obesity, and hyperlipidemia.[101] A low-intensity aerobic exercise program is also reasonable to achieve cardiovascular fitness. [102]

Symptomatic Patients

The major goal of pharmacologic therapy in symptomatic patients with HCM is to alleviate symptoms of exertional dyspnea, palpitations, and chest discomfort, which may reflect pathophysiologic mechanisms such as LVOT obstruction, reduced supply of myocardial oxygen, mitral regurgitation, and impaired LV diastolic relaxation and compliance. [3,4,71]

Beta blockers are the mainstay of pharmacologic therapy and the first-line agents because of their negative inotropic effects [103] and their ability to attenuate adrenergic-induced tachycardia. In those patients unable to tolerate beta blockers or those with symptoms unresponsive to beta blockers, calcium channel blockers may provide effective symptomatic relief. Veraepamil has been the most intensively studied such agent[104,105]. In patients with obstructive HCM who remain symptomatic despite the use of beta blockers and calcium channel blockers, alone or in combination, disopyramide may be effective in ameliorating symptoms in many patients.[106,107]

Patients with HCM are at increased risk of AF compared with age-matched cohorts, but AF is seldom seen in young patients with HCM who are <30 years of age and becomes more prevalent with age. Risk factors for AF in HCM include age, congestive heart failure, and LA function, diameter, and volume. [108,109] AF is an indicator of unfavorable prognosis, including increased risk of HCM related heart failure, death, and stroke. [108,110] Therapy for AF includes prevention of thromboembolic stroke and controlling symptoms Occurrence of paroxysmal, persistent, or chronic AF is a strong indication for anticoagulation with a vitamin K antagonist. [111]

The 2011 ACCF/AHA/HRS Focused Updates Incorporated Into the ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial

Fibrillation" state that disopyramide and amiodarone are potential agents for rhythm control. [111]

Radiofrequency ablation may play a role in the management of AF, but further investigation is necessary. The surgical maze procedure for AF has shown some limited success[112]; however, whether a prophylactic or therapeutic surgical maze procedure is indicated for patients undergoing other open chest surgical procedures (i.e., septal myectomy) is unresolved.

Surgical treatment

On the basis of the extensive worldwide experience during more than 45 years, surgical septal myectomy remains the preferred treatment option for patients with severe drug-refractory heart failure symptoms and marked functional disability (i.e., NYHA Classes III and IV in adults, but less limitation in children) associated with obstruction to LV outflow under basal conditions or with physiologic exercise (i.e., gradient ≥50 mm Hg).[3,4,113,114]

The primary objective of surgical myectomy is reduction in heart failure symptoms and improved quality of life, by virtue of relieving outflow obstruction. Myectomy also beneficially alters the clinical course of HCM; surgical patients achieve long-term survival equivalent to that expected in the general population and superior to that of non surgical HCM patients with outflow obstruction.[113]

Alcohol Septal Ablation

Percutaneous alcohol septal ablation, an alternative to myectomy only in selected patients ,[4] alcohol ablation resolves heart failure symptoms in many patients, although follow-up is short compared with myectomy, and even in

expert centers, it may be associated with procedural mortality and complication rates exceeding those of myectomy.[114-116]

Alcohol ablation is regarded as an alternative treatment strategy for patients not considered optimal operative candidates (e.g., advanced age, significant comorbidity and increased operative risk, or strongly adverse to surgery personally).

About 20% of patients require repeated ablations because of unsatisfactory hemodynamic and symptomatic results or permanent pacing for complete heart block.[115]

Heart Transplantation

In general, the indications for heart transplantation include advanced heart disease, typically with NYHA functional class III or IV symptoms that are refractory to all other reasonable interventions. Transplant referral for refractory symptoms does not absolutely require reduced EF, although this treatment strategy is rarely recommended and performed in the presence of preserved EF. For patients with HCM, outcome after heart transplantation is not different from that of patients with other heart diseases. [33,117,118]

Left Atrial Function

Clinical evaluation of the left atrium (LA) is important in many cardiac and non cardiac diseases, requiring an in-depth understanding of anatomy and physiology. The systematic assessment of LA function is not uniformly carried out. This is due partly to the enormous attention given to the evaluation of the left ventricle (LV), a lack of familiarity with ultrasound techniques that can be used in imaging the LA and the absence of validation of an unique standardized technique to investigate LA deformation. Until recently the LA had been subordinated to the LV, but cardiologists now recognize that LA function is indispensable to normal circulatory performance, conditioning the morbidity and mortality in several diseases. So an early detection of LA dysfunction is anticipated to provide new insight into pathophysiology and clinical management of several conditions such as atrial fibrillation (AF), valvular heart disease, hypertension, heart failure (HF), and cardiomyopathy. Echocardiography is therefore the imaging modality of choice for screening and serially following patients with diseases involving the LA morphology and function. [119]

In HCM patients, the left ventricular filling pressure is associated with an increased left atrial size[120,121] that seems to be a very powerful determinant of exercise capacity, with documented prognostic value.[122,123]

The condition usually results in a hetrogenous myopathic disease affecting both the ventricular and atrial myocardium. [3,64] It is thought to be a progressive disease that most often begins with left ventricular (LV) diastolic dysfunction and / or structural remodeling of the atria, including chamber enlargement and interstitial fibrosis. [124]

Indeed, the important role of the left atrium in HCM, expressed both as exercise capacity and clinical outcome, is well documented.[125] Therefore, left atrial function appears to be a marker of the adverse loading conditions and other pathophysiological processes that are likely to be present in HCM.[109,121]

Left atrial anatomy:

The LA cavity is located in the mediastinum, oriented leftward and posterior to the right atrium (RA). LA structure is characterized by a pulmonary venous component, a lateral finger-like appendage, an inferior vestibular component, which surrounds the mitral valve orifice, and a prominent body that shares the septum with the RA. The pulmonary venous component with venous orifices a teach corner is situated posteriorly and superiorly, and directly confluent with the body. [126]

The walls of the LA can be described as superior (roof), posterior (infero-posterior), left lateral, septal, and anterior, as suggested by McAlpine[127] as figure (6).

The majority of the atrium is relatively smooth, whereas the appendage is rough with pectinate muscles. The walls are composed of one or more overlapping layers of differently aligned myocardial fibres, with marked regional variations in thickness.[128] Circular fibres are more or less parallel to the atrioventricular valve plane, whereas longitudinal fibres run nearly perpendicularly. Oblique fibres are those inclined between the two major axes.[129]

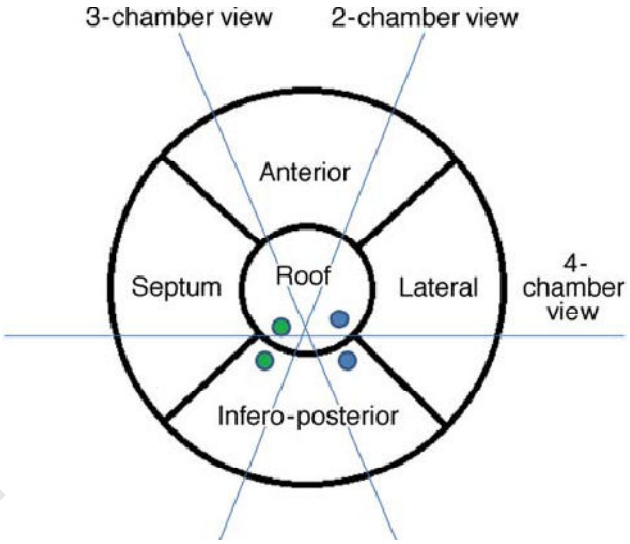

Figure (6): Proposal of a five-segment model for left atrial segmentation by transthoracic two-dimensional echocardiography[119]: The apical four-chamber view cuts the heart obliquely from the apex of the left ventricle.Conventionally, the interatrial septum is situatedmedially and the lateral wall on the opposite side, inferiorly the mitral annulus and superiorly the roof. The anterior and infero-posteriorwalls can be visualized in the apical two-chamber view. Only the infero-posterior wall can be observed, facing the aorta, in a three-chamber view. The green and blue solid dots represent right and left pulmonary veins (upper and lower), respectively.

Left atrial function:

The left atrium (LA) is far from being a simple passive transport chamber. It is highly dynamic and responds to stretch with the secretion of atrial natriuretic peptides. The counterbalance of natriuresis, vasodilatation, and inhibition of the sympathetic and renin–angiotensin–aldosterone systems allows partial restoration of fluid and haemodynamic balance.[130-132]

Phasic left atrial function

LA function has been conventionally divided into three phases as in figure (7): first, as a reservoir, the LA stores pulmonary venous return during left ventricular (LV) contraction and isovolumetric relaxation.

Secondly, as a conduit, the LA transfers blood passively into the LV.

Thirdly, the LA actively contracts during the final phase of diastole and contributes between 15 and 30% of LV stroke volume.[133-136] As a continuum of the LV, especially during diastole, its size and function are very much influenced by the compliance of the LV.[137-140]

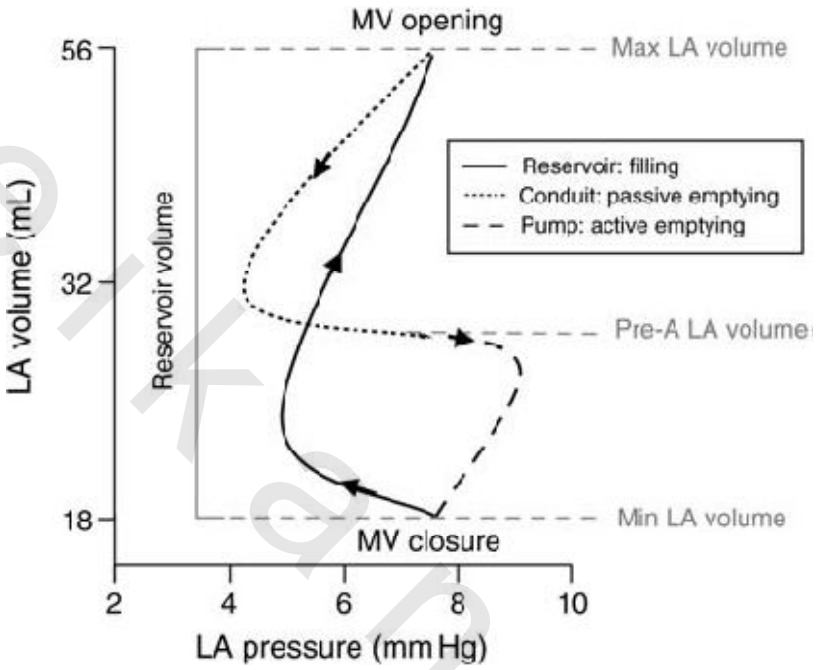

Figure (7): Left atrial (LA) pressure–volume loop [141] showing LA phasic function and volumes. Arrows indicate temporal sequence throughout the 'figure of eight' loop describing changes in LA pressure and volume during a single cardiac cycle. LA reservoir (solid line), conduit (dotted line), and pump (segmented line) function can be quantitated by measuring minimum LA volume, maximum LA volume, and pre-atrial contraction LA volume

Physiological factors affecting left atrial function

LA afterload is determined largely by its elastic properties and downstream pressure and increases with more severe LV diastolic dysfunction and elevated LV filling pressures.[142] LA preload, on the other hand, is principally volume-dependent.[137,143,144]

Studies in both animals and humans have shown that LA size increases with LA volume and pressure, with an associated initial gain in contractile

shortening. However, with progressive dilatation of the LA which eventually leads to a threshold fibre length, atrial shortening and contractility begin to decline.[145-152] This fulcrum or threshold effect appears to be similar to the LV Frank–Starling curve. Beyond that threshold, further enlargement will only result in the deterioration of atrial function.[153]

Physiologic correlates with left atrial size

***Body size and gender*:**

Left atrial size increases with increasing body size and should be indexed to body size to allow meaningful comparisons. Left atrial size indexed to the body surface area is considered the most appropriate adjustment for body size.

Men have been shown to have a larger LA size compared with women.[154]However, this apparent gender difference in LA size has been largely attributed to the differences in relative weight between males and females.[155]

***Age*:**

It has been suggested that increasing age is associated with an increasing LA size.[147,155] However, LA enlargement is not considered part of the normal aging process.[156]

In a study of normal individuals over a wide age range, total atrial emptying volume, maximum and minimum LA volumes were not significantly different between younger and older study populations.[139] There was a decrease in passive LA emptying and conduit volumes together with an increase in active atrial emptying. These changes are probably due to compensatory mechanisms to overcome the normal age-related decrease in LV relaxation. Thus, previously observed changes in atrial volume with aging

are more likely attributable to unrecognized or 'subclinical' pathological processes.(157)

When either the extent or duration of LV diastolic abnormalities exceeds what is observed with normal 'healthy aging,' shifts in the percentage of active and passive LA filling are observed,(158) with a subsequent increase in the total LA volume.

Neuroendocrine factors affecting left atrial function

Neurohumoral regulation affects the control of heart rate, blood pressure, cardiac output, and regional blood flow.(159) Chronic activation of this powerful system has negative cardiovascular consequences.(160)

For instance, increases in atrial natriuretic peptide, brain natriuretic peptide, angiotensin II, aldosterone, and other neurohormonal factors promote LA remodelling.(161-163) In particular, the sustained activation of the angiotensin–aldosterone system has been shown to be inflammatory, profibrotic with reduction in atrial contractility, proarrhythmic, and prothrombotic.(164-166)

Methods of evaluation of left atrial function

Left atrial function can be assessed both invasively and by non-invasive methods including electrocardiography,echocardiography, cardiac magnetic resonance imaging and left atrial catheterization (142).

- **Electrocardiography:**

Electrocardiographic criteria used for left atrial enlargement are: P wave duration in lead II equal to or greater than 0·12sec; a diphasic P wave with predominant terminal negative component ≥ 1 mm deep and ≥ 0.04 sec duration. (167)

In the presence of left atrial enlargement, a combination of criteria occurred more frequently than a single criterion. The overall predictive index of the electrocardiogram for left atrial enlargement was 63%, and that for absence of left atrial enlargement 78%. The index of coarse versus fine fibrillary waves was unreliable in predicting left atrial enlargement.

Changes in P wave morphology may be used as a reasonably specific but less sensitive indicator of left atrial enlargement [168]

- **Conventional Echocardiographic methods:**

***LA dimensions**:*

Increased LA size is associated with adverse cardiovascular outcomes[122,169].

The LA size is measured at the end-ventricular systole when the LA chamber is at its greatest dimension, in long-axis view (anterior-posterior diameter) and in 4-chamber view (longitudinal and transverse diameters). [170] as in figure (8)

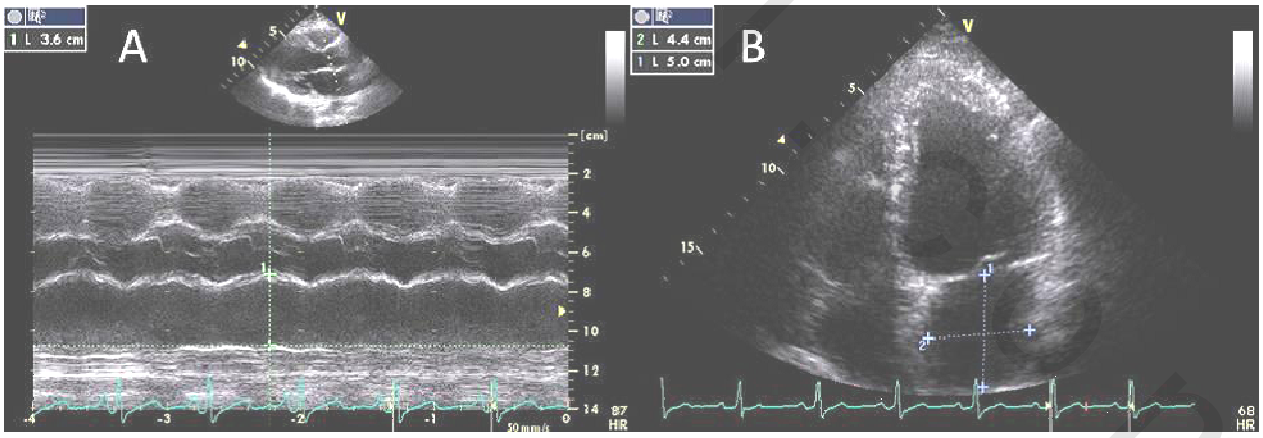

Figure (8): **LA dimensions** [171]: antero-posterior diameter in parasternal long-axis view (A); longitudinal and transverse diameters in 4-chamber view (B).

Although linear measurements have been shown to correlate with angiographic measurements and have been widely used in clinical practice and research, they inaccurately represent true LA size, given that the LA is not a symmetrically shaped 3D structure. Evaluation of the LA in the AP dimension assumes that a consistent relationship is maintained between the AP dimension and all other LA dimensions as the atrium enlarges, which is often not the case [172]. Expansion of the LA in the AP dimension may be constrained by the thoracic cavity between the sternum and the spine. Predominant enlargement in the superior-inferior and medial-lateral dimensions will alter LA geometry such that the AP dimension may not be representative of LA size and it should be accompanied by LA volume determination in both clinical practice and research [170-172].

- **Volumetric assessment of left atrial function**

LA phasic function can be assessed non-invasively by echocardiography, which has been well validated.[142,146,173,174] Volumetric assessment of LA size is a more accurate assessment than linear measurement.[175] Although one can argue that echocardiographic quantitation of LA volume tends to be 'underestimating' when compared with magnetic resonance imaging (MRI) or computed tomography (CT) techniques,[176,177] or that MRI or CT tends to 'overestimate' when compared with echocardiography, a more fundamental issue is actually identifying a method of evaluation that gives reproducible values and suitable for risk assessment and follow-up. At present, echocardiography remains the simplest, least invasive, and most cost-effective method. Thus, the minor degree of difference in volume measured by echocardiography vs other imaging techniques is clinically irrelevant, as long as the measurement of interest is compared with the normal values determined by the same imaging technique using the same methodology.

To assess the phasic function by the volumetric method, LA volumes are measured at different time points of the cardiac cycle maximal LA volume at the end of T wave on electrocardiogram, just before opening of the mitral valve; minimal LA volume at QRS complex, just at the closure of the mitral valve; and preceding atrial contraction (pre-A) at the beginning of P wave. Biplane area– length and biplane Simpson's method are both satisfactory, using apical four- and two-chamber views.[146,178,179] Indexed to body surface area, the normal maximal LA volume is 22+5–6 mL/m^2; minimal LA volume is 11+4 mL/m^2; and pre-A LA volume is 15+5 mL/m^2.[139,150,180,181]

Recently, three-dimensional echocardiography assessment of atrial volumes has been shown to have little inter- and intra-observer variabilities. The findings correlate well with biplane two dimensional (2D) methods, but offer no incremental diagnostic or predictive information. [182-184]

- **Tissue Doppler imaging of left atrial function**

Tissue Doppler imaging (TDI) allows characterization of intrinsic myocardial wall low velocities with a high sampling rate.[185,186]

It is relatively load-independent and provides additional prognostic values in cardiac diseases.[187]

The TDI profile of the mitral annulus generally shows three major deflections: peak ventricular systolic velocity (S′), peak early ventricular diastolic velocity (E′), and during atrial contraction (A′).[188]

The excellent correlation between mitral annulus A′ and atrial function has been demonstrated in a large number of studies.[174,187-197] . It correlates very well with LA ejection fraction, LA ejection force, and LA kinetic energy in patients with various degrees of LV diastolic dysfunction.[198]

The TDI measurements should be obtained during end expiration with an average of three sinus beats, and the sample volume should be placed on the atrial side of the mitral annulus at the basal inter-atrial septum from the apical four-chamber view.[199] The velocity range should be set at 20 to 220 cm/s with minimum gain and lower filter settings.

As with other Doppler techniques, tissue Doppler velocities are affected by their angle and translation from the neighbouring myocardium,[185,192,199] and special care must be taken to place the sample volume within the endocardial boundary. In contrast to E′, there is generally no significant difference between the basal septal and basal lateral peak A′ velocities.[200]

In healthy subjects, there is an age and heart rate related increase in the tissue Doppler A′ velocities,[195] and in one study of 165 normal subjects, the value for the peak A′ is 7.3 (7.1–7.6) m/s.[201] Patients with various cardiac issues and ventricular dysfunction, A′ of ,4 cm/s, appeared to be highly predictive of overall cardiac mortality.[201]

Both LV systolic and diastolic functions affect LA contractile function. A higher LV ejection fraction is associated with higher A′, and restrictive LV diastolic filling is associated with lower A′.[193] However, TDI A′ assessment provides information on global LA function only. It does not allow detailed regional LA functional assessment.

- **Strain and strain rate**

Although pulsed-wave tissue Doppler echocardiography is affected by myocardial tethering and acquisition angle, strain and strain rate (SR) imaging have been proposed as novel non-invasive echocardiographic techniques to quantify regional myocardial function independent of tethering. Strain

represents myocardial deformation, whereas SR represents the speed at which myocardial deformation occurs (expressed in s^{-1}).

Myocardial shortening during the LA contractile phase results in SR values that are negative.[202] Alternatively, strain and SR values during the reservoir phase are positive due to LA chamber dilatation and wall stretch. In the SR profile, two peaks subdivide the LA reservoir period into two phases: early, corresponding to the IVC period, and late, during the ejection and IVR periods. The early peak largely reflects LA compliance, whereas the late peak occurs during LV ejection, suggesting a close correlation between reservoir function and the mitral annular descent from the cardiac base to the apex. Wakami et al.[203] LA conduit function is dependent on LV relaxation and preload. The transfer of blood to the LV is accompanied by LA myocardium shortening, resulting in negative SR values. During diastasis, LA wall deformation ends and both the strain and SR profiles plateau.

Regional LA analysis, conveyed through standard 15- or 12-segment models,[204-208] suggests significant regional differences, as in figure (9) for strain and SR values, though controversy remains.[204,205] Sirbu et al.[206] observed the lowest SR peak values and significantly longer time-to-peak SR values in the inferior wall. Others have demonstrated maximum absolute values of strain and SR in the annular regions of the inferior wall and lowest values in the roof, where the heart is anchored to the mediastinum .[209]

Atrial myocardial deformation properties values by S Doppler range, in different studies, for LA systolic S from 65,4±19,5% to 82±19%, for LA systolic SR from 3,4±1 S^{-1} to 4,4±1,6 S^{-1} [202,208,210].

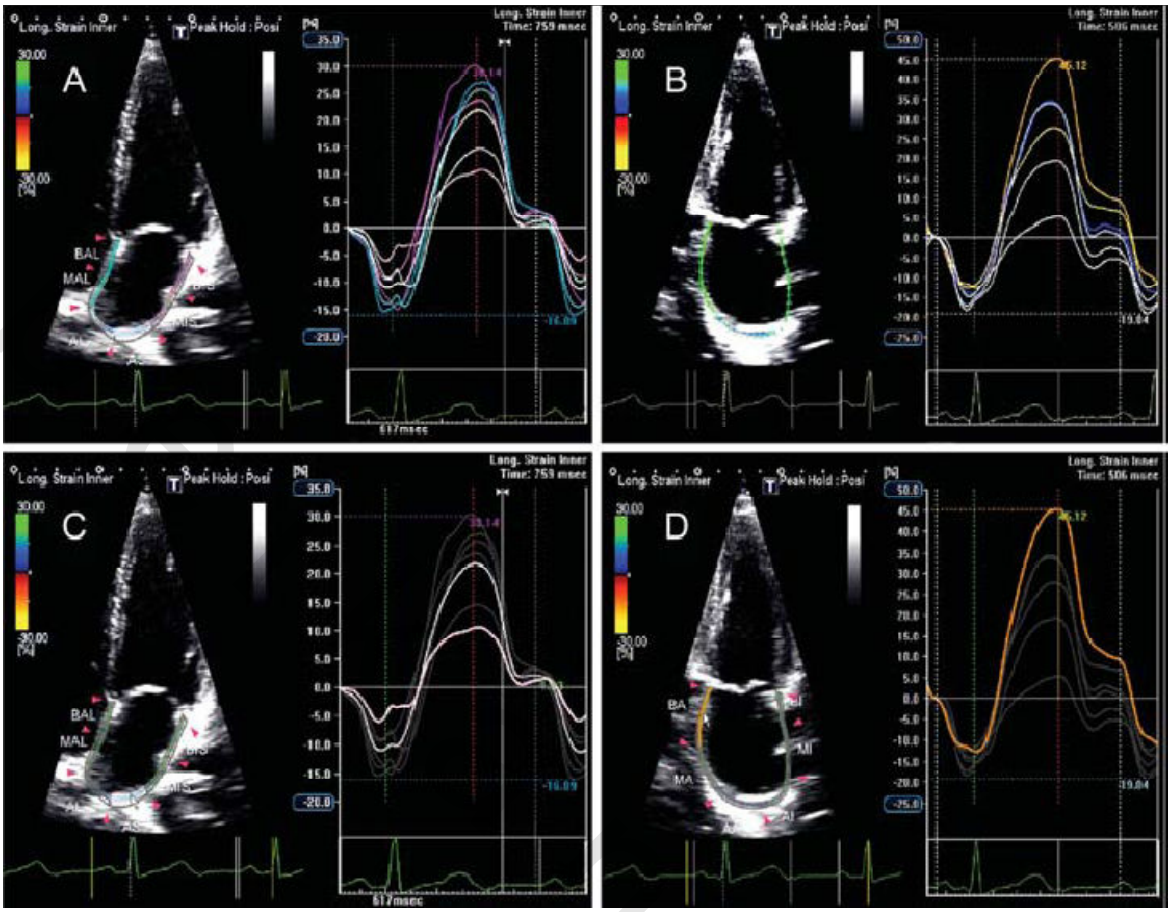

Figure (9): **Regional left atrial strain** [119]. Two-dimensional echocardiography apical four-chamber view (A) and apical two-chamber view (B) showing left atrial longitudinal strain in a normal subject. Longitudinal strain during the reservoir phase in the roof segment (C, pink line) shows lower absolute values when compared with the annular segment of the inferior wall (D, brown line).

- **Speckle tracking technique**

Deformation or strain measurement using TDI velocity is affected by adjacent structure and tethering of neighbouring segments.[211] Two dimensional speckle tracking strain imaging (2D-SI) is a novel technique for the assessment of myocardial deformation. This technique utilizes acoustic speckle tracking as opposed to Doppler myocardial velocities, and perfect ultrasound beam alignment is not necessary.

Acoustic speckle is used for reference,[212,213] and this has been recently validated against sonomicrometry and tagged MRI.[212,214,215]

First described in 2004, there has been increasing evidence suggesting that this imaging modality is highly promising for LA function assessment.[204] 2D-SI uses grey scale sector image and is based on frame-by-frame tracking of small rectangular image blocks with a stable speckle pattern.[214] Conventionally, a line is manually drawn along the LA endocardium when the LA is at its minimum volume. Software will generate the region of interest near the epicardium and mid-myocardial lines (usually ≤15 mm width). If necessary, manual adjustments can be made.[204]

- **Automated Boundary Detection Echocardiography**

Automated boundary detection is a new echocardiographic modality providing continuous on-line measurements of cavitary area throughout the cardiac cycle. Previous reports have indicated that echocardiography with automated boundary detection is useful for the non-invasive estimation of left ventricular volume. The measurement of left atrial volume also provides pivotal information in the clinical setting. Using automated boundary detection, a region of interest is set around the left atrial border and mitral annulus from an apical four chamber view. Automated boundary detection from the apical four-chamber approach could provide an accurate estimation of left atrial volume change, suggesting the potential value of this method in assessing left atrial function. [216]

Acoustic quantification technology evaluates the waveforms of left atrial area changes obtained by automated boundary detection. Left atrial areas are taken in the apical four-chamber, parasternal long-axis, and parasternal short-axis views using automated boundary detection. Instantaneous left atrial

cavity measurements with automated boundary detection are reproducible. This suggests that automated boundary detection may assist in serial non-invasive measurement of left atrial size to assess disease states and treatments.[217]

The recent development of real-time two-dimensional echocardiographic automated boundary detection suggests that left atrial dimensions can be measured instantaneously to provide on-line assessment of its systolic and diastolic functions. Instantaneous left atrial cavity area measurement by echocardiographic automated boundary detection is accurate and feasible in patients with diverse cardiac disorders. Patients with atrial fibrillation had a depressed diastolic emptying index and those with significant mitral regurgitation had, in addition, a depressed systolic expansion index. Left atrial functional indexes in both systole and diastole can be derived from quantitative evaluations of left atrial–left ventricular interactions based on noninvasive geometric assessment.[118]

Thus Doppler techniques complemented by automated boundary detection provide direct quantitative indexes of left atrial function throughout the cardiac cycle.[219]

Strain and Strain Rate

Strain is a measure of tissue deformation and is defined as the change in length normalized to the original length (Figure 10). The rate at which this change occurs is called strain rate. Deformation in a 1-dimensional object, such as a thin bar, is limited to lengthening or shortening. [220] Strain is how much the bar is shortened or lengthened relative to its original length (ie, reduction to half its original length is −50% strain, and an increase to one third longer is +33% strain and strain rate is the speed at which this change occurs). [221]

In general, peak systolic strain rate is the parameter that comes closest to measuring local contractile function in clinical cardiology. It is relatively volume independent and is less pressure independent than strain. In contrast, peak systolic strain is volume dependent and does not reflect contractile function as well. Strain and strain rate are either TDI based or speckle tracking echocardiography based. [222]

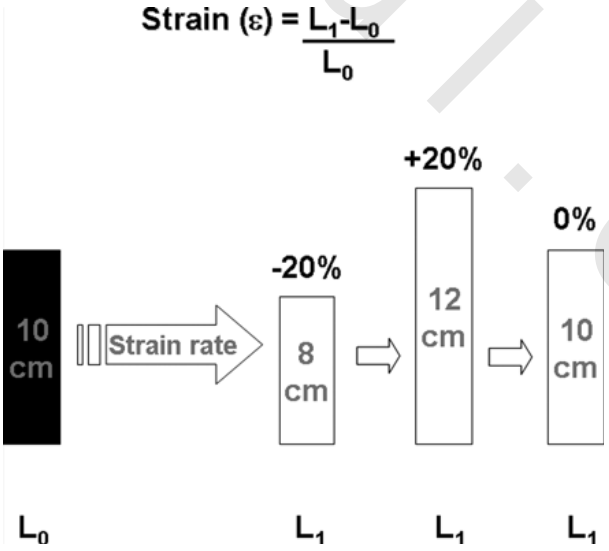

Figure (10): Strain and strain rate measurement [222]. Strain measures tissue deformation and is defined as the change in dimension or length (L1−L0) normalized to the initial length (L0) of the region of interest.

Terminology and definitions

A- Longitudinal Strain

Longitudinal strain represents myocardial deformation directed from the base to the apex. During systole, ventricular myocardial fibers shorten with a translational movement from the base to the apex; the consequent reduction of the distance between single kernels is represented by negative trend curves. Through longitudinal strain analyses in 4-chamber, 2 chamber, and apical long-axis views, both regional and global strain values (global longitudinal strain) can be obtained.

Global longitudinal strain recently has been validated as a quantitative index for global LV function. [223] The same measurement can be applied to the speckle-tracking echocardiographic analysis of longitudinal myocardial deformation of the LA and right ventricle (RV), obtaining the peak atrial longitudinal strain [205] and the RV longitudinal strain, [224] respectively.

B- Radial Strain

Radial strain represents radially directed myocardial deformation, ie, toward the center of the LV cavity, and thus indicates the LV thickening and thinning motion during the cardiac cycle. Consequently, during systole, given the progressive radial propulsion of single kernels, radial strain values are represented by positive curves. Radial strain values are obtained by speckle-tracking echocardiographic analysis of both basal and apical LV short-axis views. [225]

C- Circumferential Strain

Circumferential strain represents LV myocardial fiber shortening along the circular perimeter observed on a short-axis view. [225] Consequently,

during systole, for circumferential speckle-to-speckle distance reduction, circumferential strain measurements are represented by negative curves. As for longitudinal strain, it is possible to obtain a global circumferential strain value.

D-Twisting and Torsion

Until recently, the evaluation of LV twisting has been possible only through MRI, but currently, speckle-tracking echocardiography has emerged as a new promising tool for LV twisting analysis. [226] Left ventricular twisting is a component of the normal LV systolic contraction that arises from the reciprocal rotation of the LV apex and base during systole and constitutes an important aspect of cardiac biomechanics. [227] Intrinsic to its physiologic characteristics, the quantification of LV twisting by speckle-tracking echocardiography is made possible by analyzing the reciprocal rotation of the LV apex and base during systole. Left ventricular twisting is then calculated as the net difference in mean rotation between the apical and basal levels. Left ventricular torsion is defined as LV twisting normalized with the base-to-apex distance**.** [228]

E-Untwisting

Growing attention has been also recently given to the role of untwisting in diastolic LV filling mechanics. [229] Untwisting velocity is thought to be a critical initial manifestation of active relaxation, which makes this measurement relevant for investigating diastole and, mainly, isovolumic relaxation because it seems to be less dependent on load compared to other diastolic parameters. [230]

Speckle-tracking echocardiography

Speckle-tracking echocardiography (STE) is a new noninvasive ultrasound imaging technique that allows for an objective and quantitative evaluation of global and regional myocardial function independently from the angle of insonation and from cardiac translational movements. [231]

Speckle-tracking echocardiography is based on an analysis of the spatial dislocation (referred to as tracking) of speckles (defined as spots generated by the interaction between the ultrasound beam and myocardial fibers) on routine 2-dimensional sonograms. Before the introduction of this sophisticated echocardiographic technique, only tagged magnetic resonance imaging had enabled an accurate analysis of the several deformation components that characterize myocardial dynamics.[232] Although tagged MRI may be considered the reference standard in this area of study, its routine use is limited by its high costs, poor availability, relative complexity of acquisitions, and time-consuming image analysis. [233]

By tracking the displacement of speckles during the cardiac cycle, speckle-tracking echocardiography allows semi-automated elaboration of myocardial deformation in 3 spatial directions: longitudinal, radial, and circumferential. In addition, speckle-tracking echocardiography offers an evaluation of the occurrence, direction, and velocity of LV rotation. [234] The semi-automated nature of speckle-tracking echocardiography guarantees good intra-observer and interobserver reproducibility. [235]

Limitations of the strain

Like other Doppler modalities, DTI-derived strain measurements are dependent on the direction of the Doppler angle of incidence in relation to

myocardial motion. The need to manually track the LA wall and reposition the region of interest on each of the walls, frame by frame, makes using this method in a clinical setting prohibitively time-consuming (about 20 minutes per patient) and decreases the reproducibility. A technical limitation of speckle tracking is that this technique is load dependent, and it is dependent on frame rate as well as image resolution. Because specific software to LA both by strain Doppler and speckle tracking has not yet provided, we applied a program intended for left ventricular strain to analyse left atrial strain. In future studies, changes in the software may be needed to improve the tracking ability of the Doppler and speckle tracking system for LA functional study.

Clinical applications

Several studies have analysed S Doppler and speckle tracking in different physiopathology conditions associated with atrial dysfunction, such as atrial fibrillation (AF), valvular diseases, heart failure, hypertension, diabetes, cardiomyopathies etc [202-206,208-210,236-243]. Population-based studies have demonstrated the prognostic value of the LA analysis for long-term outcome [237,244]. Global LA S, both Doppler, both speckle tracking, is a strong and independent predictor of cardiovascular events (AF, congestive heart failure, stroke, transient ischemic attack, myocardial infarction, coronary revascularization, and cardiovascular death) and appears to be superior to conventional echocardiographic parameters of LA analysis (LA dimension, LA area, LA volume, LA ejection fraction). [211,237,244]

Strain Doppler Method in LA

For S Doppler evaluation, real-time 2D colour Doppler myocardial imaging data are recorded from the LA, using standard apical views at a high frame rate (>180 fps). The data are stored in digital format and analysed

offline with dedicated software, that allows to calculate three parameters: local peak systolic velocity, local peak systolic SR and its integral, local peak systolic S[210,245]. During LV systole, LA acts as a reservoir: passive stretching of the LA walls, during LV systole, leads to LA longitudinal lengthening, and lengthening is recorded as a positive S and SR value [155]. During LV diastole, there is atrial shortening, that is recorded as a negative S and SR value. Analysis may be performed for atrial longitudinal V, SR, and S at 3 segments (basal, medium and near the atrial roof) from the apical views of the LA septum, LA lateral wall (from the apical 4-chamber view), and LA inferior and LA anterior wall (from the apical 2-chamber view). To derive V, SR, and S profiles from the studied segment, a 6 x 3 mm region of interest with elliptical shape is chosen and is continuously manually tracked frame by frame to maintain its position within atrial wall with a proprietary semi-automated tracking algorithm. Peak positive systolic, early diastolic, and late diastolic values were calculated from the extracted curves and averaged, in some studies, calculating as the sum of the peak values recorded in each LA wall divided by the number of the studied walls. While the study of atrial myocardial velocity shows curves similar to those of the ventricular myocardium, confirming the influence of the drag on the myocardial velocities, atrial S shows curves with morphology opposite to those ventricular. In fact during cardiac cycle, ventricles and atria move in opposite directions. During LV systole, atrial myocardium stretches along the longitudinal plane and LA wall longitudinal lengthening was represented with a peak positive S value. Instead ventricular myocardium shortens during LV systole and myocardial longitudinal shortening was represented with a peak negative S value, because of the A-V plane displacement toward the apex. Ventricular SR curves are also opposite to atrial SR curves.