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Mitral Valve Insufficiency, a Constituent of Left Atrial Myxoma: Pathobiology, Physiopathology, and Pathophysiology of Left Atrial Myxoma; Are Long-Term Results Still Feasible?

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Additional information is available at the end of the chapter

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Abstract

Mitral valve is a complex cardiac structure whose function depends on a proper synchronization between each mitral valve apparatus. Considerable headway over the years has been made toward unraveling the theoretical aspects which unifies the dynamic function, structural properties, and pathobiological, pathophysiological performance of the cardiac valves. However, the aspect of mitral valve regurgitation caused by left atrial myxoma still remains a gray area in the field as the mechanism(s) behind the masked and/or the resultant mitral valve regurgitation in relation to left atrial myxoma remains elusive. Although the regurgitations in most scenarios are masked due to the presence of the myxoma itself, however, both invasive and noninvasive techniques employed cannot ascertain if the regurgitation seen is a resultant or concomitant factor as the underlying pathological processes causing mitral valve regurgitation play key roles in the disease pathology as it could be a series of activated measures caused by the myxoma itself. Elucidating the role left atrial myxoma plays in mitral valve regurgitation is critical to improving our understanding as the aim of this chapter is to discuss the current knowledge of mitral valve regurgitation caused by left atrial myxoma in succinct with the elusive underlying pathological sequential cascade activated due to the presence of this neoplasm.

Keywords: myocardial infarction, myxoma, cardiac imaging techniques, echocardiography, embolism, mitral valve insufficiency, ischemic heart disease, degenerative heart disease, rheumatic heart disease, endocarditis

1. Introduction

Atrial myxomas are primary cardiac tumors which are more than usually found accidentally on routine clinical investigations toward other medical ailments commonly growing on the interatrial septum with the fossa ovalis been the most common site. However, it might also arise from the posterior, anterior and left atrial appendage. Cardiac myxomas are generally a rare occurrence with benign left atrial myxomas (LAM) being the most predominant type after pathological examinations. They are however two known basic types of cardiac myxoma; firm smooth and gelatinous irregular fond-like surface type with LAM mainly exhibiting symptoms of left-sided heart failure such as dyspnea when lying flat or on either the left or right side, arrhythmias, pulmonary edema, and even paroxysmal nocturnal dyspnea as a result of obstruction of the mitral valve orifice. Other associating symptoms such as malaise, Reynaud phenomenon, clubbing localized swelling, weight loss without trying and joint pain present themselves as the myxoma increases in size. LAM could also be sessile or pedunculated with pedunculated myxomas being the more frequent of the two. LAM is a multifactorial entity as at its diagnosis could spell the presence of diverse underlying cardiac alignments apart from the classic Goodwin's triad while been silent and/or masked as some could be asymptomatic or vague presenting with just fever and fatigue. Apart from the required prompt clinical investigative and the timely surgical interventions long-term morbidity and the permanent damage done by the constant pendulum-like movement to the mitral valve and its associated apparatus only but leads to possible irreversible progressive permanent cardiac damage and eventually sudden death. The resultant life-threatening complications encountered with LAM such as stroke, acute heart failure, arrhythmias and sudden death produces a thromboembolic- ischemic effect, valvular obstructions and other constitutional symptoms due to the silent masking nature of all LAM with vague symptoms which eventually lead to evident mitral valve insufficiencies [1].

Normal heart valve ensures a one-way blood flow all through the entire cardiac cycle with little interference and without any form of regurgitation. The semilunar valve [i.e., the aortic valve and the pulmonary valve] prevents backflow of blood into the ventricles during the diastolic phase, and the atrioventricular valves [mitral valve and tricuspid valve] prohibit reverse flow from the ventricle to the atrium during systole. The ability for the mitral valve to allow unrestricted forward flow largely depends on the structure, pliability, integrity, and mobility of the entire mitral valve apparatus. The longtime continuous left atrial pendulum-like movement made by the LAM leads to disturbances in the function of the mitral valve which affects the entire cardiac function due to the failure of the valve to shut properly allowing blood leak into the left atrium [regurgitation]. Significant changes done to the structure of the mitral valve such as annular dilatation results to an increase in mechanical stress over the entire valve structure sufficient enough to eventually produce Mitral valve regurgitation coupled with poor leaflet appositions or leaflet tears caused by the size of the myxoma as it constantly rebounds against the leaflets protruding into the left ventricle during systole as far as rupturing the tendinae and over extending both the papillary muscle base initiating a vicious circle leading to mitral regurgitation. The resultant thromboembolic-ischemic effect of the papillary muscle caused by the multi-level blockage of the coronary artery plays a major role to the degree of mitral regurgitation seen [mild, moderate and severe] as the posterior aspect of the muscle receives blood supply from branches of the posterior descending artery,

taking its course from either the right or the circumflex coronary artery, depending on which is the dominant system as its much inclined to ischemia and necrosis produced by the occlusion as compared to the anterior muscle which invariably secures its supply from either the branches of the circumflex artery and the septal left anterior descending artery which is less predisposed to ischemia and rupture caused by occlusion [1–3].

However, achieving a favorable better long-term results with any effective medical interventions used in the management or treatment of mitral valve regurgitation produced by the resultant LAM is dependent on tackling the known types of processes responsible for mitral valve insufficiencies namely; rheumatic, ischemic, degenerative, infectious type [endocarditis] and other related etiological factors such as calcific degeneration and collagen vascular disorders [2, 3]. Being the most common type of heart valve disorders with vast non-surgical and technical surgical methods used in treating mitral valve regurgitation, in-depth knowledge to the known underlined process involved with mitral valve insufficiencies as a result of the consequent presence of the LAM is pivotal to achieving favorable long-term results as masked mitral valve regurgitation are always almost evident at diagnosis. It is therefore imperative for practicing cardiologist, pulmonologist, echo-cardiologist, cardiac surgeons and any other therapist and/or interventionist involved at the diagnostic work up to bear in mind the high possibility of a resultant mitral valve regurgitation produced by the atrial myxoma not also forgetting the associative know processes of mitral valve insufficiencies as all this could be masked by the presence of the myxoma itself limiting the chance for a proper intervention both therapeutically or surgically [1].

Be it as it may, this only adds to the existing questions in the field by practitioners regarding the pathology and physiology of LAM, the accompanied masked regurgitations, mitral valve prolapse and the underlying process involved with mitral valve insufficiencies along with the long-term prognosis. This scientific chapter aims to discuss the clinical implications of mitral valve regurgitation produced by LAM and the underlying processes involved with mitral valve insufficiencies.

2. Anatomy and physiology of mitral valve

The mitral valve is a complex anatomical structure made of an annulus, two leaflets, chordae tendineae, and the anterior and posterior papillary muscle. A synchronized movement of all the mitral valve apparatus is essential for the valve to function normally and their structural architecture enables them to cause a very low level of mechanical stress during the ventricular systole. Mitral valve insufficiencies occur due to structural defects or change affecting the normal architecture of the mitral valve apparatus as an effective function of the mitral valve solely depends on an efficient interaction of the whole mitral valve components including the left ventricle itself. The annulus is generally saddled in shape taking a kidney-like shape in systole and a round shape at diastole. However, it is anatomically divided into two distinct parts; an anterior and posterior portion with the former considered to be non-distensible found between two fibrous bodies while the latter accounts for about 2/3 of the mitral valve orifice and is considered to be easily prone to distention and dilatation with LAM and other

diseases affecting the mitral valve and the left heart [4, 5] (**Figure 1**). The two leaflets are also described as anterior and posterior with the anterior leaflet being wider with a shorter base while the posterior leaflet is narrower but with a much broader attachment. Three distinctive scallops can be related to the posterior leaflet which is clinically distinctive and vital for proper mitral valve function in addition to the lateral and medial small commissural scallops namely; medial, middle and a lateral scallop with the middle scallop being the largest among the three (**Figure 2**) [6–8]. The rough zone of each leaflet comes in contact with that of its other counterpart as the total surface area of the leaflets is twice the total surface area of the mitral orifice itself giving a border surface area for leaflet coaptation during systole which in turn decreases the mechanical stress during a single cardiac circle. A decrease in mechanical stress is achieved with a synchronous contractive action produced by the papillary muscles during left ventricular systole which further leads to an adequate tethering of the mitral valve thereby ensuring that the rough zones of both leaflets are in a properly oriented vertical direction [9–11]. Any destructive or nondestructive change to the normal structure and architecture of the mitral valve apparatus caused by the resultant long-standing pendulum-like effect of the LAM such as annular dilatation [anterior and posterior], leaflet prolapse and/or retraction

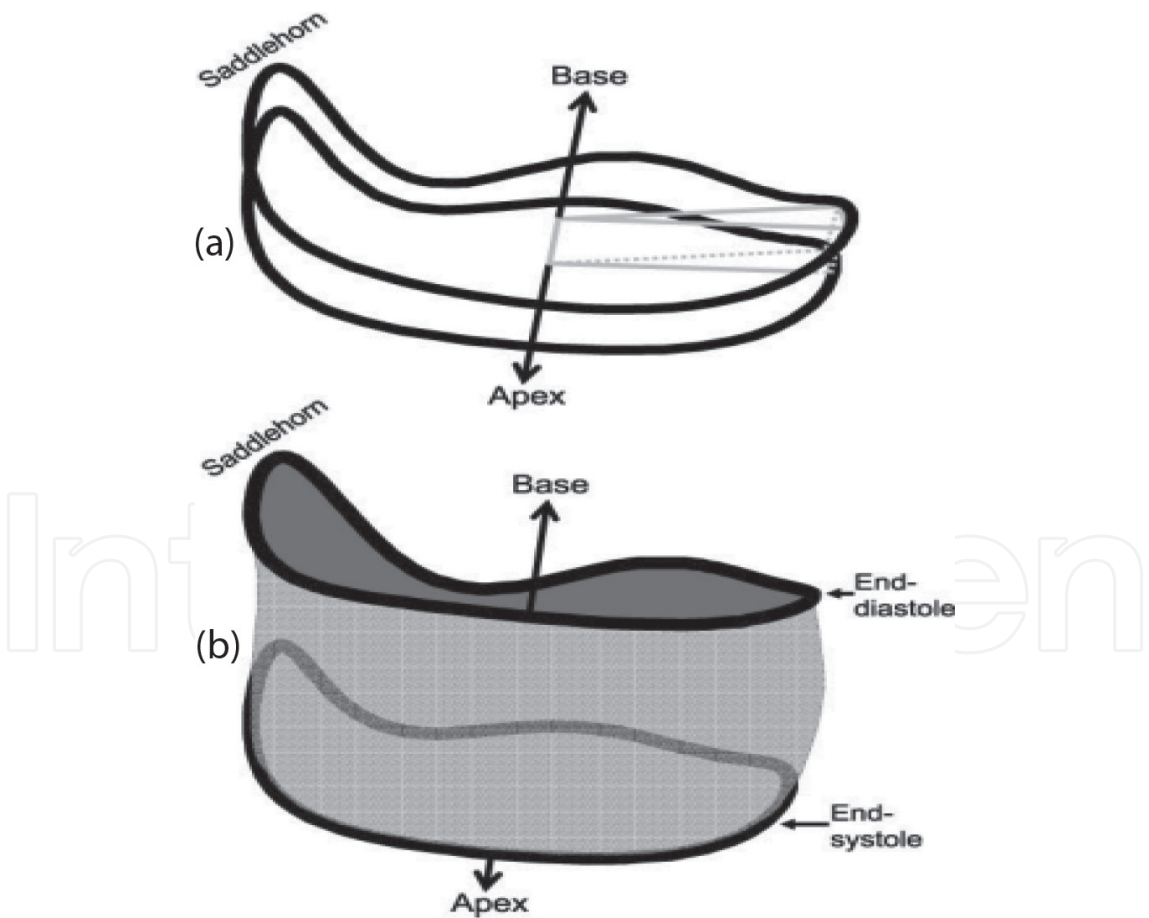


Figure 1. Schematic of the mitral annulus (black lines) (A): Time frames during the cardiac cycle and the volume change (gray lines) between both time frames (B): End systole and diastole (shaded gray). Saddle horn, the annular region closest to the aortic annulus.

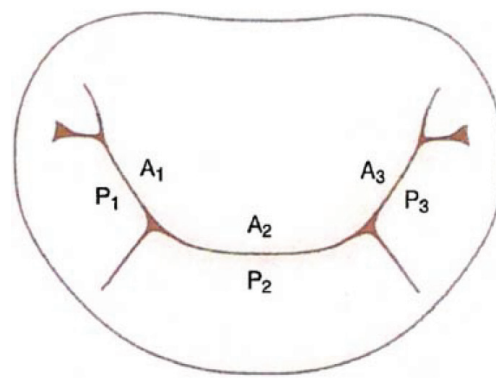


Figure 2. Carpentier classification of a well-structured mitral valve leaflet. A: anterior; P: posterior.

[anterior and posterior], chordae tendineae rupture or elongation and left ventricular abnormalities produced during the course of forward and backwards movement into the left ventricle and back to the left atrium during systole and diastole results in mitral valve regurgitation [1, 4, 7, 11] .

3. Left atrial myxoma

Myxomas are the most prevalent primary cardiac tumors, with 80–85% found in the left atrium and an annual incidence of 0.5 per million commonly arising from the interatrial septum at the fossa ovalis to be precise but can, however, be found in any chamber of the heart and structures with timely surgical resection playing a vital role in its treatment and recovery. The “tumor plop” sound heard during auscultation is a pathognomonic sign as a result of the penetrating myxoma in and out of the left ventricle. Symptoms caused by LAM are intermittent due to the occasional prolapse of the tumor through the atrioventricular valve and is also highly dependent on body position [1]. Cardiac myxomas usually occur between the third and sixth decades of an adult life taking a preference for the female sex with varying growth rate ranging from an absolute nonexistent growth to several millimeters per month. Familial inheritance, multicentricity, metastasis and inadequate excision increases the chance of cardiac myxomas recurrences, increased morbidity and mortality rates leading to poor prognosis and further possibly irreversible cardiac conditions either by medicamentous therapy alone and/or in combination with other various surgical therapies. Planned scheduled follow-up is of great importance in ruling out the possibility of a tumor reoccurrence even after proper surgical therapy employed. Cardiac computed tomography, magnetic resonance imaging, Doppler assessment and a combination of both outpatient transthoracic echocardiography with intra and postoperative Transesophageal echocardiography are essential for identifying and grading the regurgitation which is essential for an adequate left atrial myxoma therapy as they help in making precise judgment and assessment of anatomical valvular structures, which are destroyed by the tumor and are easily missed as most regurgitation are masked by the sole presence of LAM, different loading conditions, body structure and position [1, 12–24].

4. Pathology and physiopathology

The tendency of mitral valve regurgitation and the adjunct mitral valve prolapse development is inevitably high with the presence of left atrial myxoma either before or after any interventions been made. The development of mitral valve prolapse is due to the persistent rebound pendulum-like motion of the left atrial myxoma on the valve apparatus during each cardiac circle. Echocardiographically, mitral valve prolapse is defined as the upward displacement of the mitral leaflets above 2 mm in diastole [silent] which is usually the case in patients presenting with LAM and above 3 mm [massive] which increases the regurgitant jets seen during the echocardiographic studies. However, mid-systolic click to late systolic murmur is pathognomonic auscultatory findings with mitral valve prolapse and underlying regurgitation as it varies from being benign to a gradual or sudden advance stage depending on the prolapse and regurgitation grade either before or after therapeutic interventions with a significant morbidity and mortality rate. Fortunately, apart from the massive prolapse, bacterial endocarditis, thromboembolism, atrial fibrillations, myxomatous degenerations [Barlow's disease] and rheumatic heart diseases play key roles in the resultant regurgitations caused by the left atrial myxoma. Histological features of mitral valve prolapse and regurgitation are marked spongiosa proliferation, mucopolysaccharide acid replacement of the leaflet collagen causing thickening and leaflet redundancy. As a result of the changes made such as fibrotic leaflets, thinning and/or elongation of the chordae tendineae, proper valve coaptation during systole is rendered impossible due to the redundant and elongated leaflets coupled with overshooting into the left atrium and the disrupted tendineae which eventually ruptures leading to regurgitation.

5. Mitral regurgitation

Mitral valve regurgitation is a complex entity that could be caused by either one of the following etiological factors such as; Marfan syndrome, acute rheumatic valve disease, degenerative [myxomatous], bacterial endocarditis, acute ischemia, papillary muscle rupture. However, mitral regurgitations are further categorized into two broad groups; acute and chronic [primary and secondary] mitral regurgitation and into two generally accepted classifications namely; Carpentier and Duran's classification. Although identifying patients at risk, symptomatic, asymptomatic and progressive stage of mitral valve regurgitation encountered in clinical settings have been made easier as compared to previous years with the most recent American Heart Association (AHA) and the American College of Cardiology (ACC) guidelines for patient management (see appendix A and B) [25].

Common clinical presentations encountered with LAM are either stenosis due to tumor prolapse into mitral orifice or regurgitation due to tumor induced valve trauma. Furthermore, Mitral valve regurgitation associated with LAM is caused by ventricular and annular dilatation, failure of leaflet coaptation and the direct damage of the leaflets and/or subvalvular apparatus due to the presence of the myxoma body itself as it transverses through the mitral

valve during each systolic and diastolic phase coupled with the myxoma body adherence to nearby structures of the mitral valve. The myxoma prolapse from the left atrium toward the left ventricle during the entire cardiac cycle eventually leads to mitral valve regurgitations of varying degrees, cause volume overload propagating both left atrial and left ventricular dilatation, annular dilatation due to the continuous mechanical stretch of the prolapsing tumor on the mitral annulus during each systolic and diastolic phase. However, the extent of valvular obstruction varies with body position as the presence of the myxoma body itself affects trans-mitral blood flow and also tends to mask mild and moderate to severe mitral regurgitations due to the huge and floating myxoma body where large myxomas with long stalk produces a temporally complete obstruction of the mitral valve orifice resulting in syncope. The continuous pendulum like or “wrecking ball” effect of the myxoma during each cardiac circle against the entirety of the mitral valve apparatus gives raise to regurgitations and its severity is highly dependent on the resultant effect of the myxoma body itself on the mitral valve [26–35]. The grade and severity of the regurgitation is highly dependent on the myxomas body size, stalk length [small, large, prolapsing and non- prolapsing] and to some varying degree body position and the resultant changes of blood flow through the left heart [36].

5.1. Carpentier classification

As widely used and proposed by Carpentier, the anterior leaflet is indicated as A1, A2, and A3 but lacks a clear distinction between A1 and A2 and also between A2 and A3 because of its smooth surface. However, the analogous segments of the posterior leaflets are also indicated as P1 [anterolateral], P2 [middle], and P3 [posteromedial] and highly distinctive from each other [37]. Regurgitations occur when there is an annular dilatation and/or the free edge of one or both leaflets overrides the entire valve orifice during systole, chordae tendineae destruction or rupture, a papillary muscle tear or detachment, architectural left ventricular destruction and acute ischemia as a result of embolization due to the myxoma friability (**Table 1**). Regurgitations caused by LAM express themselves differently according to grades, degree, and size of the myxoma, different loading conditions, body structure, position and other masked underlying pathology so therefore, for a successfully understanding of mitral regurgitation caused by LAM, a clear knowledge of the components and anatomy of the mitral valve apparatus, possible functional alterations, analysis of the leaflet motion, and a proper grading system is essential for a better prognosis after management or repair [1] (**Figure 2**).

Type A	The manifestation or appearance of mitral regurgitations is as a result of annular dilatation
Type B	The manifestation or appearance of mitral regurgitations is as a result of .one of either leaflets overriding the annular plane during systole
Type C	The manifestation or appearance of mitral regurgitations is as a result of restricted leaflet motion during both systole and diastole
Type D	The manifestation or appearance of mitral regurgitations is as a result of restricted leaflet motion during systole only

Table 1. Carpentier’s classification of regurgitation of the mitral valve.

- Type A is evident when there is annular dilatation only or in combination with leaflet perforation, as in endocarditis.
- Type B is caused by elongated chordae tendineae, as constantly seen in degenerative disease, or thinning of the papillary muscle, found in ischemic heart disease.
- Type C occurs when there is leaflet perforation or chordal rupture, as found in rheumatic diseases.
- Type D there is chordal rupture [rheumatic] or in combination with papillary muscle detachment or displacement [ischemic].

5.2. Duran classification

Kumar et al. proposed their classifications based on the chordae tendineae insertion gotten from the two papillary muscle groups. Thus, the posterior leaflet scallops were designated as P1 [anterolateral] and P2 [posteromedial] and the larger middle scallop as posterior middle which was subdivided as PM1 and PM2 based on chordal origins while the anterior leaflets were divided into A1 with chordae crossing from the anterolateral papillary muscle and A2 with chordae from the posteromedial papillary muscle [38] (**Figure 3**).

5.3. Acute mitral regurgitation

Acute mitral regurgitation occurs due to annular prolapse and the disruption of other different structures of the mitral valve. The papillary muscle rupture or the detachment of the chordae tendineae from the papillary muscles caused by the resultant myxoma pendulum-like movement during each cardiac cycle causing disrupted valve motion and a rise in volume overload in combination with the high friable tendencies of LAM leading to embolization of the coronary arteries which eventually ends in myocardial infarction. The acute volume overload on the left ventricle combined with the regurgitant flow of blood into the left atrium during systole results in acute pulmonary congestion, dyspnea, and poor cardiac output [39].

5.4. Chronic mitral regurgitation

When categorizing chronic mitral regurgitation caused by left atrial myxoma, it is important that the physician gives a proper distinction between chronic primary [degenerative] and chronic secondary [functional] mitral regurgitation as it clearly helps in identifying the underlying pathology in relation to the resultant effect caused by the myxoma itself.

- *Chronic primary mitral regurgitation:* This regurgitation is as a result of the myxomas destruction of a single valve component either in its function or architecture such as annular dilatation with regurgitant jets from the left ventricle to the left atrium. However, the prolonged and severe volume overload produced eventually causes irreversible myocardial damage, episodic periods of heart failure and finally sudden death
- *Chronic secondary mitral regurgitation:* In this type of regurgitation, the entire valve apparatus is somewhat normal but the regurgitant jets are caused by embolization of the coronary arteries on different levels from the fragments of the myxoma giving rise to myocardial

infarction precipitating severe left ventricular dysfunction and adverse remodeling which eventually causes papillary muscle detachment, tethering leaflets with associated annular dilatation preventing proper coaptation [40].

5.5. Ischemic heart disease

Ischemic mitral regurgitation is defined as a moderate to severe mitral leak precipitated by acute myocardial infarction caused by partial or total complete obstruction of one or more coronary arteries on a different level due to the myxoma friability which gives rise to various degree of mitral regurgitation by changing the geometry of the ventricle [spherical shape], distorted wall motion, lateral and apical deracinated papillary muscles or its deformation due to ischemia [41].

5.6. Degenerative heart disease

This type of regurgitation is perpetuated as little pieces of embolus from the myxoma gets stocked at the edges of the leaflets forming small nodules which prevents complete valve closure

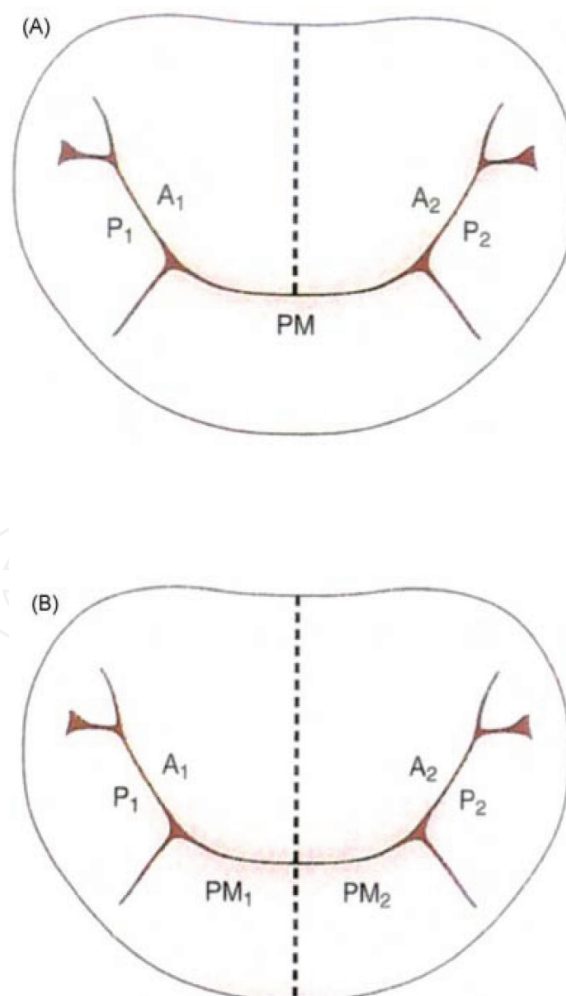


Figure 3. (A) Duran classification of a well-structured mitral valve leaflet, A: anterior; PM: posterior middle; P1: posterior lateral; P2: posterior medial. (B) Modified type A: anterior. P: posterior. PM: posterior middle [1: lateral. 2: Medial].

leading to regurgitant backflow of blood into the left atrium during the course of each cardiac circle which over time leads to an enlarged left atrium and ventricle causing heart failure.

5.7. Rheumatic heart disease

Myxoma [Latin Greek word “muxe” for mucus] means a myxoid tumor of primitive connective tissue, a primary tumor affecting adult hearts commonly in the left atrium but can, however, be found in other locations. LAM inflammatory process gives rise to a rapid sequence of chordal thickening and retraction, commissural fusion and finally thickened leaflets [incomplete opening and closure of the leaflets] with an enlarged annulus which eventually leads to regurgitation. Though an uncommon relation to the underlying processes involved with LAM throughout its development until therapy, pathologist has confirmed postoperatively the pathological component of LAM to be a spindle tumor with mucus production histologically made up of fusiform, stellate, and or polygonal cells [42–45] and histologically associated with interleukin-6 [46].

5.8. Endocarditis

This type of regurgitation caused by LAM is rare as compared to other underlying resultant pathological cause and may even be described by some physicians, surgeons, and interventionist as idiopathic due to its ambiguity. The vegetations formed involves series of the pathological process which is activated as a result of incomplete resection of the LAM in combination with natural human oral streptococcal inhabitants [*Streptococcus sanguinis* and/or *dysgalactiae*] which gets into the bloodstream when opportunities present themselves such as during surgeries and colonize the heart valves especially the mitral valve. The result at first is noninfective, but as the collection of platelets, fibrin, microcolonies of microorganisms, and the scant inflammatory cells increases, it shifts to a subacute stage and finally to full-blown endocarditis due to bacterial accumulations as they lodge and aggregate at the site of the incomplete LAM resection [1, 47].

6. Conclusion and future directions

Being the most common primary cardiac neoplasm in adults, the present state of research on its set cause, Pathobiology, physiopathology, and pathophysiology are still elusive as clinical and research efforts are being channeled toward its morbidity, mortality and its possible reoccurrence after surgery. If resultant mitral regurgitations and long-term survival for patients is to be achieved as it's the main goal in all neoplastic diseases, a proper understanding of myxomas pathology and the probable underlying process that could occur before and after therapeutic and/or surgical interventions employed is highly essential to tackle the unresolved issue in the field. Management of this condition requires adequate therapeutical background knowledge of the various possible outcomes to allow for an early identification of masked regurgitations caused by the LAM as a result of the probably altered valve motion or damaged valve apparatus in combination with the activated underlying processes

involved with a well-planned follow-up regimen as regurgitations in some cases might not be detected immediately after the intraoperative Transesophageal echocardiography is used to check if the myxoma was totally resected and the surgery satisfactory as it could be termed by the physician as a physiological residual regurgitation seen after such kind of surgery which could be detrimental in the long term. However, current clinical features and echocardiographic criteria's are not sufficient enough to detect mitral regurgitations and probable underlying pathological conditions early to achieve an effective medical management and/or surgical therapy.

The most challenging problem both surgeons and interventionist face is the doubtful nature surrounding possible resultant masked regurgitations with LAM as this could be residual following myxomas resection coupled with the underlying pathological factors aligned with this neoplasm as it propagates the destruction, perforation, elongation, thinning, tethering, thickening, retraction, displacement and ischemic changes seen in mitral valve regurgitation and/or prolapse. Bearing this in mind, at the slightest suspicion of hemodynamic and architectural change in mitral valve apparatus and ventricular geometry [remodeling] during medical management or surgical intervention, a thorough assessment of the mitral valve apparatus should be made using Transthoracic echocardiography [outpatient settings] and Transesophageal echocardiography [inpatient settings] in combination with the surgeons direct vision assessment if surgery was the treatment of choice irrespective of the known diagnosis [myxoma] in order to rule out any possible concomitant pathology such as coronary embolization to achieve favorable long-term prognosis. Finally, future directions and approaches made by the various scientific communities should be directed toward identifying the key dynamic concepts behind LAM biological, physiological and pathological components, clinical features and the echocardiographic criteria's to be used in an early detection of mitral valve regurgitation and the possible underlying pathological processes and/or complications that could precipitate silent mitral valve insufficiencies after medical management or surgical interventions as this will be an important achievement and a novel contribution to the field.

Conflict of interest

The authors declare no conflict of interest.

Author's contributions

We the authors appreciate the contributions Iroegbu Phoebe Chioma and Adeghe Peace Eseose made to the manuscript.

ICD: Concept and design, a major contributor to the interpretation and writing of the manuscript.

ZZ, ZH & JL: Critically revised and analyzed the manuscript for scientific logic and reasoning.

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List of abbreviated words

LAM	left atrial myxoma
AHA	American Heart Association
ACC	American College of Cardiology

AppendixA. American Heart Association (AHA) and the American College of Cardiology (ACC) guidelines for the clinical management of patients with primary mitral regurgitations.

Class	Class interpretation	Anatomy	Valvular hemodynamics	Resultant consequence	Symptoms
I	At potential risk of mitral valve regurgitation development	*Valve prolapse [mild] but with adequate coaptation *Valvular thickening accompanied with restriction of both leaflet	Absence of any visible regurgitant jets with Doppler and little vena contracta of 0.3 cm	Nonexistent and uneventful	None
II	Gradual progressive mitral regurgitation	*Valve prolapse [severe] but with an adequate leaflet coaptation *Loss of leaflet coaptation probably cause by [rheumatic valve] *previous infective endocarditis	*Evident regurgitant jets <50%, vena contracta of <0.7 cm, with an effective regurgitant orifice of <0.40 cm ² and an angiographic grade between 1 and 2 ⁺	Adequate pulmonary pressure with a mild left atrial enlargement and normal left ventricle geometry.	None
III	Tolerant asymptomatic mitral regurgitation [Severe]	Same as the above with an addition of leaflets thickening with radiation heart disease	Same as the above but with an increase in: angiographic grade 3–4 ⁺	Possible pulmonary hypertension, with a moderate to severe left atrial and ventricular enlargement	None
IV	Symptomatic Severe mitral regurgitation	Same as the above	Same as the above	Pulmonary hypertension is evidently present with a moderate to severe left atrial and ventricular enlargement	Decreased exercise tolerance, Exertional dyspnea

AppendixB. American Heart Association (AHA) and the American College of Cardiology (ACC) guidelines for the clinical management of patients with secondary mitral regurgitations.

Class	Class interpretation	Anatomy	Valvular hemodynamics	Resultant consequence	Symptoms
I	At potential risk of mitral valve regurgitation development	Normal valve architecture in patients with cardiomyopathy or coronary diseases	Absence of any visible regurgitant jets with Doppler and little vena contracta of <0.30 cm	*Motion abnormalities with probably dilated left vertical with geometric change *Myocardial disease	Evident symptoms are those of coronary ischemia which could be reversed with adequate therapy
II	Gradual progressive mitral regurgitation	Loss of leaflets coaptation centrally combined with annular dilatation and motion abnormalities which are regional	ERO <30 cm ² and a regurgitant volume and fraction of <30–40 ml and <50% respectively	*Motion abnormalities with probably dilated left vertical with geometric change *Myocardial disease	Evident symptoms are those of coronary ischemia which could be reversed with adequate therapy
III	Tolerant asymptomatic mitral regurgitation [Severe]	Loss of leaflets coaptation centrally combined with annular dilatation and motion abnormalities which are regional	ERO ≥30 cm ² and a regurgitant volume and fraction of ≥30–40 ml and ≥50% respectively	*Motion abnormalities with probably dilated left vertical with geometric change *Myocardial disease	Evident symptoms are those of coronary ischemia which could be reversed with adequate therapy
IV	Symptomatic Severe mitral regurgitation	Loss of leaflets coaptation centrally combined with annular dilatation and motion abnormalities which are regional	*ERO 0.20 cm ² *Regurgitant volume 30 mL *Regurgitant fraction 50%	*Motion abnormalities with probably dilated left vertical with geometric change *Myocardial disease	* Evident symptoms are those of coronary ischemia which could be reversed with adequate therapy *Exertional dyspnea *Decreased exercises tolerance level

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