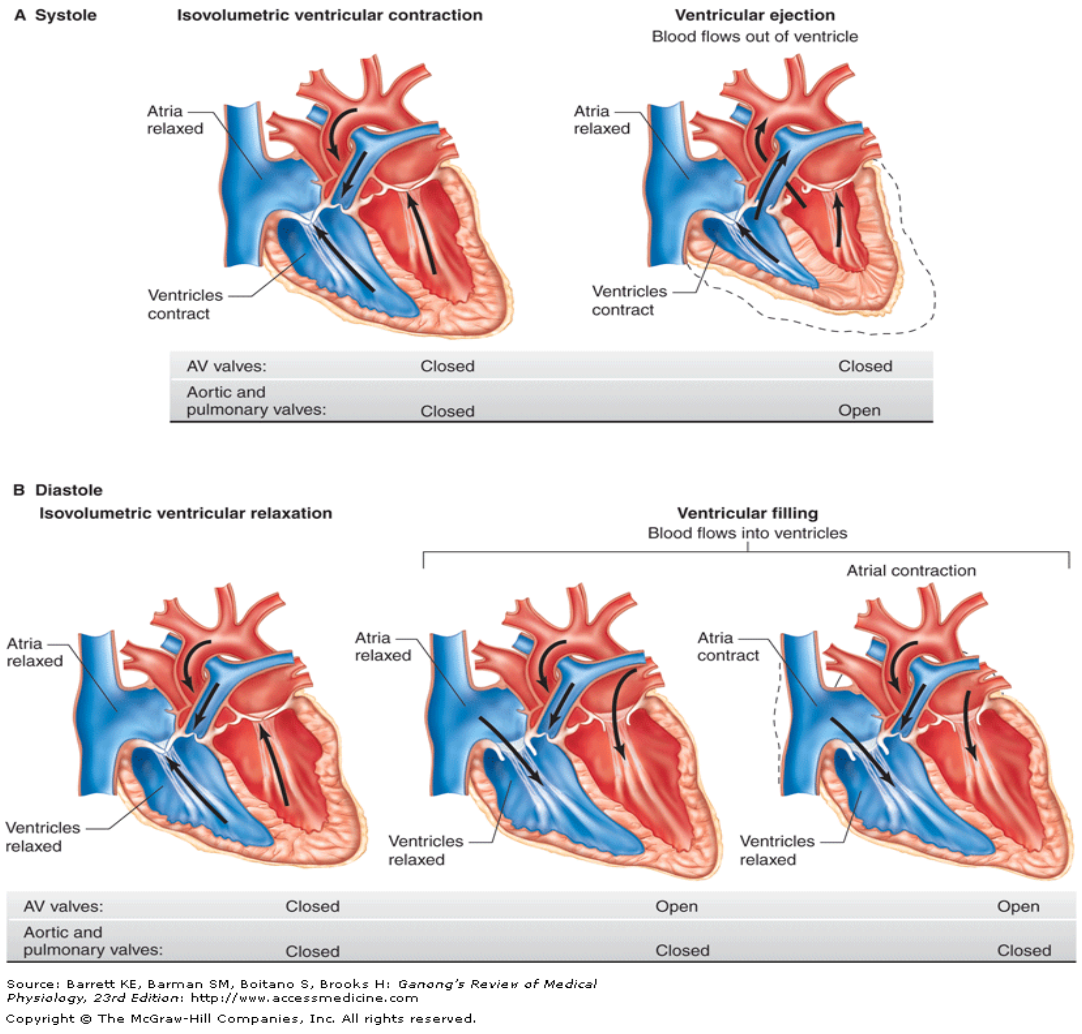
VALVULAR HEART DISEASE

Kenneth Alonso, MD, FACP

Blood flow and myocardial contraction



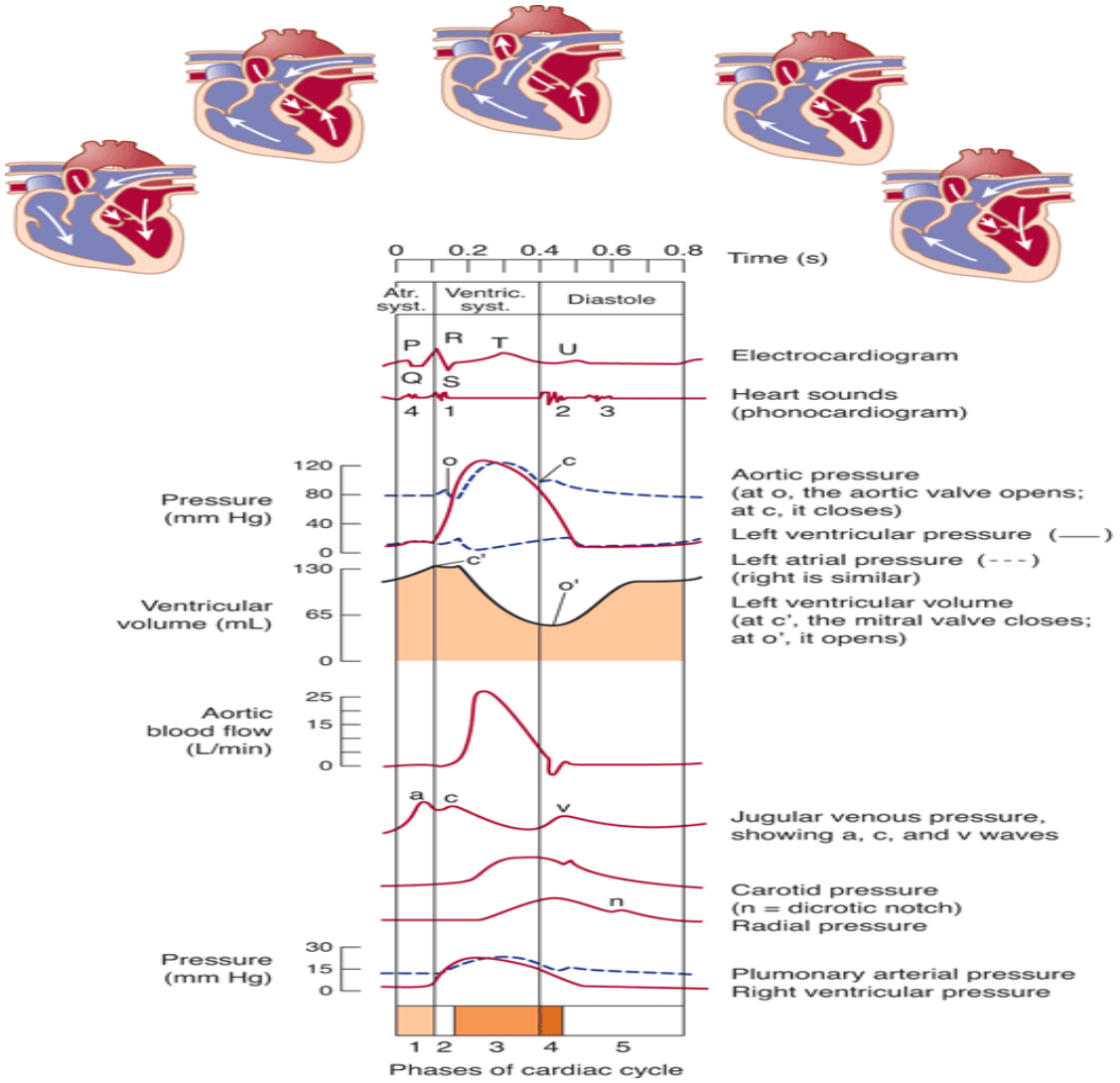
Late in systole, aortic pressure actually exceeds left ventricular pressure.

However, the momentum of the blood keeps it flowing out of the ventricle for a short period.

The pressure relationships in the right ventricle and pulmonary artery are similar.

Fig. 31-2 Accessed 02/01/2010

Cardiac cycle



Phases
1. Atrial systole
2. Isovolumetric ventricular contraction
3. Ventricular ejection
4. Isovolumetric ventricular relaxation
5. Ventricular filling.

Fig. 31-3 Accessed 02/01/2010

Blood flow and myocardial contraction

- Phases
- 1. Atrial systole
- 2. Isovolumetric ventricular contraction
- 3. Ventricular ejection
- Late in systole, aortic pressure actually exceeds left ventricular pressure.
- However, the momentum of the blood keeps it flowing out of the ventricle for a short period.
- 4. Isovolumetric ventricular relaxation
- 5. Ventricular filling.
- The pressure relationships in the right ventricle and pulmonary artery are similar.

Physiologic splitting

- During expiration
- The aortic and pulmonic components of the second heart sound are separated by <30 ms
- Are appreciated as a single sound.
- During inspiration
- The splitting interval widens
- The components are clearly separated into two distinct sounds.

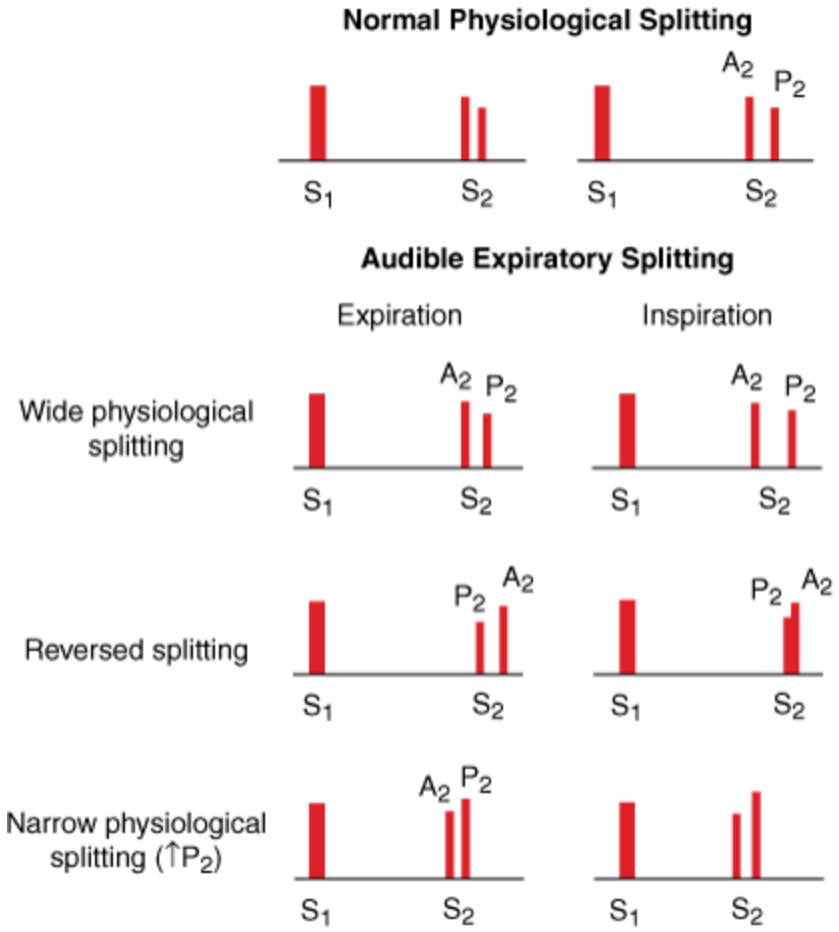
Pathologic splitting

- Narrow physiologic splitting
- Occurs in pulmonary hypertension
- Both components are heard during expiration
- Because of the increased intensity and high-frequency composition of P_2.
- Wide physiologic splitting is caused by a delay in pulmonic valve closure.
- Complete right bundle branch block

Pathologic splitting

- Reversed splitting
- Delay in aortic valve closure
- Usually due to impaired left ventricular emptying
- With inspiration, the splitting interval narrows
- Aortic stenosis, left bundle branch block, hypertrophic cardiomyopathy
- Paradoxical splitting
- Early pulmonic valve closure
- Wolf-Parkinson-White syndrome

Splitting



(From JA Shaver, JJ Leonard, DF Leon, Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 17. Copyright, American Heart Association.)

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Abnormal heart sounds

- Fixed split of S_1
- Right bundle branch block
- Fixed split of S_2
- Associated with atrial septal defect
- S_3 pathognomonic for volume overload
- S_4 pathognomonic for stiff ventricle
- S_3 and S_4 originating from the right ventricle diminish with expiration and increase with inspiration
- S_3 and S_4 originating from the left ventricle, increase with expiration and decrease with inspiration

Turbulence

- Blood flow is streamlined
- Concentric layers of fluid slip past each other
- The slowest layers are at the interface between blood and vessel wall
- The fastest layers are in the center of the blood vessel
- When the critical velocity is reached, turbulent flow results.
- Flow does not increase as much for a given rise in pressure because energy is lost in the turbulence.

Cardiac murmurs

- Associated with an underlying cardiac abnormality
- Holosystolic murmur(positive likelihood ratio, LR+, 8.7; LR-, 0.2)
- Loud murmur (LR+, 6.5; LR-, 0.1)
- Systolic thrill (LR+,12)
- Decreased carotid upstroke
- Diastolic murmurs always important.

Table 20–4.

Pathologic murmurs.

Systolic Ejection	Pansystolic	Diastolic	Continuous
Semilunar valve stenosis (AS/PS/truncal stenosis)	VSD	Semilunar valve regurgitation	Runoff lesions
ASD	AVVR (MR/TR)	AI/PI/truncal insufficiency	PDA/AVM/aortopulmonary collaterals
Coarctation		AV valve stenosis (MS/TS)	

Current Diagnosis & Treatment: Pediatrics, 25e

Systolic heart murmurs

- Early systolic:
- Large ventricular septal defects with pulmonary hypertension
- Very small muscular ventricular septal defects.
- Tricuspid regurgitation occurring in the absence of pulmonary hypertension
- Common in narcotics abusers with infective endocarditis

Mid-systolic murmurs

Cause	Location	Radiation	Quality	Shape	Pitch
Hypertrophic cardiomyopathy	Left lower sternal border	None	Harsh	Crescendo-decrescendo	High
Aortic stenosis	Aortic valve	Neck	Harsh	Crescendo-decrescendo	High
Pulmonic stenosis	Pulmonic valve	None	Blowing	Crescendo-decrescendo	High
Innocent	Left sternal border	None	Soft	Crescendo-decrescendo	High

https://journals.lww.com/jaapa/fulltext/2019/12000/cardiac_auscultation__using_physiologic_maneuvers.4.aspx

Systolic heart murmurs

- Mid-systolic (diamond shaped):
- Aortic stenosis
- Pulmonic stenosis
- Late systolic:
- Papillary muscle dysfunction
- Holosystolic:
- Mitral regurgitation
- Tricuspid regurgitation
- Ventricular septal defect.

Holosystolic murmurs

Cause	Location	Radiation	Quality	Shape	Pitch
Mitral regurgitation	Apex	Left axilla	Soft	Pansystolic	High
Tricuspid regurgitation	Tricuspid valve	Left sternal border and xiphoid process	Soft	Pansystolic	High
Ventricular septal defect	Lower left sternal border	None	Harsh	Pansystolic	High

https://journals.lww.com/jaapa/fulltext/2019/12000/cardiac_auscultation__using_physiologic_maneuvers.4.aspx

Diastolic heart murmurs

- Early (decrescendo):
- Aortic regurgitation
- Pulmonic regurgitation
- Mid-diastolic:
- Mitral stenosis
- Tricuspid stenosis

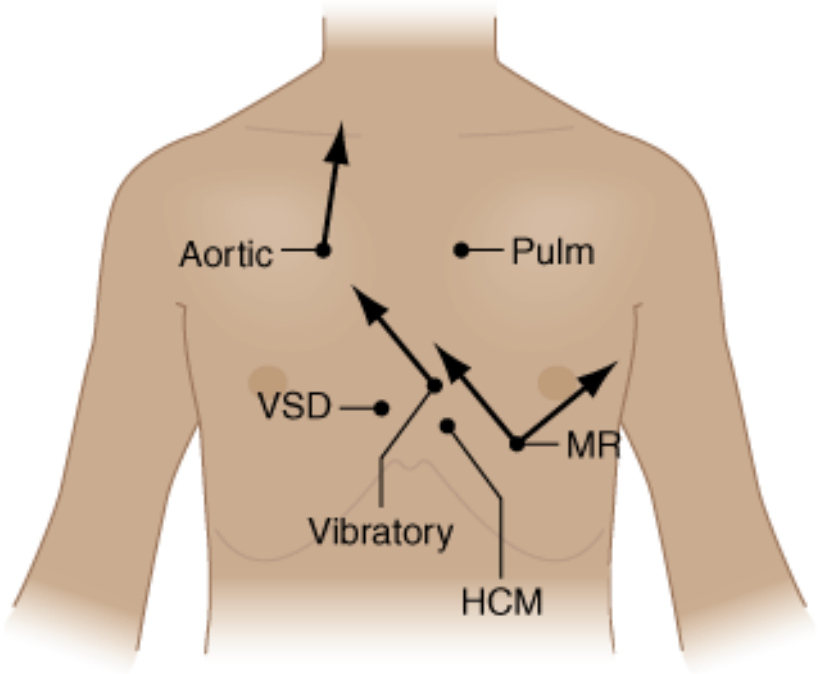
Diastolic murmurs

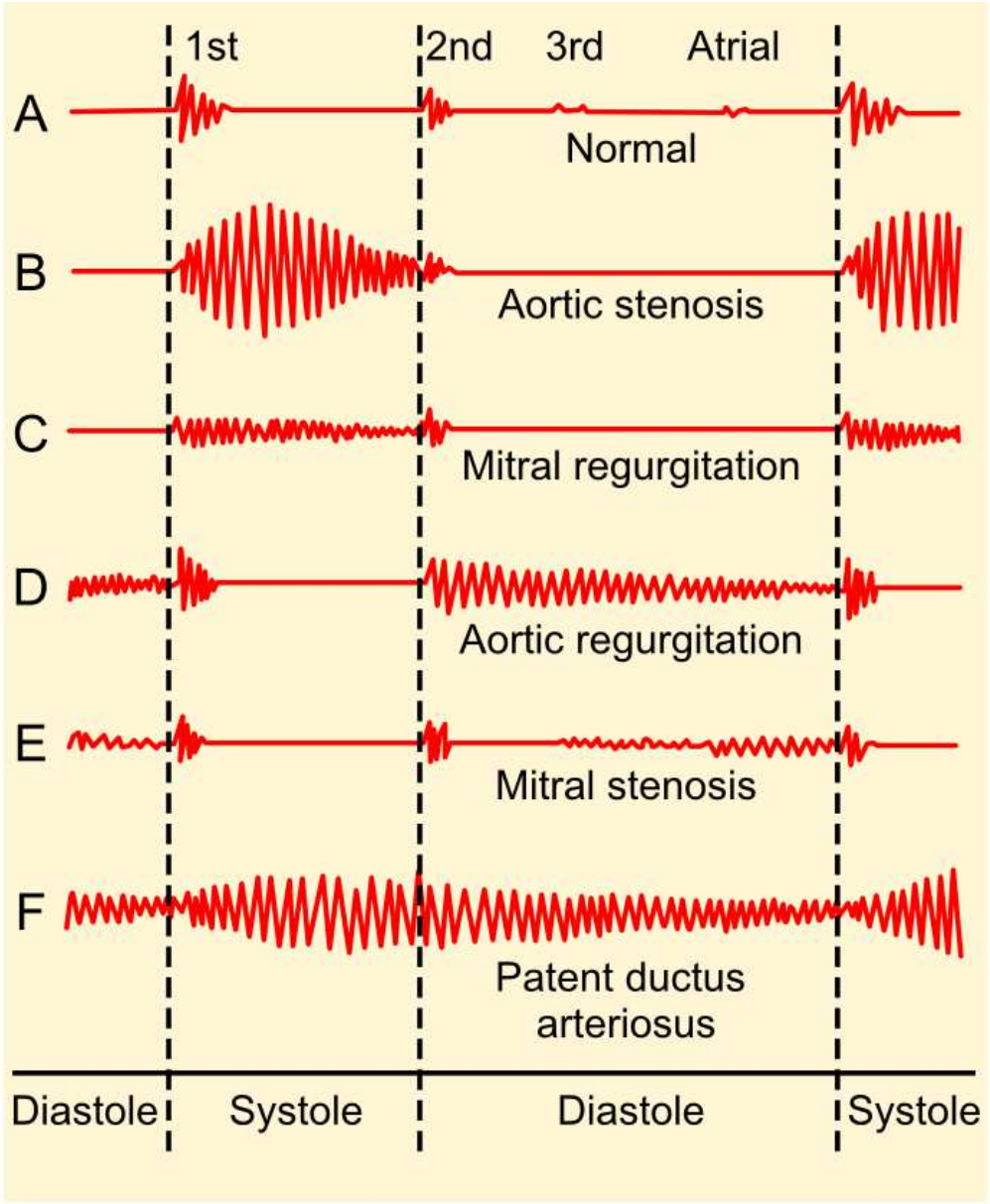
Cause	Location	Radiation	Quality	Shape	Pitch
Aortic regurgitation*	Left second and third intercostal space, patient leaning forward with breath held	Apex	Blowing	Decrescendo	High
Mitral stenosis	Apex, with patient in left lateral decubitus position	None	Rumbling	End-diastolic crescendo	Low

* An Austin Flint murmur is associated with severe aortic regurgitation, does not radiate, and has a low-pitched rumbling quality.

https://journals.lww.com/jaapa/fulltext/2019/12000/cardiac_auscultation__using_physiologic_maneuvers.4.aspx

Maximal intensity and radiation of six isolated systolic murmurs





Phonocardiograms from normal and abnormal heart sounds

https://en.wikipedia.org/wiki/Heart_murmur#/media/File:Phonocardiograms_from_normal_and_abnormal_heart_sounds.png

Heart murmurs

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

(From JA Shaver, JJ Leonard, DF Leon, Examination of the Heart, Part IV, Auscultation of the Heart. Dallas, American Heart Association, 1990, p 55. Copyright, American Heart Association.)

Continuous murmur

- Abnormal communication between high-pressure and low-pressure systems
- Large pressure gradient exists throughout the cardiac cycle, producing a continuous murmur.
- A classic example is patent ductus arteriosus.
- A continuous murmur crescendos to around S_2, and decrescendos to S_1.
- Another example is a large ventricular septal defect.
- Holosystolic or pansystolic murmur

To-fro murmur

- Combination of systolic ejection murmur and a murmur of semilunar valve incompetence.
- A to-fro murmur has two components.
- The mid-systolic ejection component decrescendos and disappears as it approaches S_2.
- Aortic stenosis and regurgitation.

Change in position affects dynamics

- Standing decreases preload
- Murmur decreases in intensity
- Squatting increases venous return to the right side of the heart with compression of the veins in the lower extremities.
- There is increased right-sided preload; thus increased left-sided preload

Change in position affects dynamics

- With a Valsalva maneuver, there is increased intrathoracic pressure.
- This also causes increased vascular resistance in the left side of the heart and the pulmonary venous system.
- This reduces intraluminal pressure in the pulmonary vessels and reduces left ventricular filling
- Decreased right-sided preload causes decreased left-sided preload

Change in position affects dynamics

- With the exception of mitral vale prolapse and hereditary hypertrophic cardiomyopathy, all other murmurs decrease with Valsalva.
- Passive leg raising increases preload
- Murmur increases in intensity but not in hereditary hypertrophic cardiomyopathy

Change in position affects dynamics

- Standing from a squatting position decreases preload and is associated with an initial increase in intensity of murmur if mitral regurgitation, but not mitral valve prolapse
- Squatting from a standing position increases preload AND increases afterload

Change in position affects dynamics

- Hand grip maneuver increases afterload
- The murmurs of aortic regurgitation, mitral regurgitation, and VSD increase in intensity
- The intensity of the diastolic murmur in mitral regurgitation increases
- May also accentuate gallops
- The murmurs of aortic stenosis, hereditary hypertrophic cardiomyopathy, and mitral valve prolapse decrease in intensity.

Change in position affects dynamics

- Inspiration increases right-sided heart murmurs (tricuspid and pulmonary valves) and expiration increases left-sided murmurs (mitral and aortic valves)
- Valsalva maneuver accentuates right sided murmurs
- Increased inspiration but not Valsalva accentuates S_2 splitting and a right sided S_3 (gallop).
- This is Carvallo's sign.

Mid-systolic murmurs

- If the cause is hypertrophic cardiomyopathy, standing and Valsalva maneuvers increase the murmur; squatting and handgrip maneuvers decrease it.
- If the cause is aortic stenosis, squatting and leg raises increase the murmur; standing, Valsalva, and handgrip maneuvers decrease it.
- If the cause is pulmonic stenosis, inspiration increases the murmur.
- 20% of children with an “innocent” murmur (diminishes upon standing) have congenital heart disease.

Holosystolic murmurs

- If the cause is mitral regurgitation, squatting and handgrip maneuvers increase the murmur; standing and Valsalva maneuvers decrease it.
- If the cause is tricuspid regurgitation, inspiration increases the murmur.
- If the cause is a ventricular septal defect, squatting and handgrip maneuvers increase the murmur; standing decreases it.

Diastolic murmurs

- If the cause is aortic regurgitation, squatting, leg raise, and handgrip maneuvers increase the murmur; standing and Valsalva maneuvers decrease it.
- If the cause is mitral stenosis, the murmur increases with the handgrip maneuver, or when the patient is placed in the left lateral decubitus position with his or her breath held in exhalation

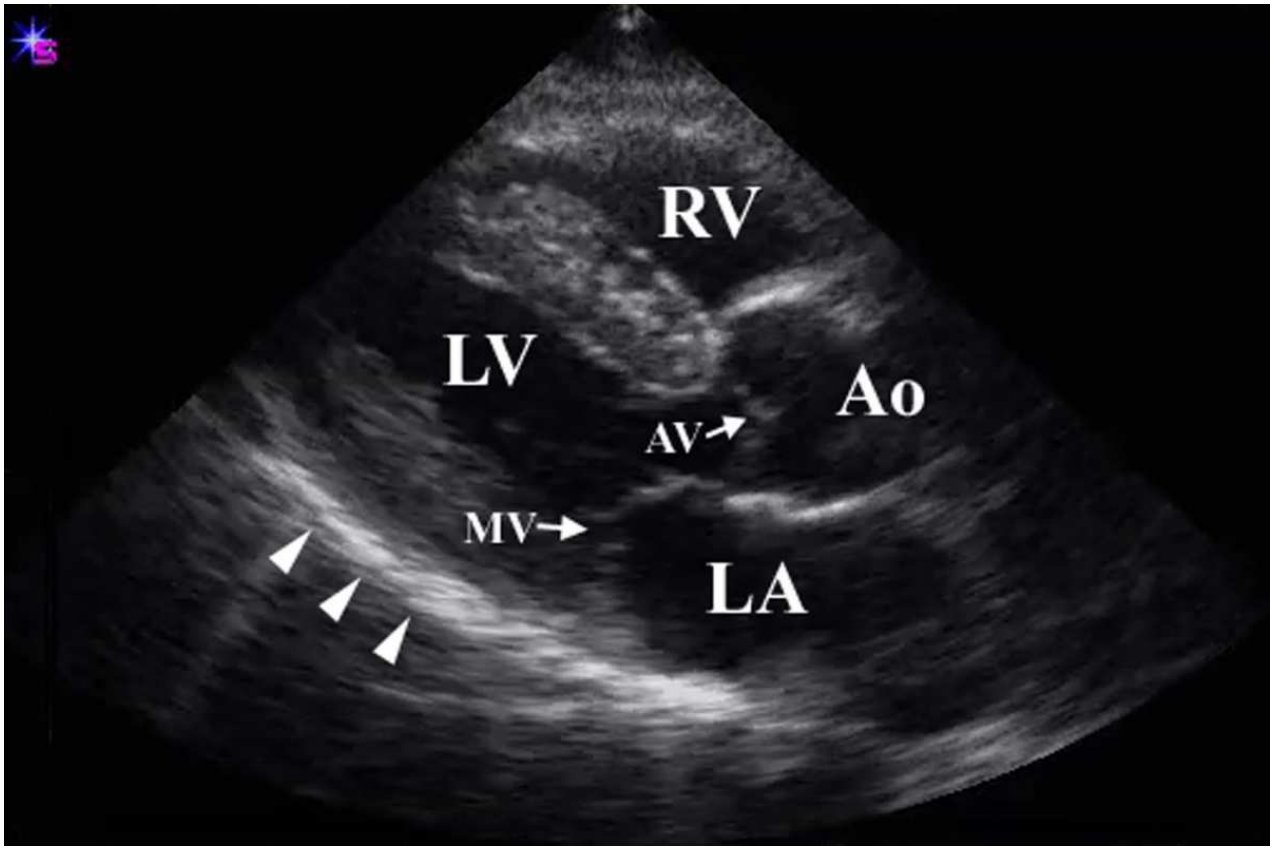
Acute coronary syndrome murmurs

- Ventricular septal rupture may develop after an anteroseptal infarction.
- The patient will exhibit respiratory distress and acute heart failure.
- Auscultation will reveal a loud, harsh, holosystolic murmur with a palpable thrill.
- Left ventricular dilation secondary to ischemia or heart failure can cause mitral regurgitation and a holosystolic, high-pitched murmur.
- An isometric handgrip or leg raising will increase the murmur's intensity.

Acute coronary syndrome murmurs

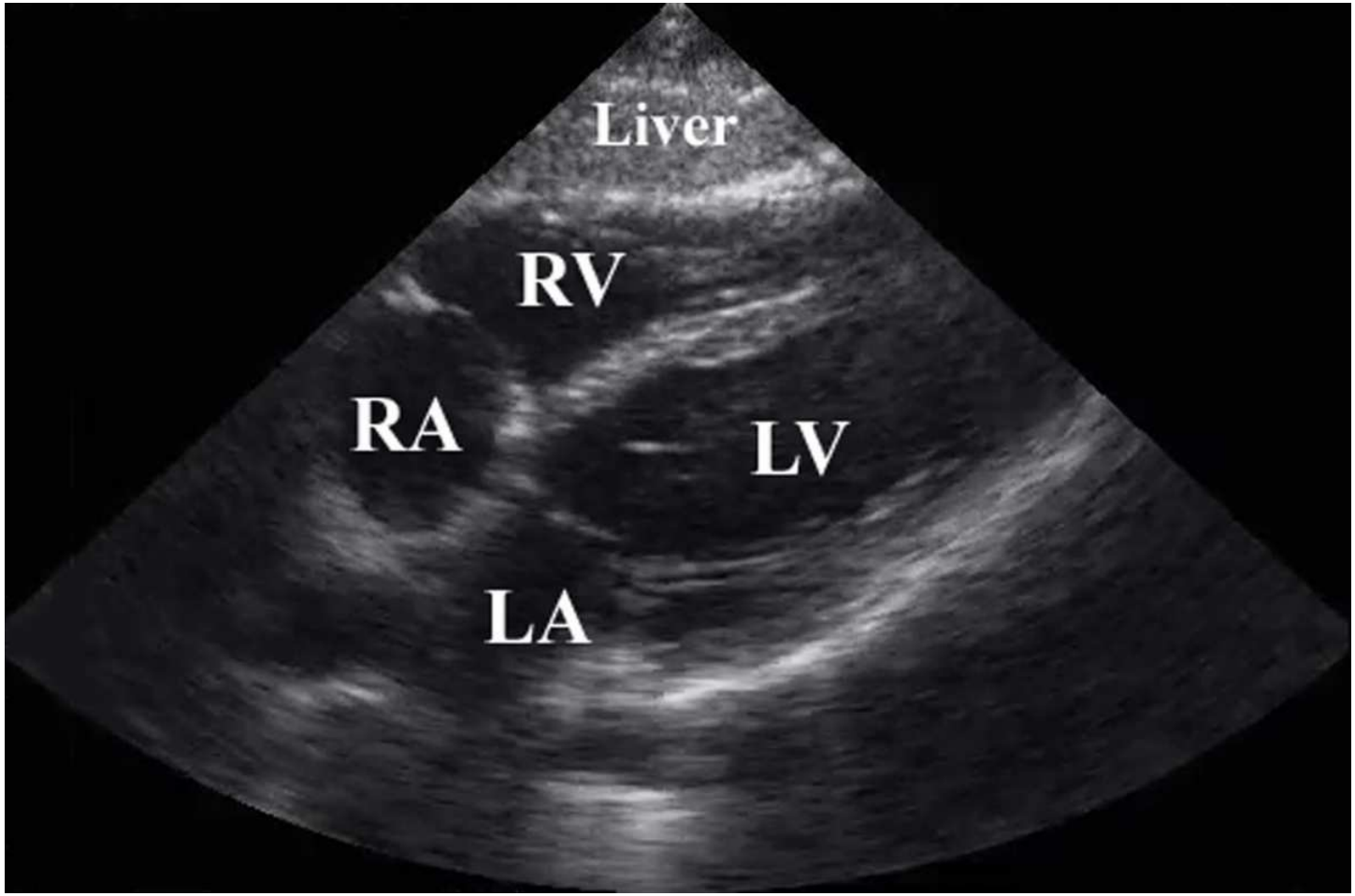
- Chordae tendinae rupture, papillary muscle rupture, and papillary muscle dysfunction are complications of acute coronary syndrome and can cause acute mitral regurgitation and a new holosystolic harsh murmur.
- Another complication after ACS is a reactive pericarditis (Dressler syndrome) that can cause a pericardial friction rub.

Cardiac Ultrasound Parasternal view long axis



www.acep.org/sonoguide/cardiac.html Accessed 09/10/2019

Cardiac Ultrasound
Subxiphoid view



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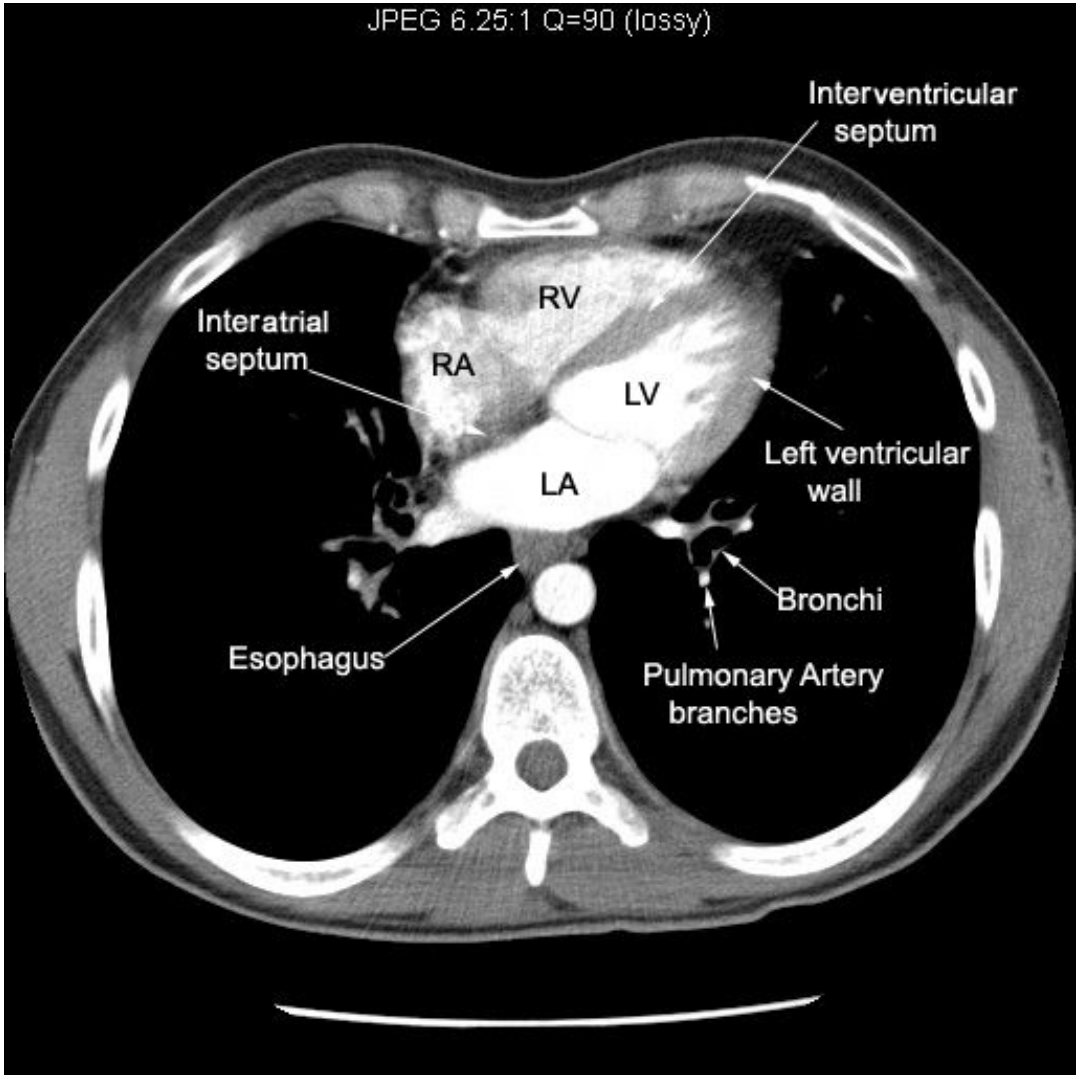

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Accessed 12/07/2019

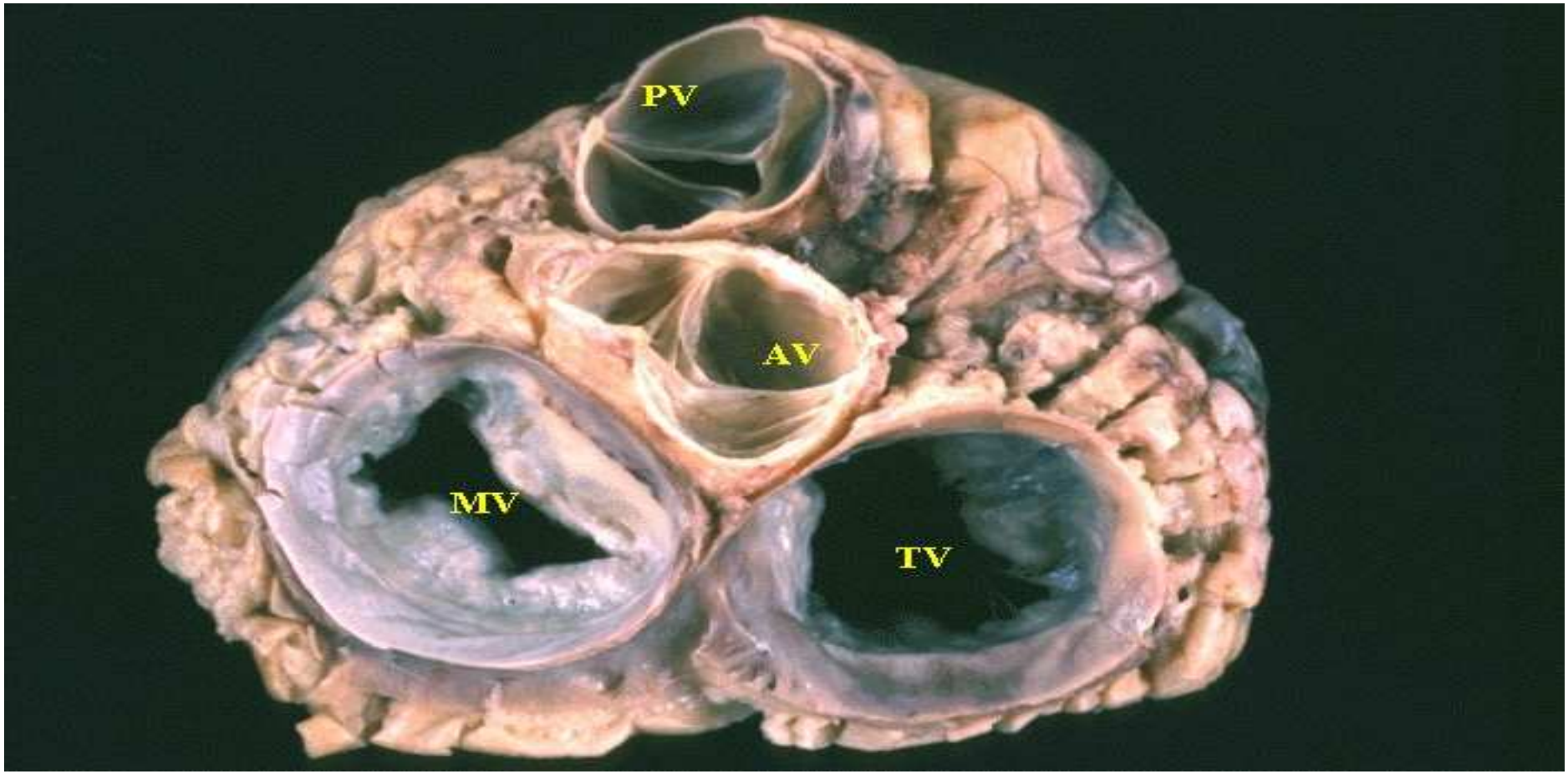
MIRROR IMAGE

Valve distribution

The arrow points to a ballooned mitral valve. The other valves are structurally normal.

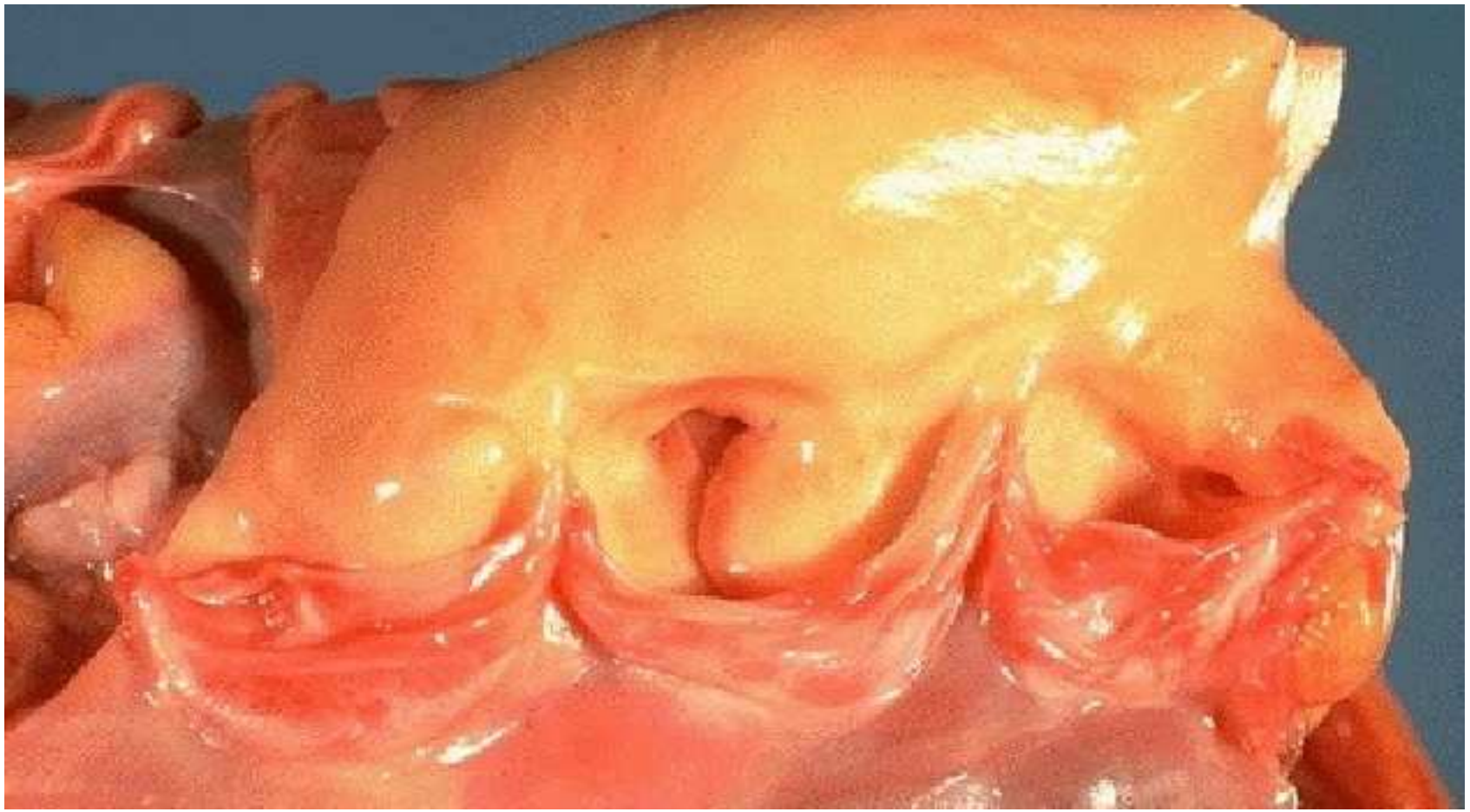
Schoen, and FJ, Mitchell, RN, “Heart”, in Kumar, V, Abbas, AK, Aster, JC (eds.), Robbins and Cotran Pathologic Basis of Disease, 9th edition. 2015. Elsevier. Philadelphia. Fig. 12-22.

Native heart valves



med.uottowa.ca Accessed 09/10/2019

Native Aortic Valve



Klatt, EC, Robbins and Cotran Color Atlas of Pathology. (2015) Elsevier. Philadelphia. Fig. 2-7
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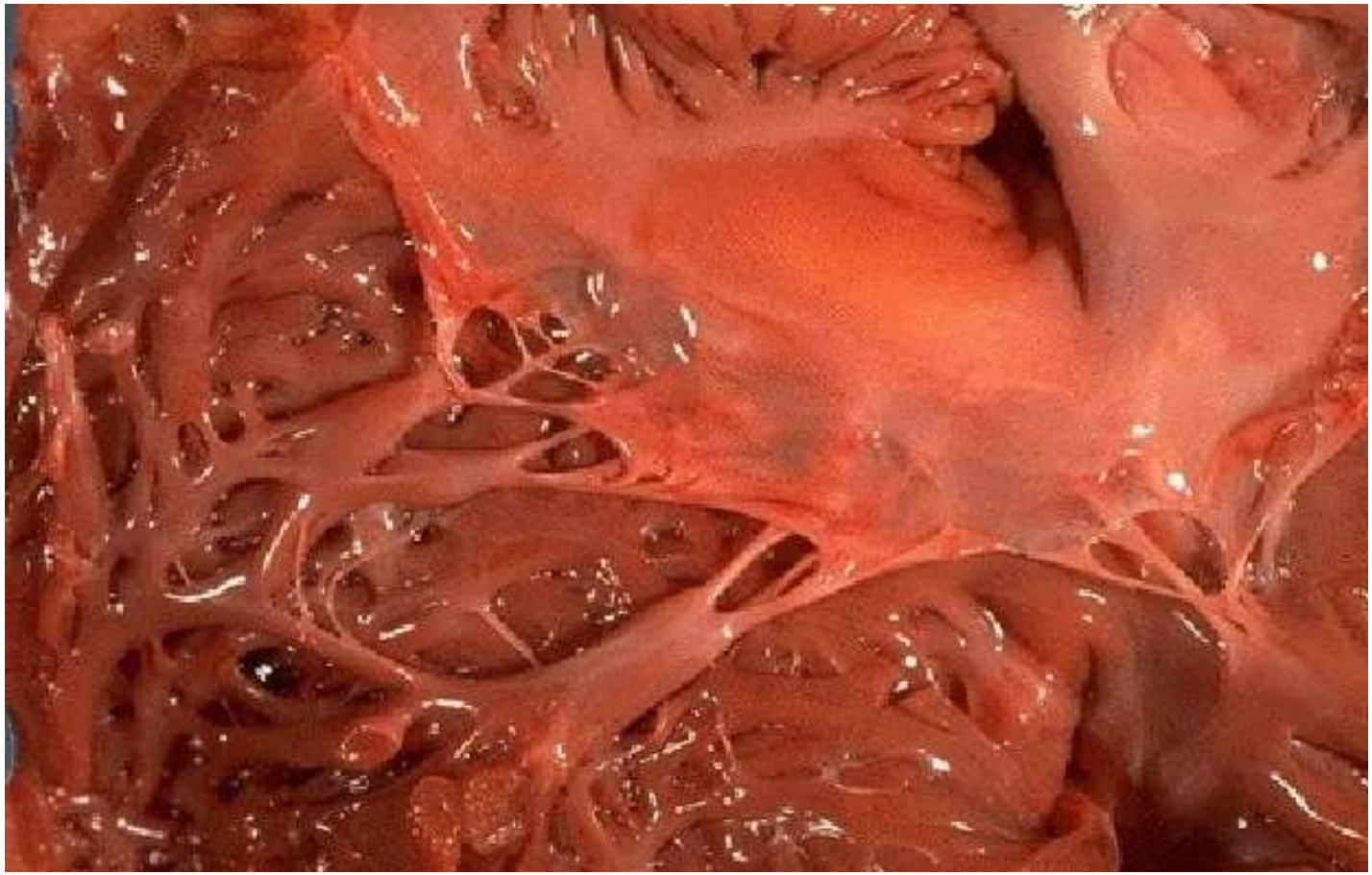
Native Tricuspid valve



Klatt, EC, Robbins and Cotran Color Atlas of Pathology. (2015) Elsevier. Philadelphia. Fig. 2-8
Accessed 09/01/2019

Valvular disease

- The valves are subject to repetetive injury
- Open/close
- High trans valvar pressures at opening/closing
- This leads to transient deformation of the valve
- Diseases of the valves cause either stenosis
- Blockage of blood flow through the valve
- OR regurgitation
- Leakage of blood back through the valve
- A misshapen valve that does not open all the way is not likely to close completely.
- In “combined” stenosis and regurgitation, one hemodynamic abnormality typically predominates.

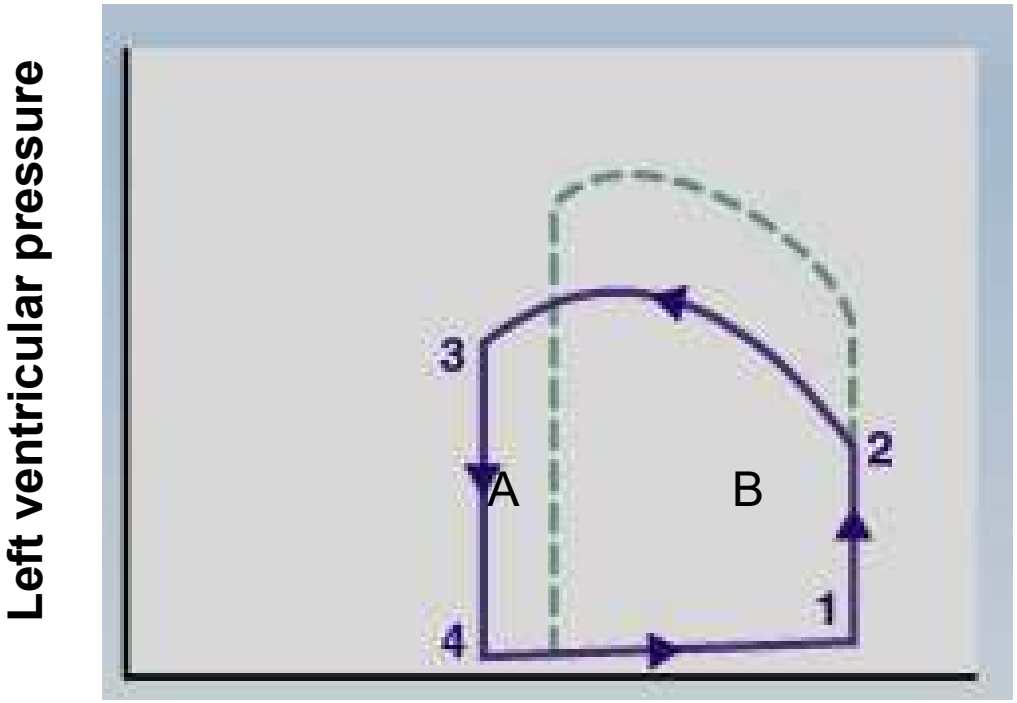
Valvular disease

- Stenosis develops chronically
- Regurgitation can develop acutely or chronically
- Chronic conditions affecting the valves allow for compensatory changes
- Acute conditions do not allow for compensatory change.
- Functional regurgitation stems from abnormality to supporting structure
- An abnormally formed valve leads to pressure overload of the involved atrium or ventricle.
- An incompetent valve leads to volume overload

Obstruction to left ventricular outflow

- Produces systolic pressure gradient between the left ventricle and the aorta.
- The left ventricle responds by dilatation and reduction of stroke volume.
- Left ventricular output is maintained by the presence of concentric left ventricle hypertrophy.
- When hypertrophy becomes maladaptive, left ventricle function declines.
- Hypertrophy elevates myocardial oxygen requirements.
- Coronary artery perfusion decreases as increased muscular pressure compresses coronary arteries.

Increase in afterload



A. Normal
B. Increased afterload

1. Increased systolic pressure (1-2)
2. Decreased stroke volume (mid-width of PV loop)
3. Increased end systolic volume (baseline)

TABLE 256-1

Major Causes of Aortic Stenosis

Valve Lesion	Etiologies
Aortic stenosis	Congenital (bicuspid, unicuspid)
	Degenerative calcific
	Rheumatic fever
	Radiation

Aortic stenosis

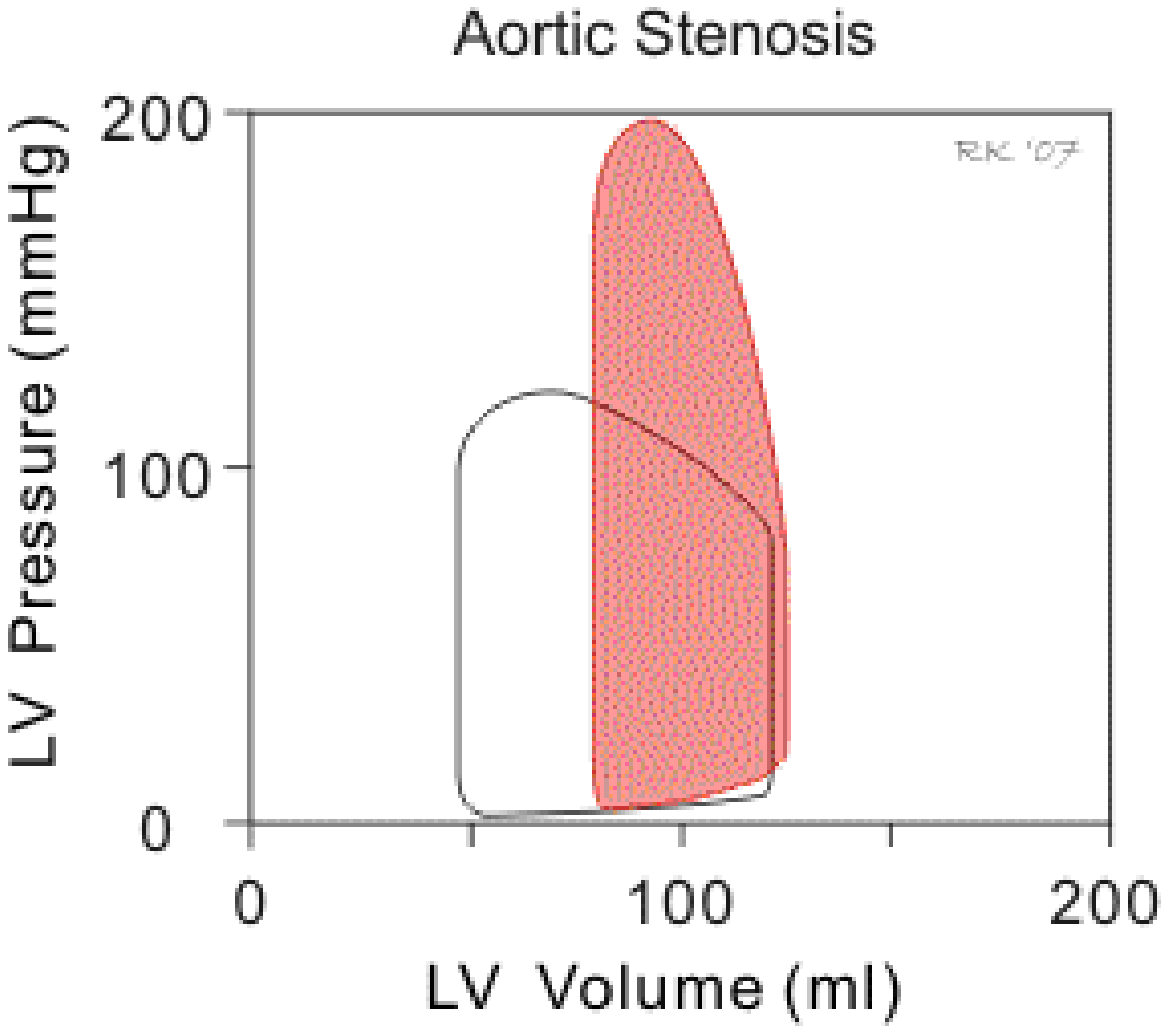
- In aortic stenosis left ventricular emptying is impaired because of high outflow resistance caused by a reduction in the valve orifice area when it opens.
- This high outflow resistance causes a large pressure gradient to occur across the aortic valve during ejection, such that the peak systolic pressure within the ventricle is greatly increased.
- This leads to an increase in ventricular wall stress (afterload), a decrease in stroke volume, and an increase in end-systolic volume.

Aortic stenosis

- Stroke volume decreases because the velocity of fiber shortening is decreased by the increased afterload
- Because end-systolic volume is elevated, the excess residual volume added to the incoming venous return causes the end-diastolic volume to increase.
- Stroke volume falls because the end-systolic volume increases substantially more than the end-diastolic volume increases.
- The fall in stroke volume can lead to a reduction in arterial pressure.
- Stroke volume falls even further if the ventricle begins to exhibit systolic and diastolic dysfunction.

Aortic stenosis

- Compensatory increases in end-diastolic volume will be limited by ventricular hypertrophy that occurs due to the chronic increase in afterload.
- This hypertrophy can lead to a large increase in end-diastolic pressure that is associated with reduced end-diastolic volumes because the increased stiffness of the ventricle prevents normal ventricular filling.

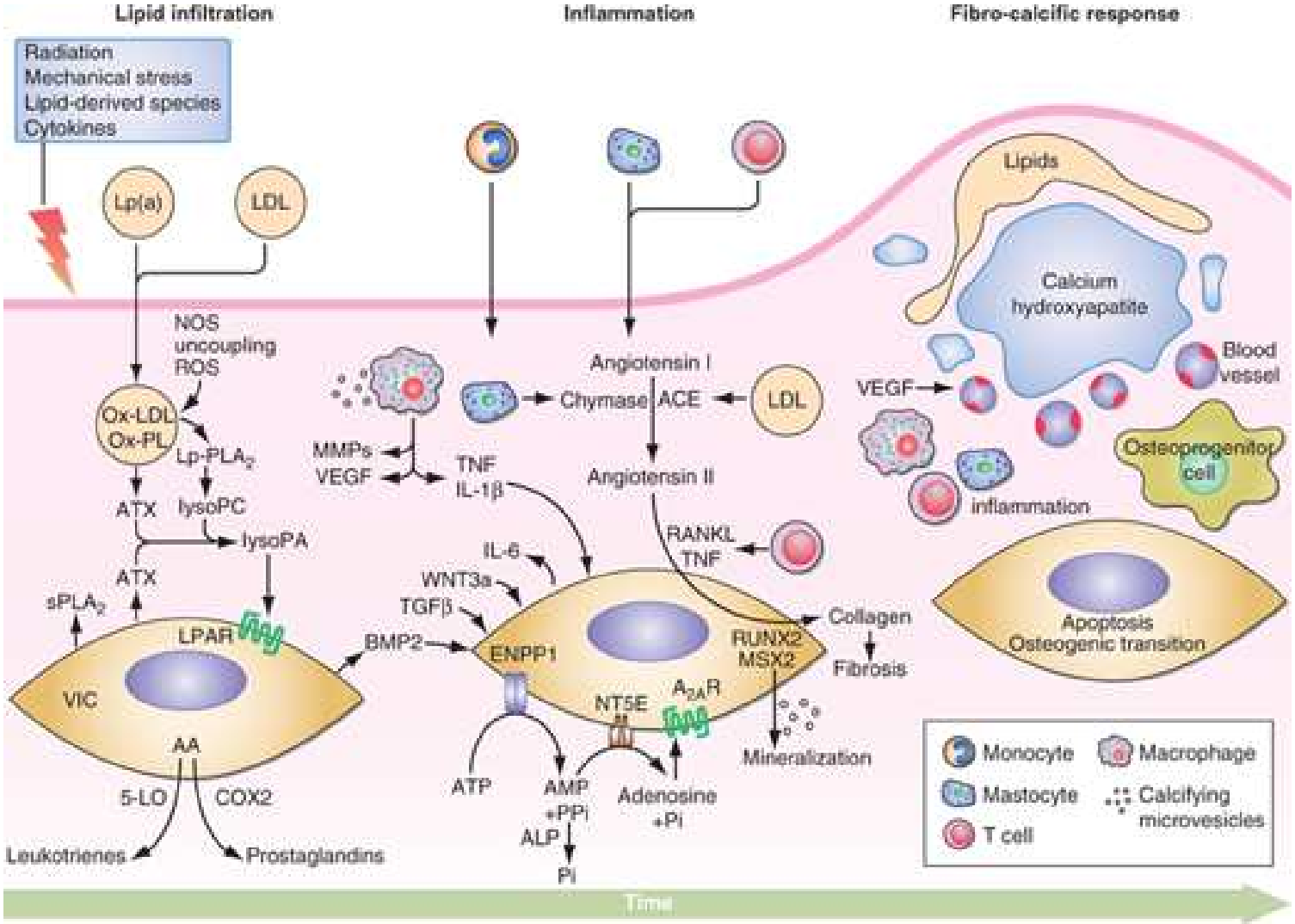


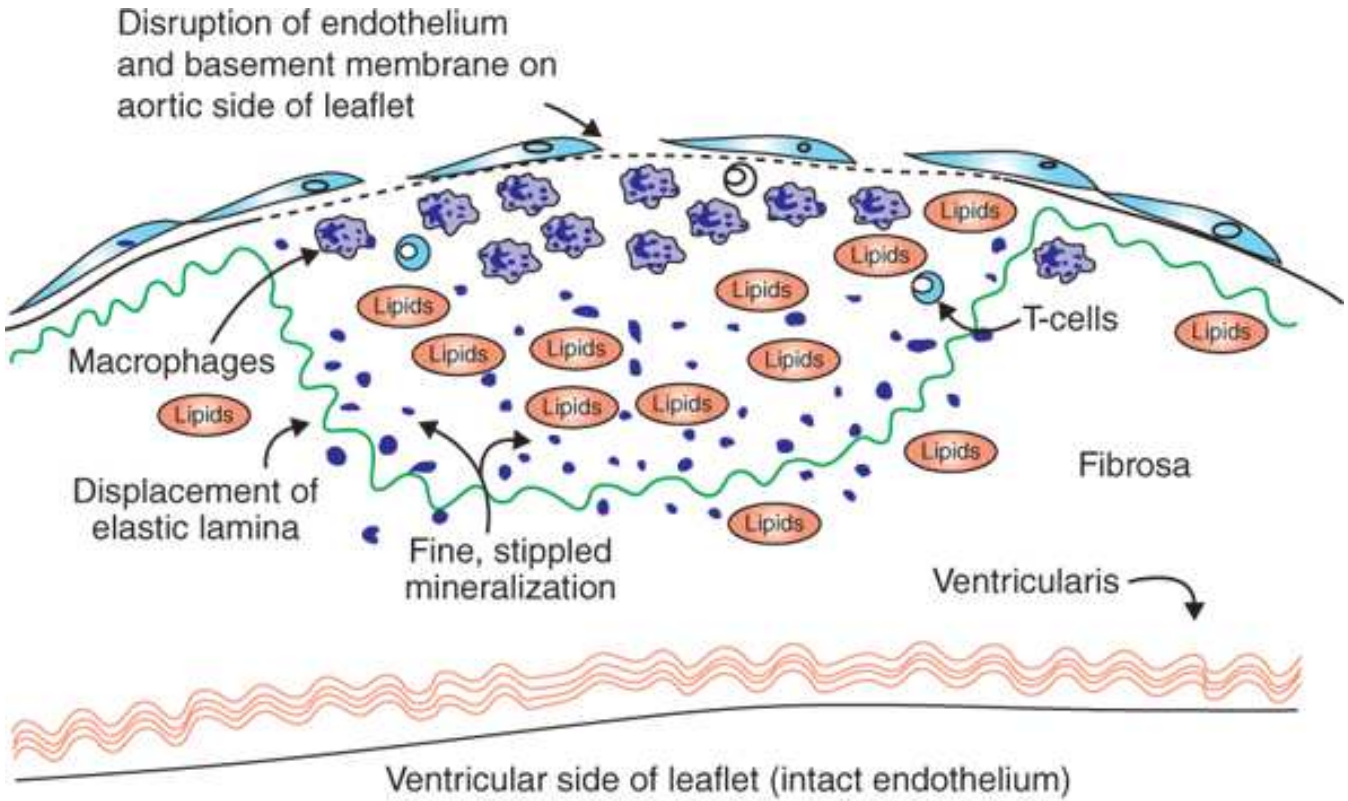
Aortic stenosis (red)

https://www.cvphysiology.com/Heart%20Disease/HD009b

Aortic stenosis

- In developed countries, the etiology of aortic stenosis (AS) is a process akin to but is not atherosclerosis
- The initial lesion is plaque-like with a central core of lipids and macrophages.
- Over time the plaque becomes calcified and in 15% of cases actually contains lamellar bone.
- The process holds in common many of the risk factors for atherosclerotic coronary disease, including hyperlipidemia, hypertension, and the metabolic syndrome.
- Lp(a), not LDL, associated with progression





The early plaque of aortic stenosis demonstrating similarities to an atherosclerotic plaque. Reproduced with permission from Otto CM, Kuusisto J, Reichenbach DD, et al: Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. Circulation. 1994 Aug;90(2):844-853.

Aortic valve stenosis

- Congenitally bicuspid valve.
- 1-2% of population
- One-third become stenotic
- 50% of those under 70 years of age.
- Prevalent in Turner's syndrome
- Nodules of calcium are on the sinus side of the cusps.
- In most cases, bicuspid valves have one smaller cusp and one large cusp.
- The larger cusp may have a midline raphe, representing incomplete separation of two cusps
- Major site of calcification

Aortic valve stenosis

- Ejection sound characteristic.
- Loss of function Notch 1 mutation at 9q34.3 in familial cases
- NKX2.5 (endothelial nitric oxide synthase) implicated
- Medial degeneration with aneurysm formation frequent
- LV responds by dilation and reduction of stroke volume (concentric hypertrophy)
- Echocardiogram diagnostic

Aortic valve stenosis

- Calcified aortic valve
- Degenerative change
- Most common cause in patients over 70 years of age.
- Calcification of the sinus side of the cusps with little involvement of the commissures
- Extends into sinus of Valsalva
- Metaplastic bone formation identified
- May also see calcification of mitral annulus (clinically unimportant)
- Also consequence of rheumatoid arthritis valvulitis

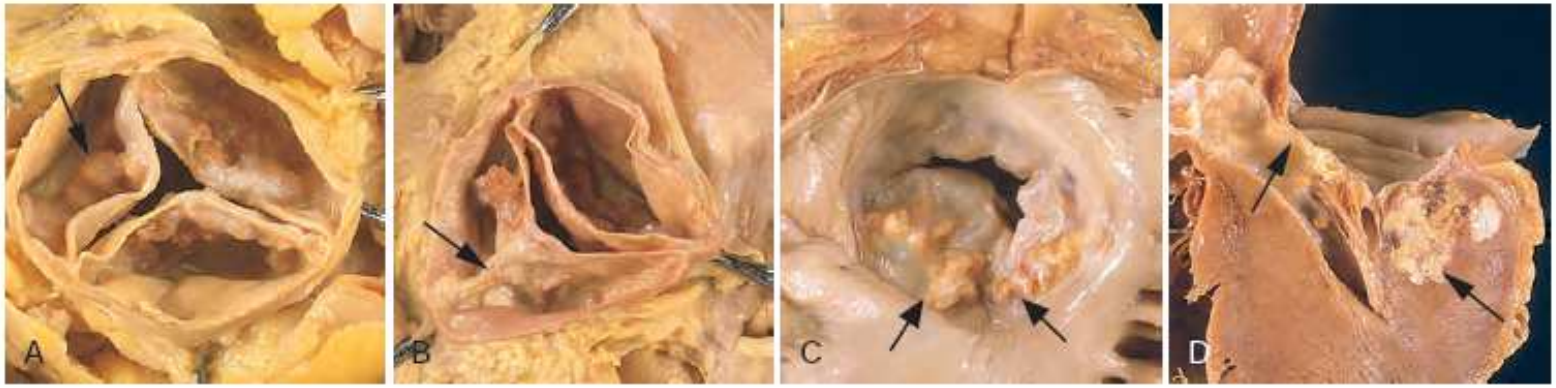


Figure 12-21 Calcific valvular degeneration. **A,** Calcific aortic stenosis of a previously normal valve (viewed from aortic aspect). Nodular masses of calcium are heaped up within the sinuses of Valsalva *(arrow)*. Note that the commissures are not fused, as occurs with postrheumatic aortic valve stenosis (see Fig. 12-23*E*). **B,** Calcific aortic stenosis of a congenitally bicuspid valve. One cusp has a partial fusion at its center, called a *raphe (arrow)*. **C** and **D,** Mitral annular calcification, with calcific nodules at the base (attachment margin) of the anterior mitral leaflet *(arrows)*. **C,** Left atrial view. **D,** Cut section of myocardium showing the lateral wall with dense calcification that extends into the underlying myocardium (*arrow*).

Aortic valve stenosis

- Angina, syncope, and congestive heart failure are the cardinal symptoms of aortic valve stenosis
- Post inflammatory rheumatic heart disease has been the principal cause in the pre-antibiotic era.
- The commissures separating the cusps may be fused.
- Symptoms appear when valve area <1cm^2
- Normal valve area 3cm^2
- Both aortic and mitral regurgitation may be present.

Consequences of aortic valve stenosis

- Concentric hypertrophy
- Ventricular adaptation to resistance to flow through the valve
- Diminished compliance
- Chest pain
- Poor filling of coronary arteries
- Increased O_2 demands of ventricular myocardium.
- Syncope
- Impaired cerebral perfusion

Aortic valve stenosis

- Attenuated carotid pulse with a delayed carotid upstroke (pulsus parvus et tardus).
- Paradoxically split S_2
- Pulmonic valve closes before the aortic valve.
- High-pitched systolic ejection-type systolic murmur (crescendo-decrescendo) at right upper sternal border.
- Radiates to carotid.
- Ejection click after S_1 as well if bicuspid valve.
- The murmur diminishes in intensity
- Abrupt standing from the supine position
- Valsalva maneuver
- Sustained hand grip.

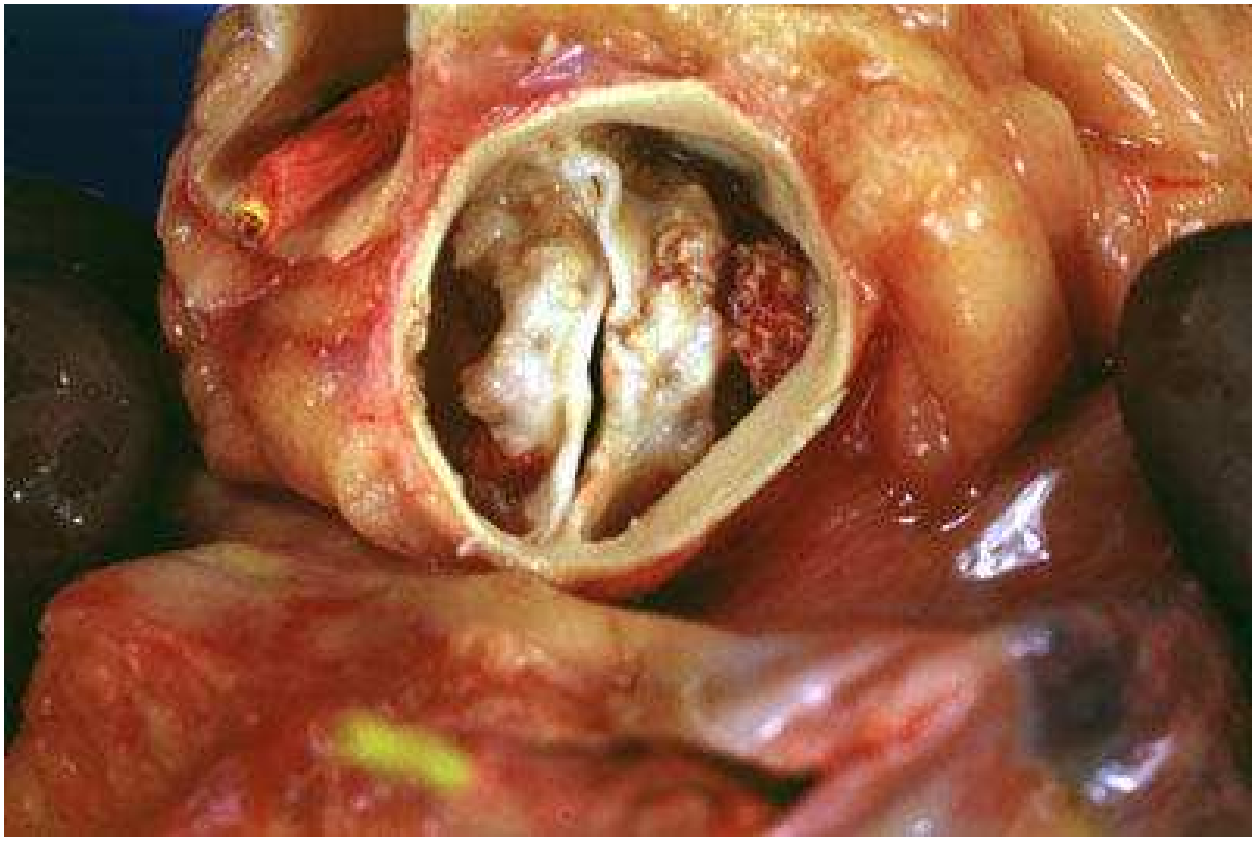
Aortic stenosis

- Moderate to severe aortic stenosis
- >40% regurgitant fraction
- Slow carotid upstroke (LR+ 9.2)
- Diminished S_2 (LR+ 7.5),
- Reduced carotid pulse volume (LR+ 2.0)
- Gallavardin's phenomenon
- Late systolic murmur that is loud over the aortic area, diminishes over the sternum, reappears at apex
- May confuse with mitral regurgitation
- Absence of radiation to right clavicle makes moderate to severe aortic stenosis unlikely (LR-

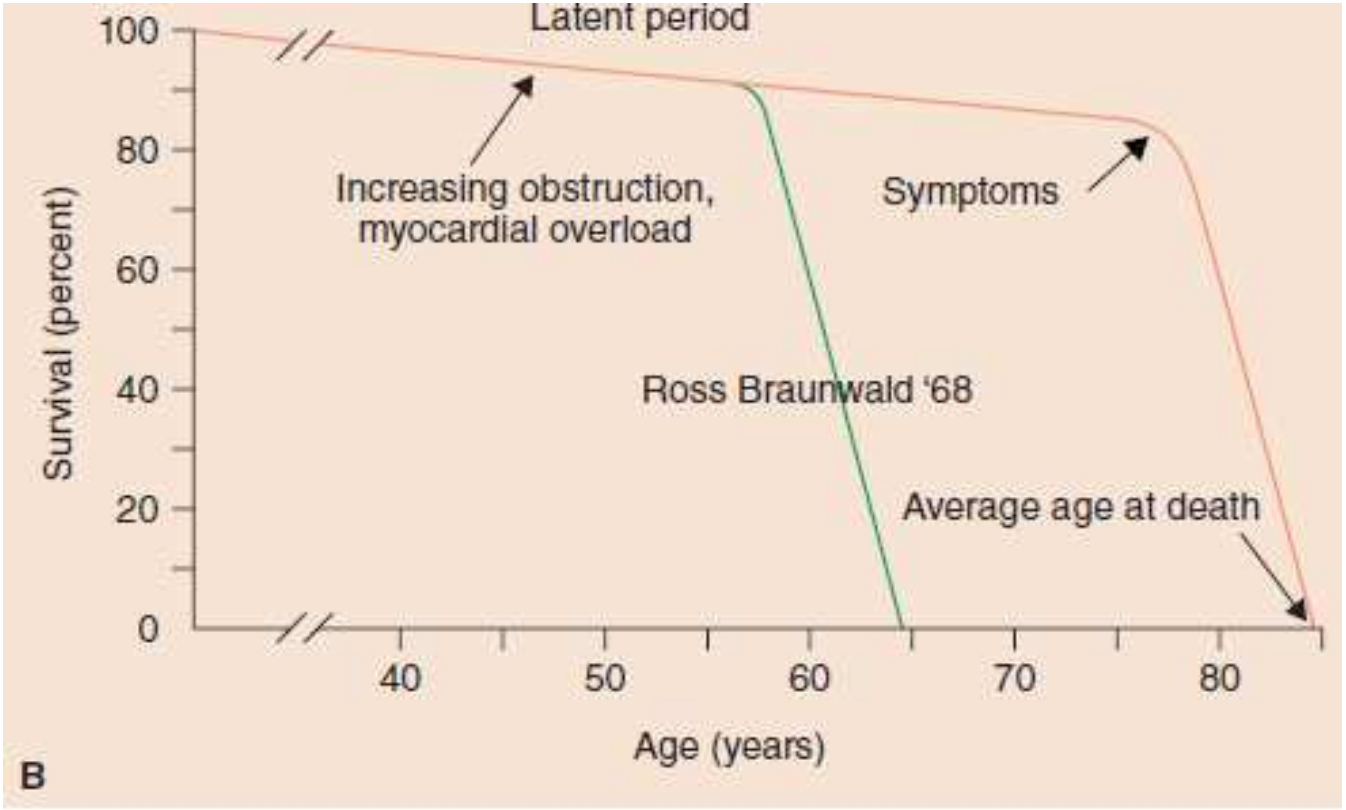
Aortic stenosis

- Current AHA/ACC guidelines subdivide the severe, symptomatic AS group of patients into three separate categories (based on echocardiography):
- High-gradient AS (D1)
- Low-flow/low-gradient AS with reduced EF (D2)
- Low-gradient AS with normal EF
- 35-51% of patients have arterial hypertension
- Increase in Brain natriuretic peptide (BNP) during exercise is a poor prognostic sign
- Acquired vonWillebrand's disease associated with bleeding
- Valve replacement is the only therapy

Bicuspid Aortic Valve



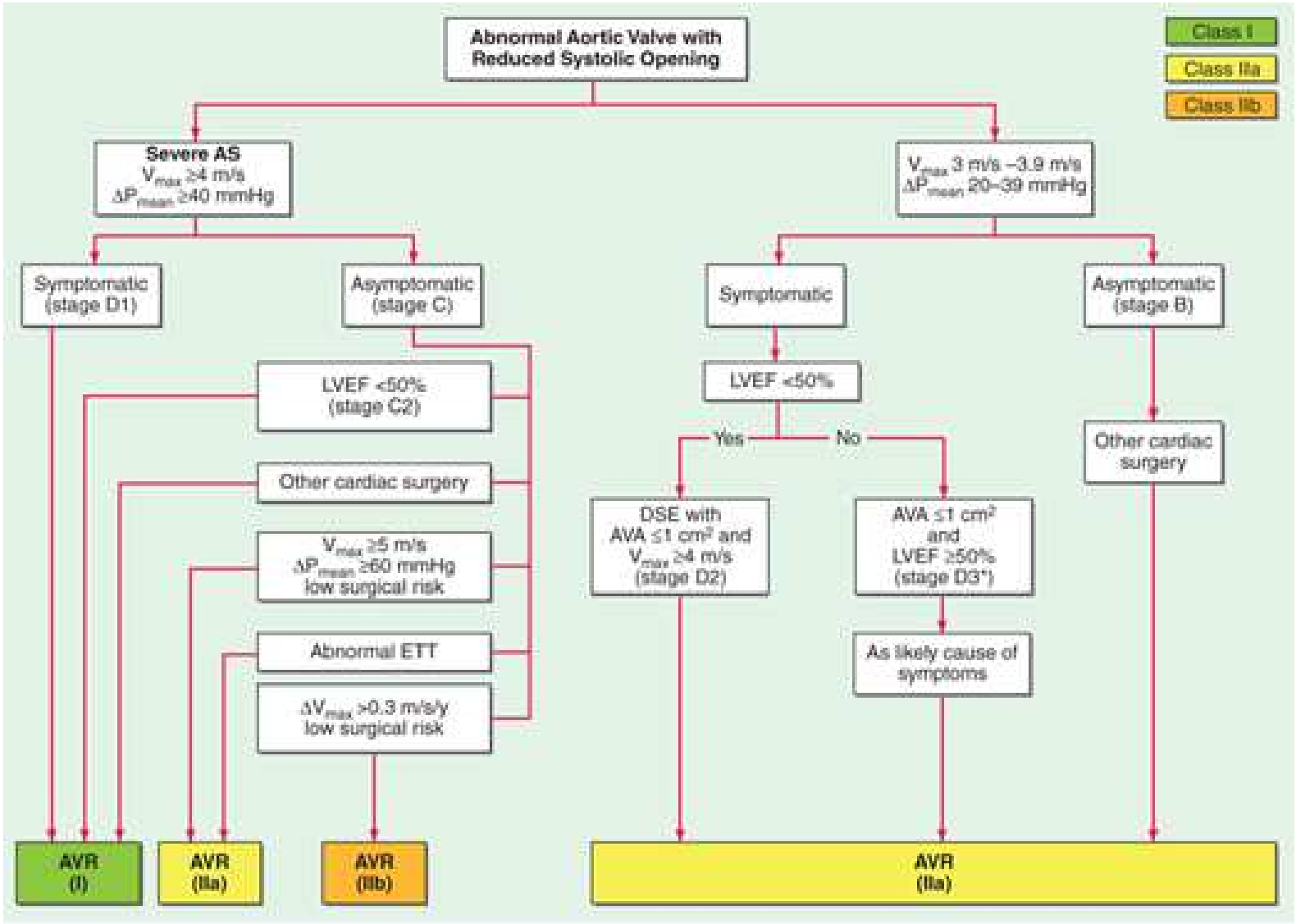
www.slideshare.net/jyotindrasingh82/bicuspid-aortic-valve. Accessed 09/10/2019.



A. The natural history of aortic stenosis demonstrating a dramatic decline in survival when symptoms develop. B. The natural history of aortic stenosis today (pink line) showing onset of symptoms at a much later age in life than in the 20th century (green line). A reproduced with permission from Ross J Jr, Braunwald E: Aortic stenosis, Circulation. 1968 Jul;38(1 Suppl):61-67. B used with permission from Dr. Robert Bonow.

Prognosis of aortic valve stenosis

- Death generally follows in:
- 5 years following presentation of angina
- 3 years following presentation of syncope
- 2 years following presentation of congestive heart failure.
- Replace valve shortly after symptom presentation.



Treatment

- Early valve replacement (even in low-risk patients) is superior to medical management as patients symptomatic only after LV dysfunction develops
- Trans-aortic valve replacement occurs in paced ventricle; filter placed to block carotid access prior to valve replacement
- 80% of patients discharged in one hospital day
- Edwards valve is balloon expandable with bovine valve on frame
- Cove valve is self-expanding with porcine valve on frame
- 10% develop AV block
- May lead to mild aortic regurgitation

Hereditary hypertrophic cardiomyopathy

- Young adults
- 30-40% of cardiomyopathies in children
- Autosomal dominant (variable penetrance)
- Defective energy transfer from mitochondrion to sarcomere
- Apical hypertrophy reduces ventricular volume
- 10% have concentric hypertrophy (restricted filling)
- Left ventricular septum three times thicker than free wall (asymmetric hypertrophy)
- Prominent in sub aortic region (25%)
- Dynamic dysfunction

Hereditary hypertrophic cardiomyopathy

- Asymmetrical septal hypertrophy without obstruction
- Asymmetrical septal hypertrophy with obstruction (hypertrophic obstructive cardiomyopathy)
- Mitral regurgitation from septum striking valve

Hereditary hypertrophic cardiomyopathy

- Maximal intensity of murmur
- 5th left intercostal space
- Radiates along the left lower sternal border.
- Passive leg elevation decreases the intensity of the murmur (LR+ 8.0; LR- 0.2).
- Squatting decreases intensity of murmur (LR+ 4.5; LR- 0.1).
- Histopathology:
- Giant myocytes
- Myofiber disarray
- Fibrosis

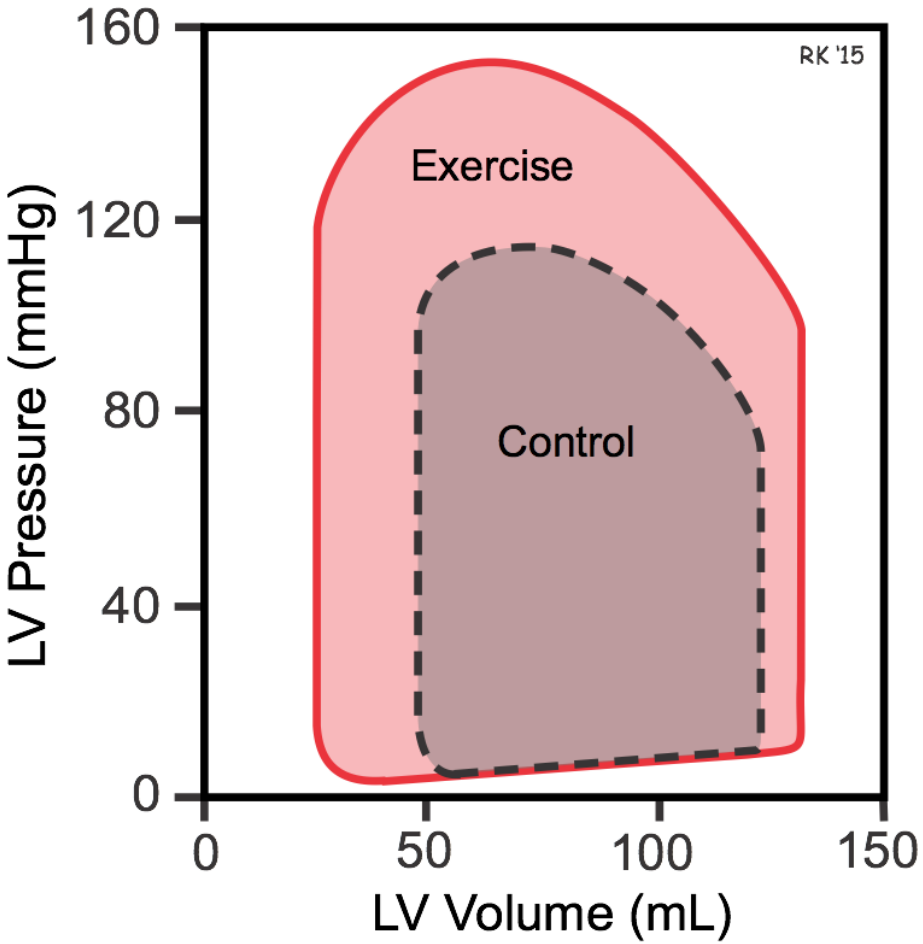
Hereditary hypertrophic cardiomyopathy

- Complications include:
- Atrial fibrillation
- Thrombus formation (and embolism)
- Ventricular fibrillation (sudden death)
- Treatment
- β-blocker
- Reduce heart rate (increase preload)
- Decrease myocardial contractility
- Implantable cardioverter defibrillator
- May have to excise myocardial tissue in outflow tract

Supravalvular aortic stenosis

- Autosomal dominant.
- 7q11.23 mutation affects elastin.
- Characterized by narrowing of the ascending aorta above the level of the sinus of Valsalva.
- Williams-Beuren syndrome characterized additionally by transient hypercalcemia, elfin facial appearance with low bridge nose, and stenosis of other major arteries.
- Developmental delay with good language skills; impaired spatial processing.

P-V LOOP IN SEVERE EXERCISE



Coarctation of the aorta

- One-third of patients with Turner's syndrome have Coarctation.
- Bicuspid aortic valve
- 25% of all coarctations
- Ejection click at right upper sternal border.
- Blood pressure in upper limbs is greater than blood pressure in lower limbs.
- Associated with saccular cerebral aneurysms.

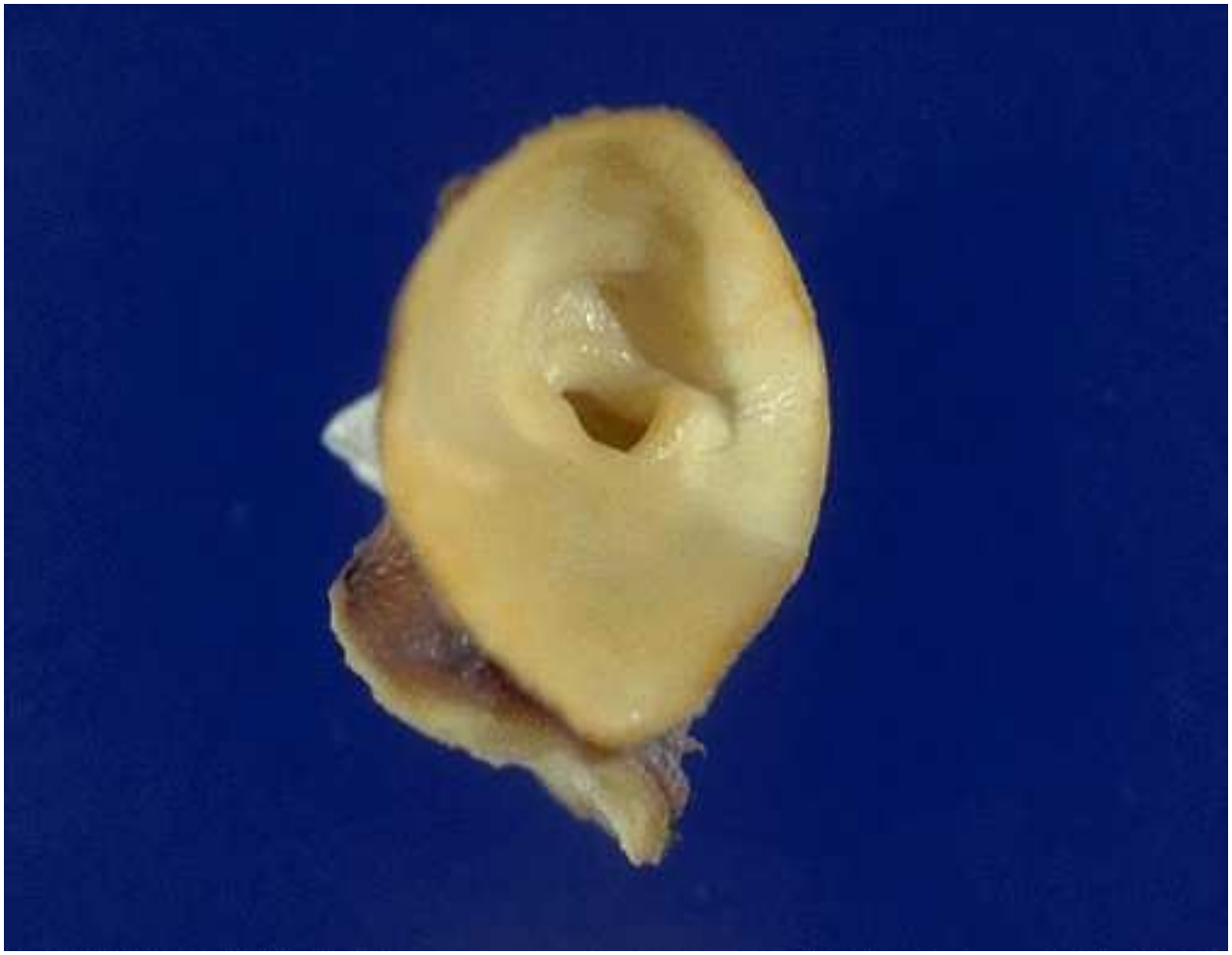
Coarctation of the aorta

- Preductal if before ligamentum arteriosum.
- Usually discovered in infancy.
- Presents with congestive heart failure
- May see right bundle branch block
- If patent ductus arteriosum is present, may see cyanosis of lower half of body.

Coarctation of the aorta

- Postductal if after ligamentum arteriosum.
- Presents as systemic hypertension
- Blood pressure in upper limbs is greater than blood pressure in lower limbs.
- S_aO_2 difference > 5% between upper limb and lower limb.
- Left ventricular hypertrophy on EKG
- May see rib notching on chest x-ray
- Caused by dilated collateral vessels.

Coarctation of the aorta



Post-ductal Coarctation. Note post-ductal narrowing of the aorta.

https://webpath.med.utah.edu/CVHTML/CV081.html
Accessed 12/10/2019

TABLE 257-1

Major Causes of Aortic Valve Disease

Valve Lesion	Etiologies
Aortic regurgitation	**Valvular**
	Congenital (bicuspid)
	Endocarditis
	Rheumatic fever
	Myxomatous (prolapse)
	Traumatic
	Syphilis
	Ankylosing spondylitis
	Root disease
	Aortic dissection
	Cystic medial degeneration
	Marfan syndrome
	Bicuspid aortic valve
	Nonsyndromic familial aneurysm
	Aortitis
	Hypertension

Aortic valve regurgitation

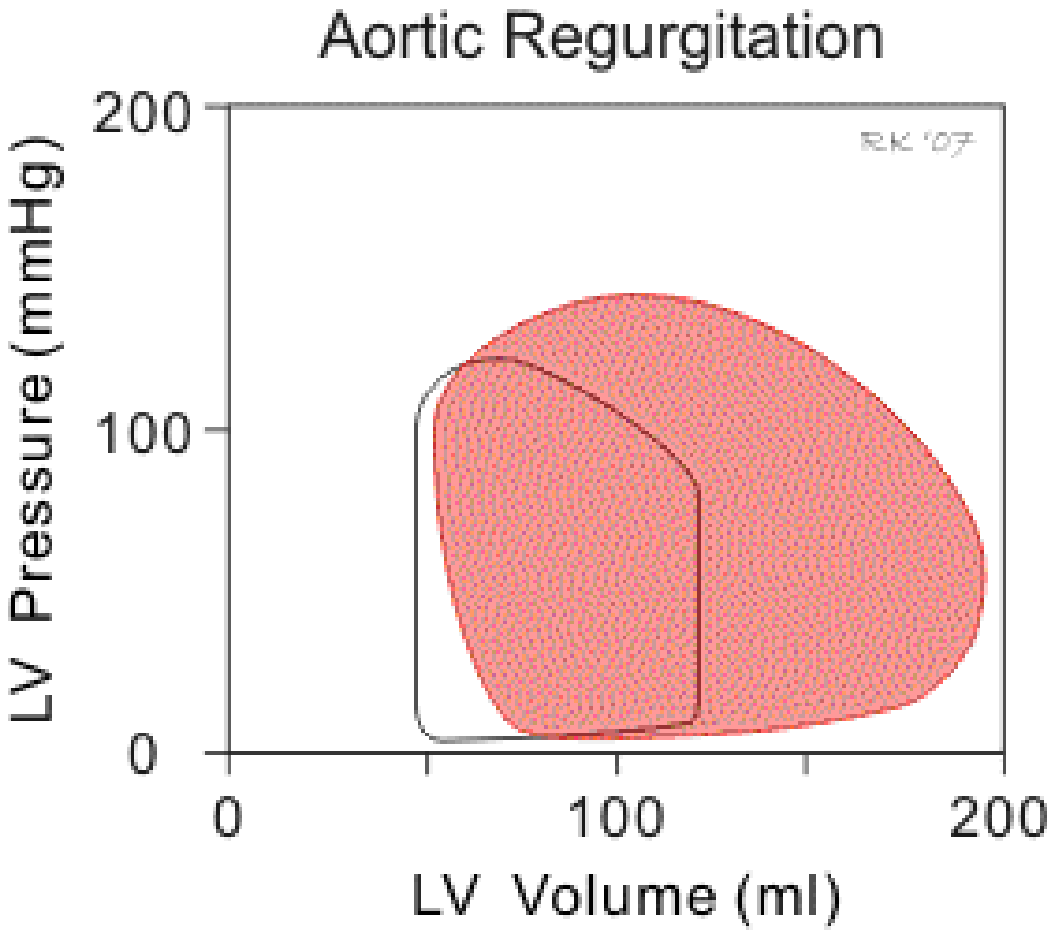
- Men 3:1
- Women, if previous history of rheumatic heart disease
- Presents when decreased cardiac output develops.
- Dyspnea
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Fatigue and weakness
- Anginal pain

Aortic valve regurgitation

- Blood pressure in the leg is more than 20 mm Hg higher than pressure in the arm (Hill sign).
- Bounding pulse (Corrigan or water-hammer pulse) due to increased pulse pressure (difference between systolic and diastolic).
- Bisferious pulse (with two systolic peaks).
- Alternate flushing and paling of the skin at the root of the nail while pressure is applied to the tip of the nail (Quincke's pulse)

Aortic valve regurgitation

- Severe aortic valve regurgitation
- >40% regurgitant fraction
- S_3 presence (LR+ of 5.9)
- Absence of S_3 does not exclude.
- Doppler echocardiography needed.



Aortic stenosis (red)

https://www.cvphysiology.com/Heart%20Disease/HD009d

Aortic regurgitation

- In aortic valve regurgitation the aortic valve does not close completely at the end of systolic ejection.
- Therefore, there is no true phase of isovolumetric relaxation because as the ventricle relaxes, even before the mitral valve opens, blood is entering the ventricle from the aorta thereby increasing ventricular volume.
- Once the mitral valve opens, filling occurs from the left atrium

Aortic regurgitation

- Blood continues to flow from the aorta into the ventricle throughout diastole because aortic pressure is higher than ventricular pressure during diastole.
- This greatly enhances ventricular filling so that end-diastolic volume is increased.
- Ventricular end-diastolic volume is also increased because in chronic aortic regurgitation the ventricle anatomically dilates (remodels) so that ventricular compliance is elevated.
- This is the major hemodynamic compensation

Aortic regurgitation

- There is no true isovolumetric contraction as the ventricle begins to contract and develop pressure, blood is still entering the ventricle from the aorta because aortic pressure is higher than ventricular pressure
- Volume continues to increase
- LV dilation increases the LV systolic tension required to develop any given level of systolic pressure (Laplace's Law)
- The dilation and eccentric hypertrophy of the LV allow this chamber to eject a larger stroke volume without requiring any increase in the relative shortening of each myofibril.

Aortic regurgitation

- The increased end-diastolic volume (increased preload) leads to an increase the force of contraction, ventricular peak (systolic) pressure, and stroke volume.
- Once the ventricular pressure exceeds the aortic diastolic pressure, the ventricle then begins to eject blood into the aorta.

Aortic regurgitation

- As long as the ventricle is not in failure, end-systolic volume may only be increased a small amount due to the increased afterload (ventricular wall stress).
- If the ventricle goes into systolic failure, then end-systolic volume will increase by a large amount and the peak systolic pressure and stroke volume (net forward flow into aorta) will fall.

Acute aortic regurgitation

- Infective endocarditis with perforation of the valve leaflet most common cause
- Dissecting aneurysm of the ascending aorta dilates the aortic ring
- There is a significant decrease in the intensity of the systolic ejection murmur
- Because of the decreased forward stroke volume.
- S_1 is markedly decreased in intensity
- Because of premature closure of the mitral valve.

Acute aortic regurgitation

- The presystolic component of the Austin-Flint (diastolic) murmur is absent at the apex.
- The early diastolic murmur at the base ends before S_1
- Because of equilibration of the left ventricle and aortic end-diastolic pressure.
- Significant tachycardia is usually present.

Chronic aortic regurgitation

- Dilatation of the aortic ring
- 60% of cases
- Syphilitic aneurysm of the ascending aorta
- Marfan's syndrome
- Ankylosing spondylitis
- Takayasu's arteritis

Chronic aortic regurgitation

- 40% of cases are of valvular origin
- Rheumatic heart disease most common cause of aortic valve regurgitation.
- Often mitral regurgitation is present as well.
- Bicuspid aortic valves as another cause.

Chronic aortic regurgitation

- A prominent systolic ejection murmur
- Heard at the base and the apex
- Ends before S_2
- Results from a large forward stroke volume
- Diastolic murmur
- Begins with S_2 and continues in a decrescendo fashion, terminating before S_1.
- Best heard at left upper sternal border with the patient sitting up and leaning forward.
- Squatting increases the intensity of the murmur.

Chronic aortic regurgitation

- Austin-Flint murmur (diastolic rumble)
- Best heard at the apex
- Arises from regurgitant jet striking anterior mitral leaflet.
- The mid-diastolic component of Austin Flint murmur is introduced by a prominent S_3.
- A pre-systolic component of the Austin Flint murmur is also heard.

Chronic aortic regurgitation

- May result in functional mitral regurgitation.
- Cardiac output decreases.
- Coronary perfusion pressure also decreases.
- Surgical intervention if severe disease.
- Vasodilator may improve hemodynamics prior to surgery.

Testing

- In chronic severe aortic regurgitation, the apex is displaced downward and to the left in the frontal projection.
- In the left anterior oblique and lateral projections, the left ventricle is displaced posteriorly and encroaches on the spine.
- When aortic regurgitation is caused by primary disease of the aortic root, aneurysmal dilation of the aorta may be noted, and the aorta may fill the retrosternal space in the lateral view.
- Echocardiograpy diagnostic

Treatment

- Valve replacement early as patients symptomatic only after LV dysfunction develops
- Ejection fraction may be 50% as afterload handled by peripheral vascular system
- Valve replacement may lead to precipitous fall in ejection fraction, reflecting serious underlying left ventricular disease
- Valve sparing aortic root reconstruction if due to annular dilatation

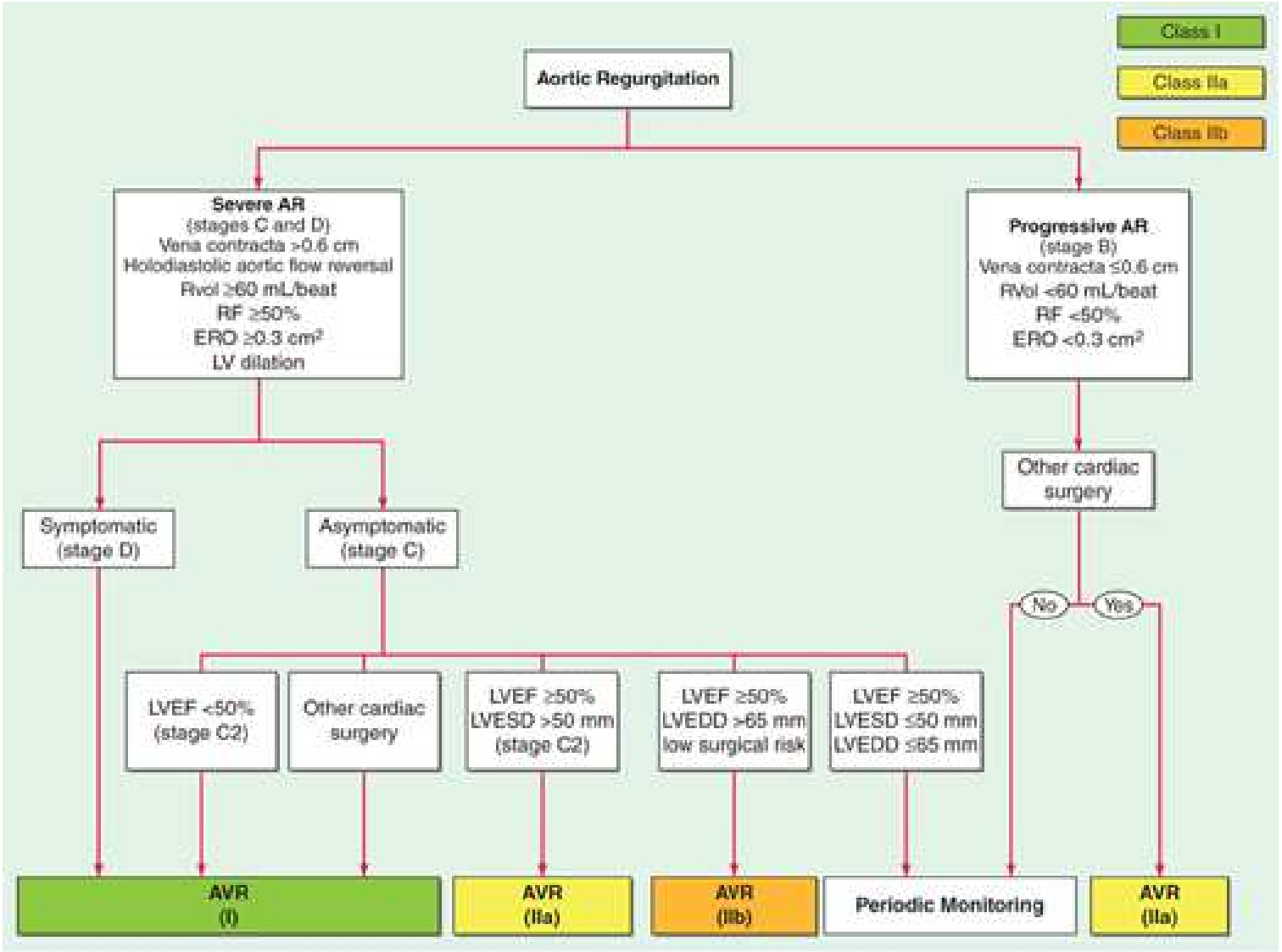


TABLE 258-1

Major Causes of Mitral Stenosis

Etiologies
Rheumatic fever
Congenital (parachute valve, cor triatriatum)
Severe mitral annular calcification with leaflet involvement
SLE, RA
Myxoma
IE with large vegetations

Mitral stenosis

- The mitral valve is the most common valve affected in rheumatic fever.
- Stenosis is caused by fusion, thickening, and shortening of the chordae tendinae and valve leaflets.
- Left atrial dilatation
- Most patients are asymptomatic
- Atrial fibrillation in 40% of patients
- Development of mural thrombi in 30%
- 60-75% of emboli to brain
- Passive pulmonary congestion with hemoptysis
- Left atrial and pulmonary arterial wedge pressures are elevated (pulmonary hypertension).

Mitral stenosis

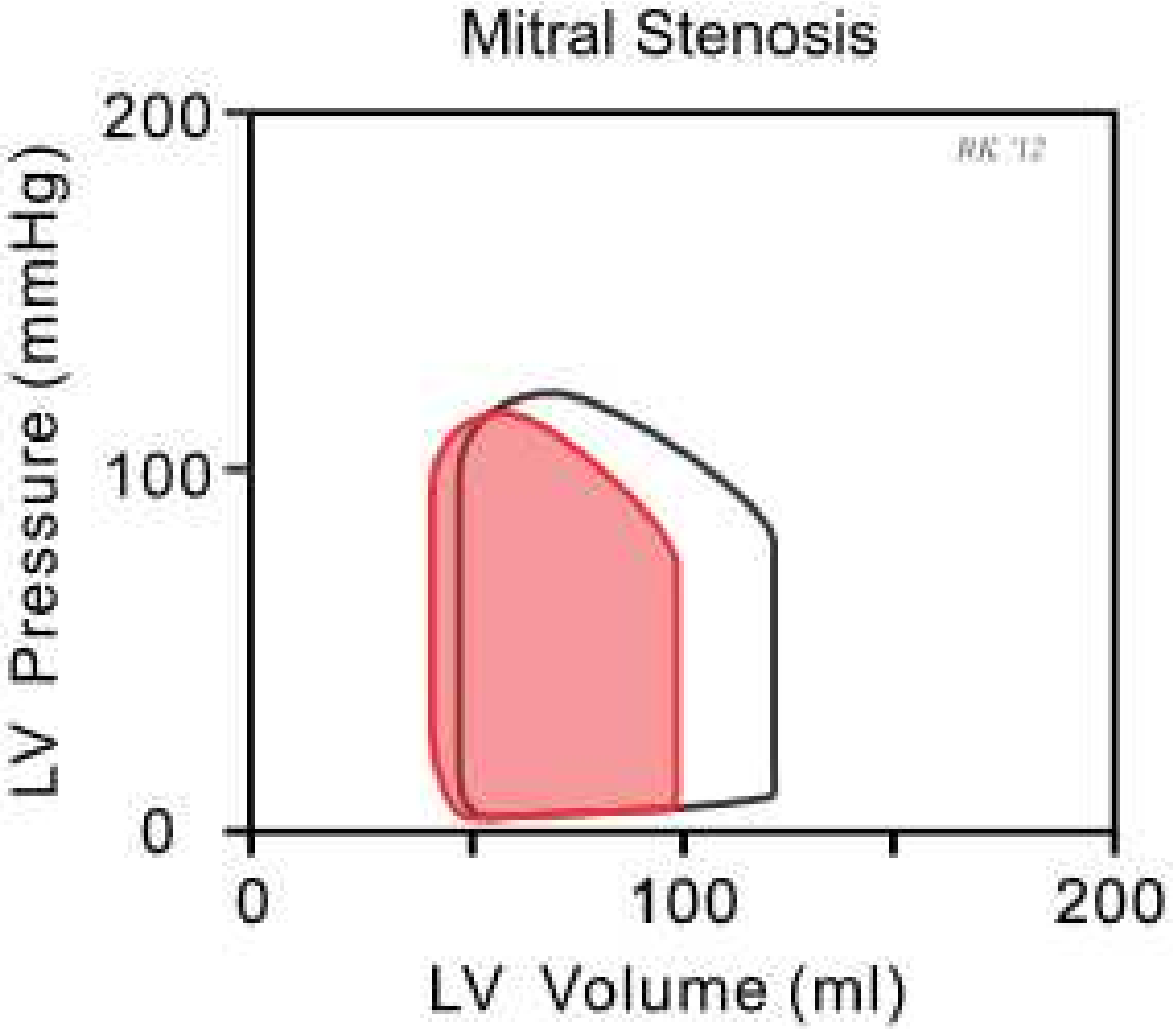
- Mitral stenosis impairs left ventricular filling
- There is a decrease in end-diastolic volume (preload)
- This leads to a decrease in stroke volume and a fall in cardiac output.
- Reduced ventricular filling and reduced aortic pressure decrease ventricular wall stress (afterload)
- Results in a small decrease in ventricular end-systolic volume that is not sufficient to offset the reduction in end-diastolic volume.

Mitral stenosis

- Is more the consequence of abnormal loading and LV remodeling than of myocardial dysfunction.
- Right ventricular failure also seems to be a consequence of increased afterload rather than of myocardial dysfunction.

Mild mitral stenosis

- Diastolic gradient across the valve is limited to the two phases of rapid ventricular filling in early diastole and pre-systole.
- Low-pitched diastolic rumbling heard best at the apex with the patient in the left lateral decubitus position.
- The rumble may occur during either or both periods.
- Mitral stenosis often produces an early opening snap from fused leaflet tips.



Mitral stenosis (red)

https://www.cvphysiology.com/Heart%20Disease/HD009a

Severe mitral valve stenosis

- A large pressure gradient exists across the valve during the entire diastolic filling period
- Rumble persists throughout diastole.
- As the left atrial pressure becomes greater
- The interval between the aortic valve component and the opening snap shortens.

Severe mitral valve stenosis

- As secondary pulmonary hypertension develops
- Loud pulmonic valve component
- Splitting interval usually narrows.
- With sustained hand grip, the diastolic murmur is accentuated.

Clinical and hemodynamic features

- Influenced importantly by the level of the pulmonary artery pressure
- Pulmonary hypertension results from:
- (1) passive backward transmission of the elevated LA pressure;
- (2) pulmonary arteriolar constriction (the so-called “second stenosis”),
- Triggered by LA and pulmonary venous hypertension (reactive pulmonary hypertension);

Clinical and hemodynamic features

- (3) interstitial edema in the walls and pulmonary venous hypertension
- Reactive pulmonary hypertension
- At end stage, obliterative changes in the pulmonary vascular bed are identified

Testing

- The earliest changes are straightening of the upper left border of the cardiac silhouette, prominence of the main pulmonary arteries, dilation of the upper lobe pulmonary veins, and posterior displacement of the esophagus by an enlarged left atrium.
- Kerley B lines are fine, dense, opaque, horizontal lines that are most prominent in the lower and mid-lung fields that result from distention of interlobular septae and lymphatics with edema when the resting mean left atrial pressure >20 mmHg.
- Echocardiography is diagnostic

Treatment

- Atrial fibrillation rate control with a β-blocker (esmolol) or calcium channel blocker (diltiazem)
- Rate control improves survival
- Ivabradine improves exercise tolerance in heart failure
- Vitamin K antagonist and low dose aspirin anticoagulation
- Antibiotic prophylaxis not required
- May require valvotomy. Valve replacement as last resort.

Rheumatic heart disease

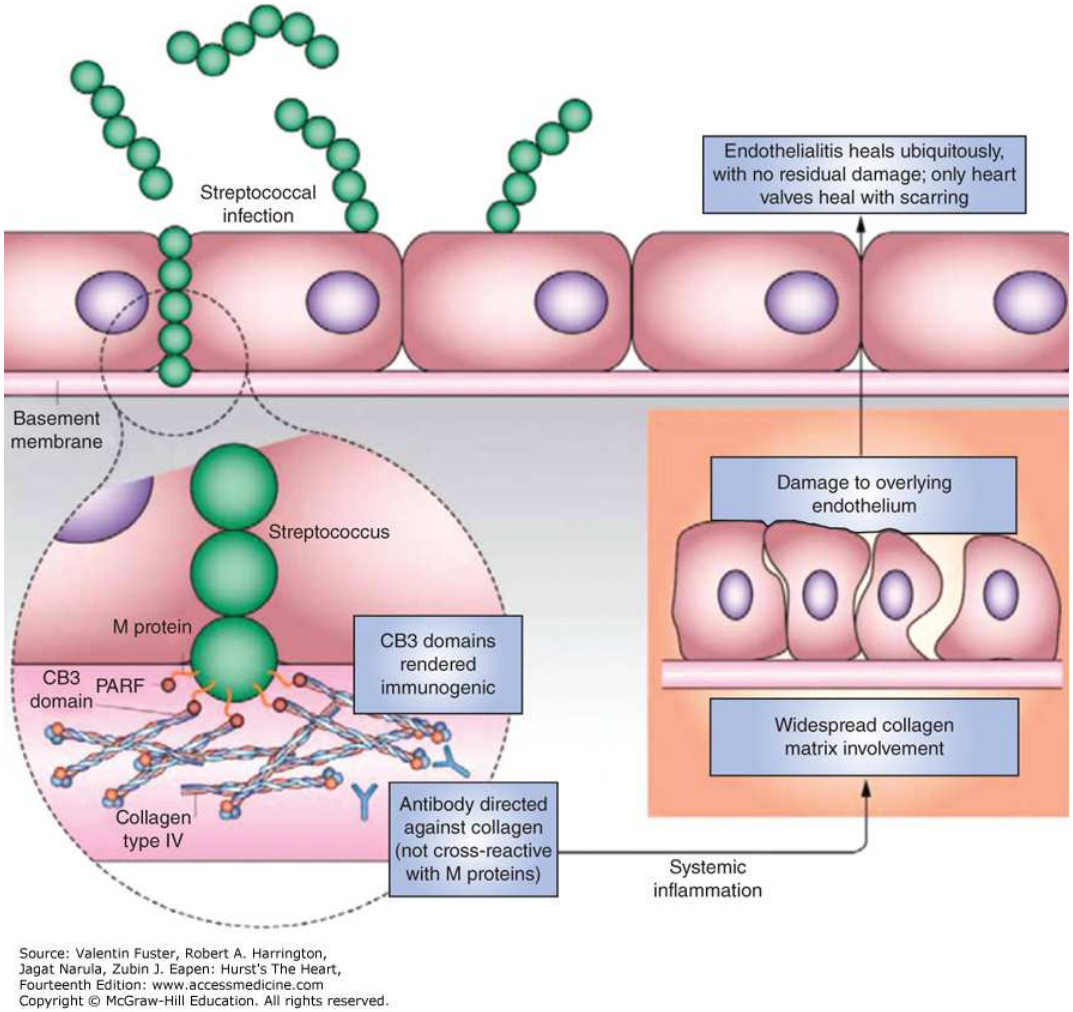
- Acute, immunologically related multisystem inflammatory disease
- Group A β-hemolytic Strep. (GAS) infection precipitates disorder
- 3% of patients
- 5-15 years of age usual
- The streptococcal M protein shares an α-helical coiled structure with cardiomyocyte contractile proteins such as myosin (Type II hypersensitivity)
-

Rheumatic heart disease

- The antibodies that contribute to rheumatic valvulitis target the N-acetyl-β-D-glucosamine–dominant epitope of the GAS carbohydrate, but also recognize sequences in α-helical proteins such as myosin and tropomyosin
- Cross-reactive M-protein antibodies recognize the intracellular biomarker antigen cardiac myosin but target the valve surface endothelial antigen laminin

Rheumatic heart disease

- The initial antibody-mediated damage to the endocardium leads to expression of vascular cell adhesion protein 1 on the valvular surface
- Facilitates the infiltration of T cells into the valve substance, resulting in scarring and neovascularization. (Type IV hypersensitivity)
- The biomarker antigen in the brain is tubulin and the antigen target on the cell surface leads to calcium/calmodulin-dependent kinase II activation and dopamine release (Sydenham chorea).



Proposed pathogenesis of rheumatic fever. Reproduced with permission from Tandon R, Sharma M, Chandrashekhar Y, et al: Revisiting the pathogenesis of rheumatic fever and carditis. Nat Rev Cardiol. 2013 Mar;10(3):171-177.[19]

Rheumatic heart disease

- Streptococcal M proteins form a complex with collagen type IV in subendothelial basement membranes
- Initiate an autoantibody response to the collagen as in Goodpasture's or Alport's syndromes
- The M-like fibrinogen binding protein of Group G Streptococcus also complexes with subendothelial IV and is associated with a clinical picture of acute rheumatic fever

Acute rheumatic fever

- ESSENTIALS OF DIAGNOSIS
- Preceding group A streptococcal infection.
- Initial acute rheumatic fever
- Two major manifestations or one major plus two minor manifestations.
- Recurrent acute rheumatic fever
- two major or one major and two minor or three minor manifestations.

Revised Jones Criteria for Acute Rheumatic Fever

****Evidence of *streptococcal* infection AND:**

Two major criteria OR one major and two minor

Major criteria	Description
Carditis	• All layers of the heart affected • New or changing murmur (mitral regurgitation)
Polyarthritis	• Migrating arthritis that typically affects the knees, ankles, elbows, and wrists
Chorea	• Also known as Syndenham's chorea or "St Vitus dance" • Abrupt, purposeless movements
Subcutaneous nodules	• usually located over bones or tendons • Nodules are painless and firm
Erythema marginatum	• Non-pruritic rash affecting the trunk and extremities, face is spared
Minor criteria	****Evidence of streptococcal infection (any of the following):** (i) increased antistreptolysin O or other streptococcal antibodies (ii) positive throat culture for Group A beta-hemolytic streptococci (iii) Positive rapid direct Group A strep carbohydrate antigen test (iv) Recent scarlet fever
Fever	
Arthralgia	
Elevated ESR or CRP	
Prolonged PR interval on ECG	

https://i.pinimg.com/736x/9f/03/70/9f0370ac3b6d69304e2550ba63a8440d--cardiology-pa-school.jpg
Accessed12/07/2019

Complications

- Carditis is the most serious consequence of rheumatic fever
- 50% of patients
- More common in children
- AV conduction delay
- 1% die
- Pancardiac inflammation
- But it may be limited to valves, myocardium, or pericardium.
- Principally valvulitis
- Usually mitral insufficiency

Complications

- Myocarditis may lead to ventricular dilatation
- Pericardial friction rub (serous effusion)
- Carey-Combs murmur is a mid-diastolic rumble that improves as the valvulitis improves (flow across thickened mitral valve).
- Best heard at the apex.
- Subcutaneous nodules
- Firm, painless, over joints
- Common in patients with carditis

Complications

- Mitral stenosis after acute rheumatic fever is rarely encountered until 5–10 years after the first episode.
- The aortic valve is the second most common valve affected
- Aortic insufficiency is occasionally encountered as the sole valvular manifestation of rheumatic carditis.
- More common in men
- More common in those of sub-Saharan origin

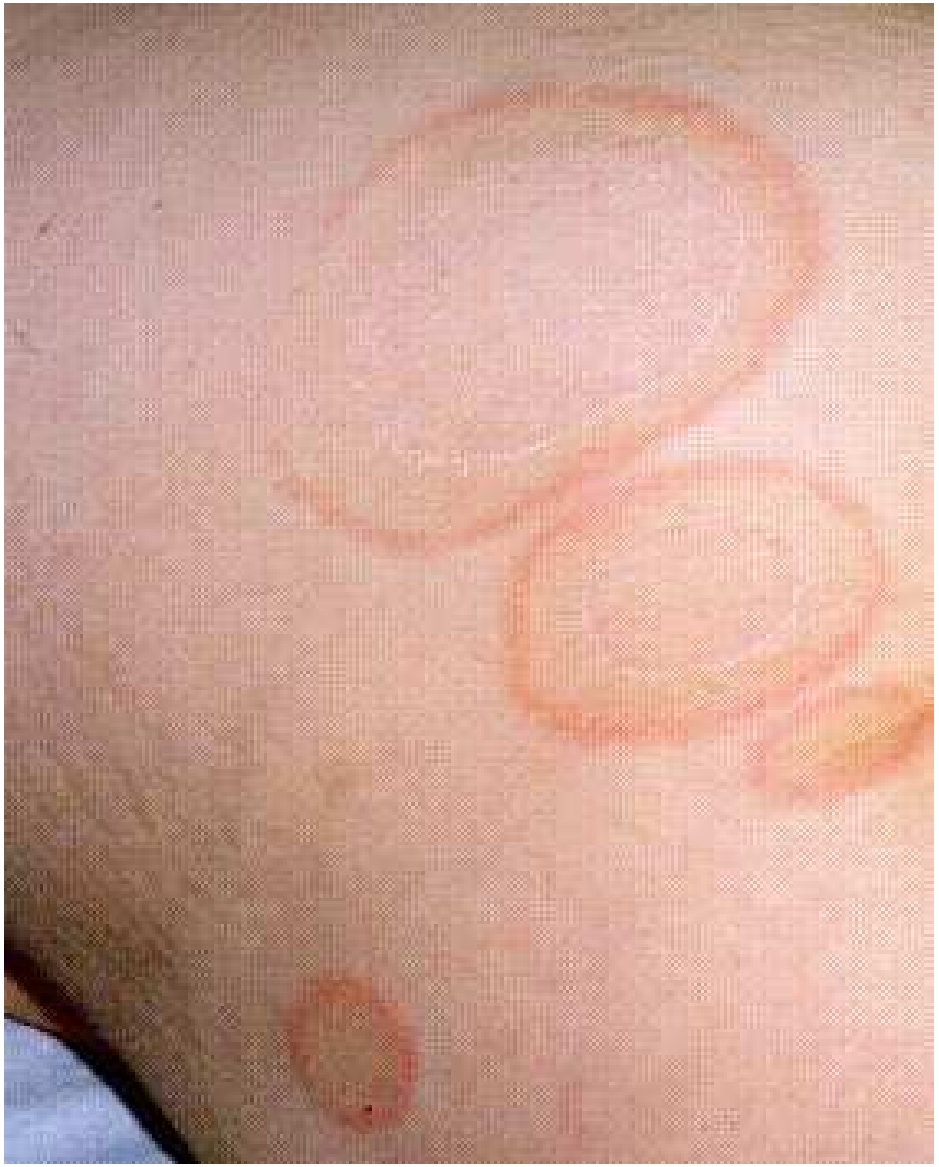
Complications

- Migratory polyarthritis
- More common in adults
- 80% of patients
- Knees, hips, wrists, elbows, and shoulders most commonly involved
- Monoarticular arthritis common in children and adolescents
- No permanent damage

Complications

- Erythema marginatum
- A macular, serpiginous, erythematous rash with a sharply demarcated border appears primarily on the trunk and the extremities.
- The face is usually spared.
- Brought out by warm bath
- 4-15% of patients
- Early presentation

Erythema marginatum



Erythematous serpiginous macular lesions with pale centers.

Not pruritic.

Accentuated by skin warming.

https://www.hxbenefit.com/wp-content/uploads/2012/07/Erythema-marginatum-Picture.jpg
Accessed 12/07/2019

Treatment

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  AV conduction delay

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- Usually mitral insufficiency

Complications

- Myocarditis may lead to ventricular dilatation
- Pericardial friction rub (serous effusion)
- Subcutaneous nodules
- Firm, painless, over joints
- Common in patients with carditis

Complications

- Sydenham chorea
- Characterized by involuntary and purposeless movements
- Often associated with emotional lability
- Symptoms become progressively worse and may be accompanied by ataxia and slurring of speech.
- Muscular weakness becomes apparent following the onset of the involuntary movements.
- Self-limiting
- Presents months to years after infection

Complications

- Up to 30% of cases
- Females predominate
- Emotional lability
- Mild chorea is demonstrated by asking the patient to squeeze the examiner's hands. Repetitive irregular squeezes are labeled as the milking sign

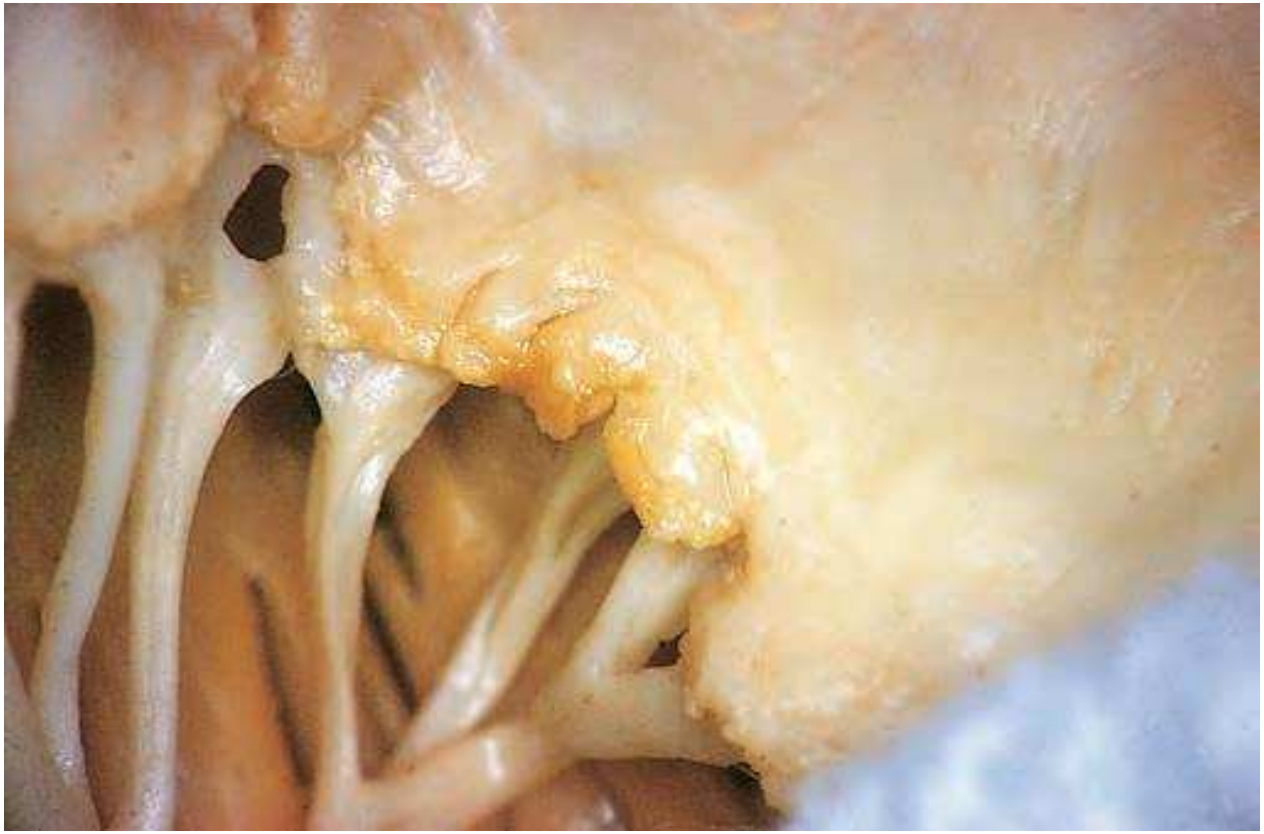
Rheumatic heart disease

- Subendothelial damage limited to shallow depths as endothelium has great capacity to heal
- If valvulitis is present, neo-angiogenesis develops within the substance of valve tissue, initiating a cycle of further inflammation and damage

Rheumatic heart disease

- Gross pathology:
- Nodular formations on mitral valve overlie areas of fibrinoid necrosis
- Leaflet thickening
- Commisural thickening and fusion
- Thickening and fusion of chorda tendinae
- "Fish mouth" appearance to valve
- Subenodcardial immune complex deposition
- MacCallum plaques are irregular thickenings in subendocardium

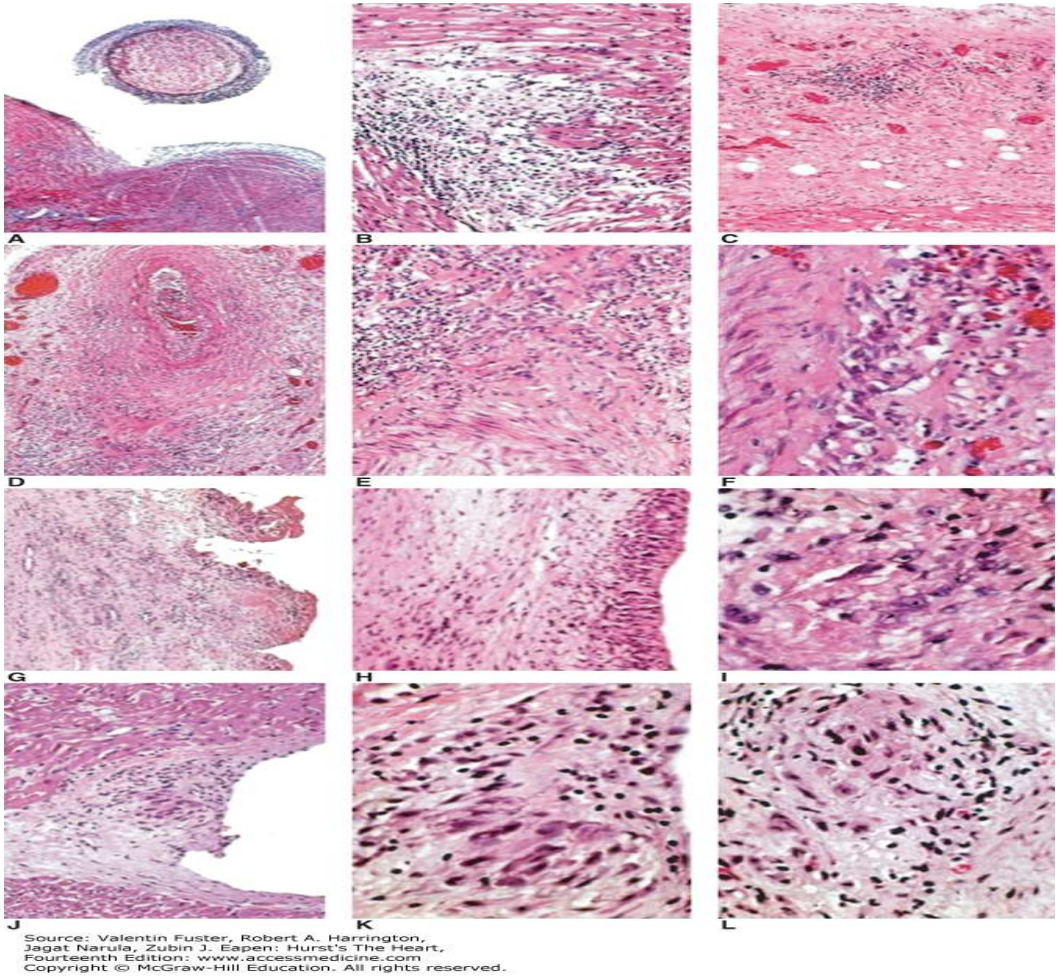
Rheumatic heart disease mitral valve



Schoen, and FJ, Mitchell, RN, “Heart”, in Kumar, V, Abbas, AK, Aster, JC (eds.), Robbins and Cotran Pathologic Basis of Disease, 9th edition. 2015. Elsevier. Philadelphia. Fig. 12-23A. Accessed 09/04/2019

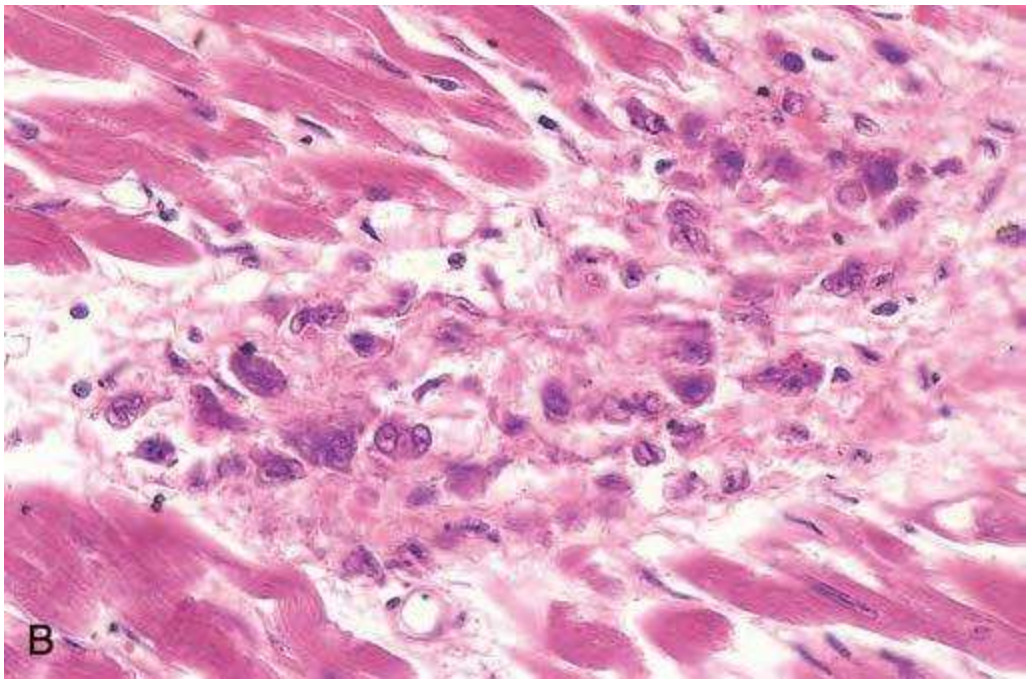
Rheumatic heart disease

- Histopathology:
- Immune complex deposition
- Aschoff bodies in myocardium are pathognomonic of rheumatic fever
- Nodules of mononuclear cells with central fibrinoid necrosis
- Presence of Anitschkow cells
- modified macrophages with nuclei that have central caterpillar-shaped chromatin
- In rheumatoid arthritis myocarditis, rheumatoid nodules are noted in myocardium



Hematoxylin and eosin staining of the heart and vasculature suggests connective tissue involvement in rheumatic fever. Modified with permission from Narula J, Virmani, R, Reddy KS, et al: Amer. Reg. Path. AFIP, Washington DC, 1999.

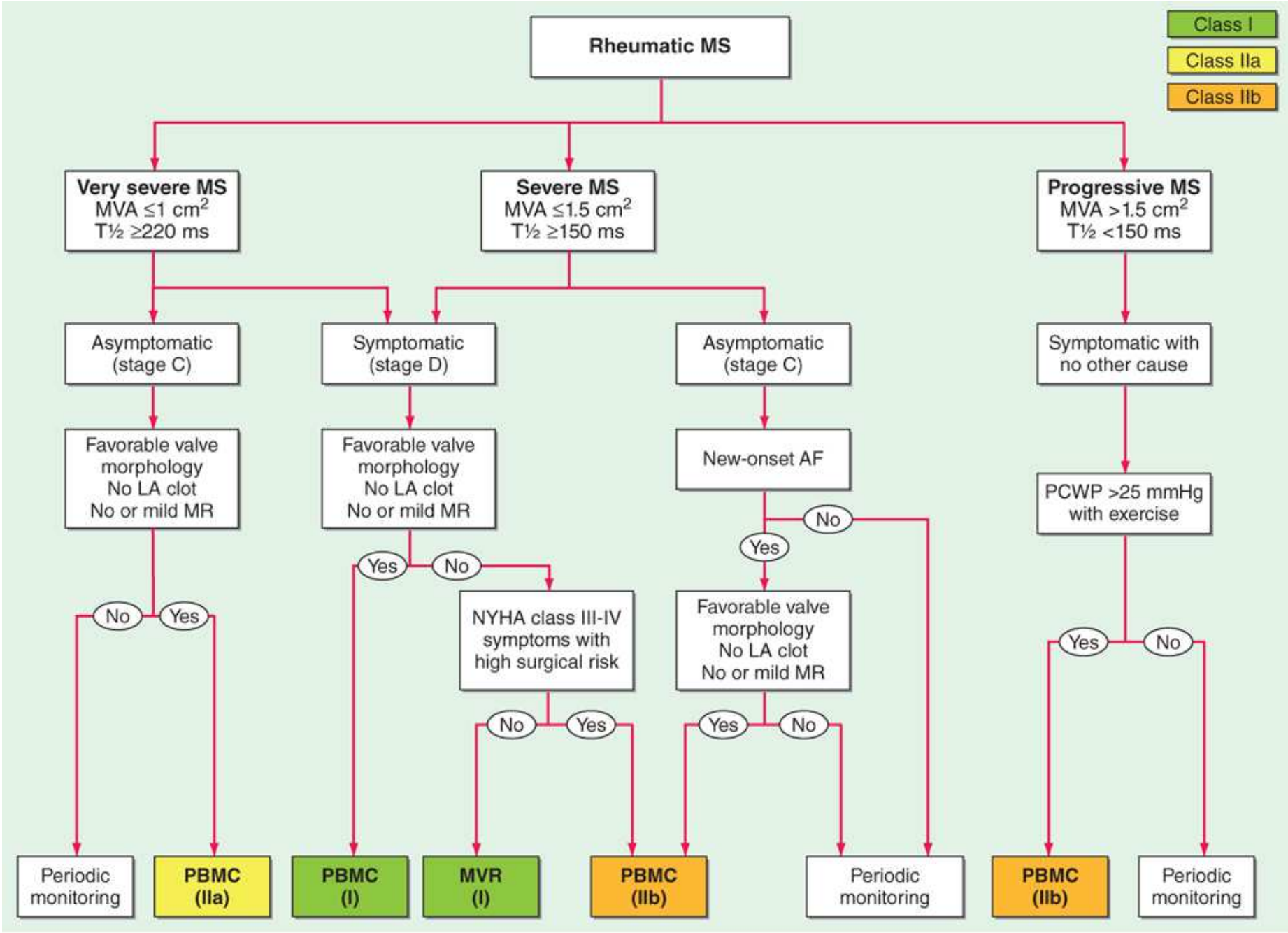
Aschoff body



Schoen, and FJ, Mitchell, RN, “Heart”, in Kumar, V, Abbas, AK, Aster, JC (eds.), Robbins and Cotran Pathologic Basis of Disease, 9th edition. 2015. Elsevier. Philadelphia. Fig. 12-23B. Accessed 09/02/2019

Treatment

- Long acting benzathine penicillin
- With no or transient cardiac involvement, 5–10 years of therapy or discontinuance in early adulthood
- In severe disease, lifelong prophylaxis
- ASA tailored to patient symptoms
- No need for high doses
- Corticosteroids if murmur present with carditis
- Remain vulnerable to later Strep. Infections



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Calcification of the annulus

- Degenerative
- Women older than 60 years of age
- As well as those with Mitral valve prolapse
- Base of the leaflets
- Clinically significant if interferes with physiologic opening/closing of mitral valve.
- Calcified nodules may impinge upon AV conduction system
- Nodules also site of thrombus formation

TABLE 259-1

Major Causes of Mitral Regurgitation

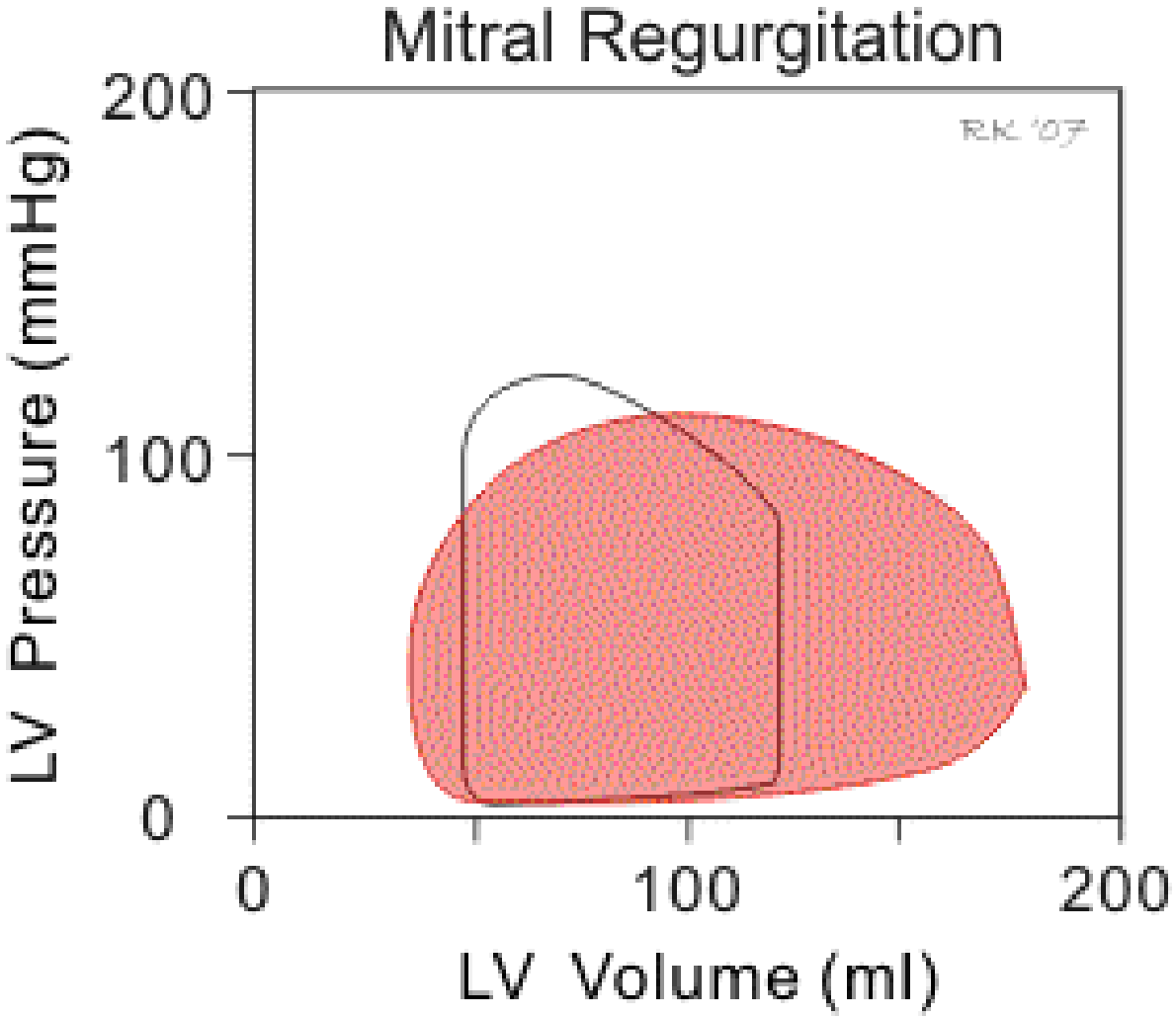
Etiologies
Acute
IE
Papillary muscle rupture (post-MI)
Chordal rupture/leaflet flail (MVP, IE)
Blunt trauma
Chronic
Primary (affecting leaflets, chordae)
Myxomatous (MVP, Barlow's, forme fruste)
Rheumatic fever
IE (healed)
Congenital (cleft, AV canal)
Radiation
Secondary (leaflets, chordae are "innocent bystanders")
Ischemic cardiomyopathy
Dilated cardiomyopathy
HOCM (with SAM)
Chronic AF with LA enlargement and annular dilatation
Mitral annular calcification[a]

Mitral regurgitation

- Post inflammatory rheumatic heart disease was the principal cause in the pre-antibiotic era.
- Mitral valve prolapse is the principal cause today.
- Infective endocarditis
- Libmann-Sacks endocarditis in systemic lupus erythematosus

Mitral regurgitation

- Chronic disease is frequently secondary to ischemia
- May occur with fibrosis of a papillary muscle, in patients with healed myocardial infarction and ischemic cardiomyopathy.
- May occur as a consequence of ventricular remodeling with papillary muscle displacement and leaflet tethering
- Annular dilation and ventricular remodeling as mechanism in those with non-ischemic forms of dilated cardiomyopathy



Mitral regurgitation (red)

https://www.cvphysiology.com/Heart%20Disease/HD009c

Mitral regurgitation

- Severe disease presents with fatigue and dyspnea
- High pitched blowing holosystolic murmur at the 5th or 6th left intercostal space at the mid-left thorax radiating to the apex and radiating into the left anterior axillary line or left axilla.
- Diastolic rumble
- Abrupt standing from a squatting position decreases the intensity of the murmurs
- Squatting from a standing position increases the intensity of the murmurs.
- Valsalva maneuver also increases the intensity of the murmur.

Mitral regurgitation

- >40% regurgitant fraction in severe disease
- Murmur intensity of Grade III (LR+ 3.5)
- Grade IV (LR+ 14).
- The absence of a murmur cannot exclude mitral insufficiency in a patient with acute myocardial infarction.
- Doppler echocardiography is diagnostic
- Palpitations may signal the onset of atrial fibrillation

Mitral regurgitation

- As the left ventricle contracts, blood is not only ejected into the aorta but also back up into the left atrium.
- This causes left atrial volume and pressure to increase during ventricular systole.
- There is no true isovolumetric contraction phase because blood begins to flow across the mitral valve and back into the atrium before the aortic valve opens as soon as ventricular pressure exceeds left atrial pressure.

Mitral regurgitation

- The afterload on the ventricle is reduced (total outflow resistance is reduced) so that end-systolic volume can be smaller than normal;
- End-systolic volume can increase if the heart also goes into systolic failure.
- There is no true isovolumetric relaxation phase because when the aortic valve closes and the ventricle begins to relax, the mitral valve is not completely closed so blood continues to flow back into the left atrium as long as intraventricular pressure is greater than left atrial pressure
- Further decreasing ventricular volume

Mitral regurgitation

- During ventricular diastolic filling, the elevated pressure within the left atrium is transmitted to the left ventricle during filling so that left ventricular end-diastolic volume (and pressure) increases.
- Ventricular end-diastolic volume is also increased because in chronic mitral regurgitation the ventricle anatomically dilates (remodels) so that ventricular compliance is elevated
- Because forward flow into the aorta is reduced, the net stroke volume falls.
- Eventually increased end diastolic volume leads to increased afterload.

Mitral regurgitation

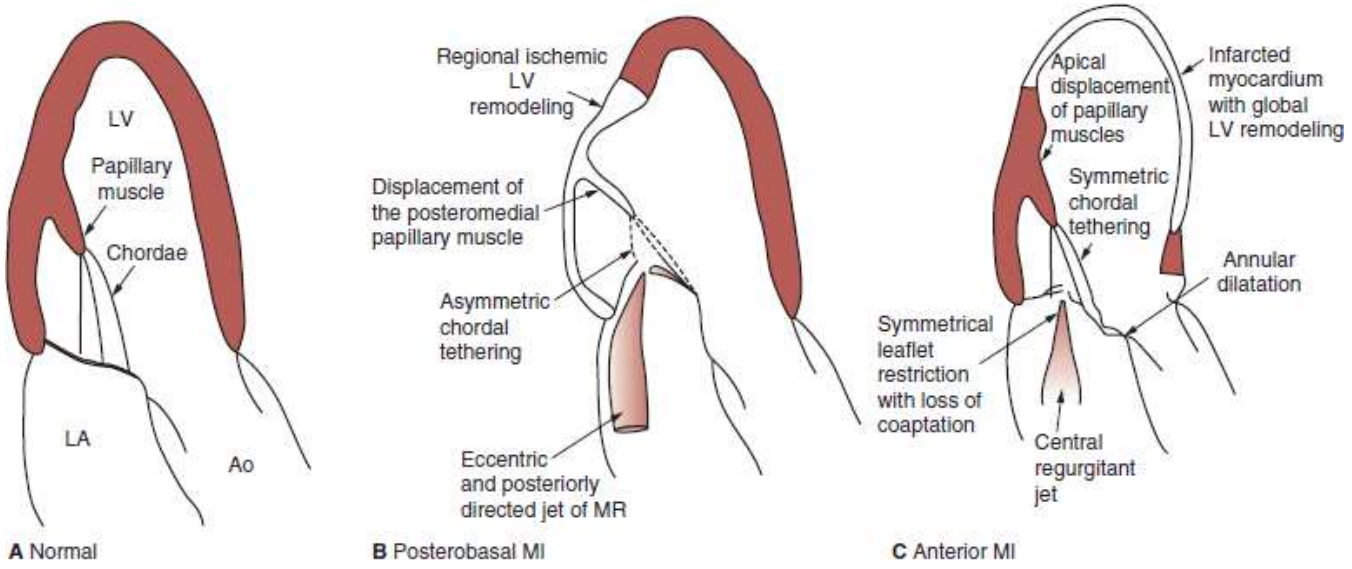
- Left ventricle volume increases progressively with time as the severity of the regurgitation increases and as contractile function deteriorates.
- Forward cardiac output falls.
- Left ventricle end diastolic pressure does not rise until late.
- Anticoagulation with either warfarin or a direct oral heparin agent should be provided if AF intervenes
- Do not use in rheumatic heart disease or with a mechanical valve
- Avoid isometric exercise

Mitral regurgitation

- Fatigue and dyspnea as cardiac output falls and pulmonary pressures rise
- LV compliance is often increased
- LV diastolic pressure does not increase until late in the course.
- The regurgitant volume varies directly with the LV systolic pressure and the area of the valve opening

Mitral regurgitation

- Infarction
- 10-20% of cases in developed countries
- The anterolateral papillary muscle has a dual blood supply from the left anterior descending and left circumflex arteries.
- The posteromedial muscle has a singular blood supply from the right or dominant left circumflex coronary artery.
- Thus, ischemic mitral valve regurgitation is more common following inferior-posterior rather than an anterior myocardial infarction



Mechanisms of ischemic mitral regurgitation (MR). Panel A demonstrates normal mitral valve and left ventricle (LV) anatomy. Panel B demonstrates mechanisms of ischemic MR following postero-basal myocardial infarction (MI) where regional LV remodeling results in displacement of the posteromedial papillary muscle with asymmetric tethering of the posterior mitral leaflet and eccentric MR. Panel C illustrates mechanism of MR following an anterior MI where global LV remodeling causes apical and lateral displacement of both papillary muscles; subsequent symmetric tethering of both mitral leaflets and annular dilatation generate central MR. Ao, Aortic root; LA, left atrium.

Mitral regurgitation

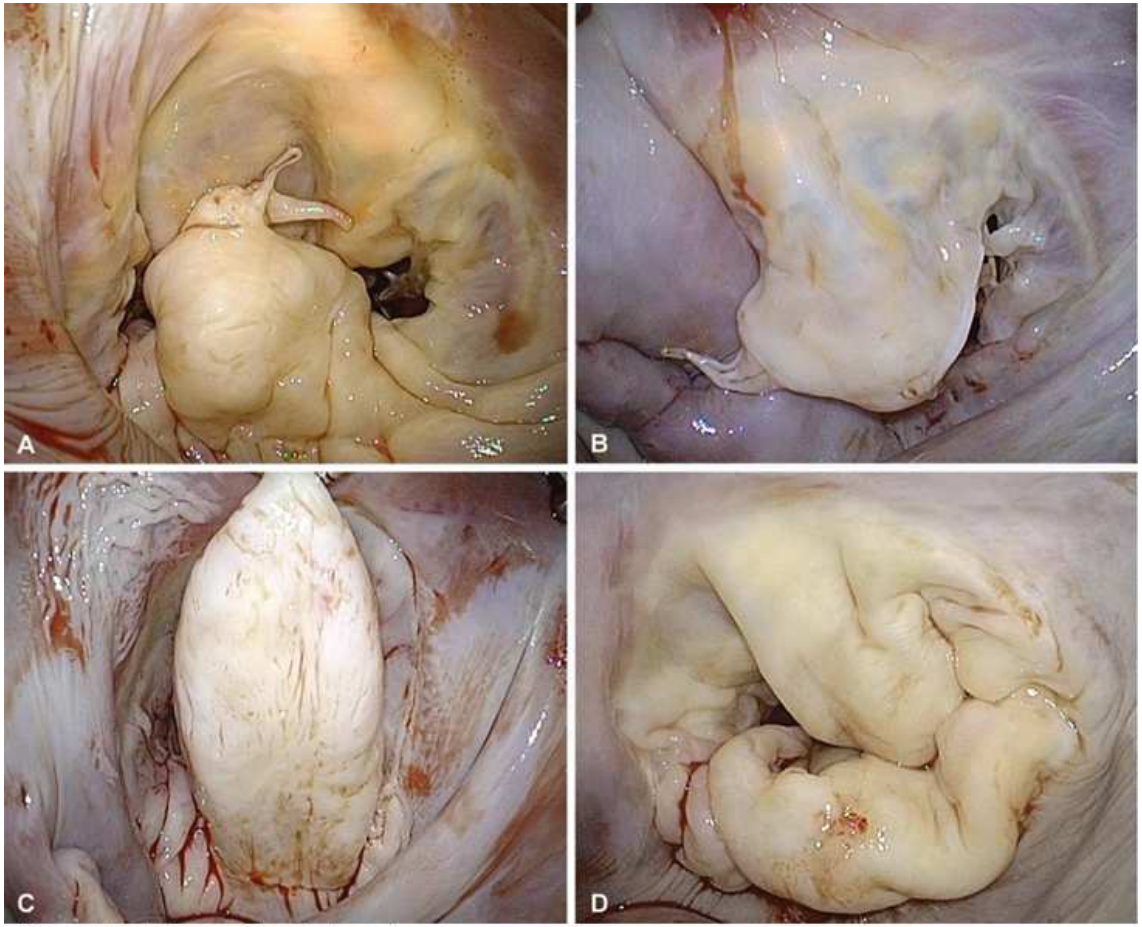
- Diuretics and intravenous vasodilators in the event of papillary muscle rupture
- Immediate valve replacement
- Surgical intervention with mitral valve repair if:
- Recent onset of atrial fibrillation
- Pulmonary hypertension
- Progressive LV dysfunction
- With ischemic disease, annuloplasty with an undersized, rigid ring, or chord sparing valve replacement with simultaneous coronary artery revascularization

Degenerative mitral valve disease

- A spectrum of lesions
- Simple chordal rupture involving prolapse of an isolated segment in an otherwise normal valve
- P2 or the middle scallop of the posterior leaflet
- Multi-segment prolapse involving one or both leaflets in a valve with significant excess tissue and a large annular size
- Two main entities:
- Fibroelastic deficiency
- Barlow disease

Type I	Type II	Type IIIA	Type IIIB
			
Normal leaflet motion (annular dilatation)	Increased leaflet motion (leaflet prolapse)	Restricted leaflet motion (restricted opening)	Restricted leaflet motion (restricted closure)
Annular dilatation Annular deformation Leaflet perforation Leaflet cleft	Myxomatous degeneration Chordal elongation Chordal rupture Papillary muscle elongation Papillary muscle rupture	Leaflet thickening, retraction Chordal thickening, retraction Chordal fusion Calcification Commissural fusion Ventricular fibrosis	Leaflet tethering Displacement of papillary muscles Ventricular dilatation Ventricular aneurysm Ventricular fibrosis
Ischemic cardiomyopathy Dilated cardiomyopathy Endocarditis Congenital	Degenerative disease Marfan syndrome Endocarditis Rheumatic disease Trauma Ischemic cardiomyopathy Ehler-Danlos syndrome	Rheumatic disease Carcinoid disease Radiation Lupus eythematosus Ergotamine use Hypereosinophilic syndrome Mucoploysaccharidosis	Ischemic cardiomyopathy Dilated cardiomyopathy

Pathophysiologic triad of mitral valve regurgitation composed of (top to bottom of each column): ventricular view, atrial view, leaflet dysfunction, valve lesions, and etiology.



Valve lesions in degenerative mitral valve disease. A. Fibroelastic deficiency; isolated P2 prolapse secondary to chordal rupture and mild segmental thickening. B. Fibroelastic deficiency; anterior leaflet prolapse as a result of multiple ruptured chordae. C. Barlow disease; very tall and thickened P2 segment with otherwise normal P1 and P3 segments. D. Barlow disease; large valve with redundant, thick, bulky leaflets. Note the blurring of the junction between atrium and leaflet with fissures.

	Fibroelastic deficiency	Fibroelastic deficiency +	Forme fruste	Barlow's disease
Age at diagnosis	> 60 years old	Likely > 60 years old	Likely < 60 years old	< 60 years old
History of MR	< 5 years	Likely < 5 years	Likely > 10 years	> 10 years
Annular dilatation	≤ 26 mm	Likely ≤ 32 mm	Likely 32 mm - 36 mm	≥ 36 mm
Leaflet tissue	Thin, translucent ○ ○ ○	Translucent, mild thickening ● ○ ○	Moderate excess ● ● ○	Diffuse excess ● ● ●
Segmental distribution	Single segment (P2)	Single segment (P2)	Posterior segments	Multisegmental
Chordae tendinae	Thin, ruptured	Thin, ruptured	Elongated, ruptured	Irregular, elongated
Degree of calcification	○ ○ ○	○ ○ ○	● ○ ○	● ● ●
Repair phylosophy	Respect tissue	Likely respect tissue	Small resection	Resection
Difficulty of repair	● ● ○	○ ○ ○	● ○ ○	● ● ●
Repair techniques	Chordal transfer PTFE neochordoplasty Loop techniques	Leaflet displacement Free edge plication Loop techniques Triangular resection	Leaflet displacement Triangular resection Limited quadrangular Annular plication Limited sliding plasty Posterior leaflet flip	Leaflet displacement Targeted resections Cleft closure Quadrangular resection Sliding plasty Commissuroplasty Posterior leaflet flip

Characteristic clinical and surgical differences between fibroelastic deficiency and Barlow disease. MR, mitral regurgitation; PTFE, polytetrafluoroethylene.

Fibroelastic deficiency

- 1-3% of population
- Presents in patients older than 60
- Presents as mitral valve prolapse
- Chordal rupture permits the middle scallop of the posterior valve leaflet to prolapse into the left atrium
- Usually murmur is holosystolic and severe
- May be autosomal dominant.
- Fibrillin-1 mutation
- Associated with Marfan's syndrome
- Associated with Ehler-Danlos syndrome

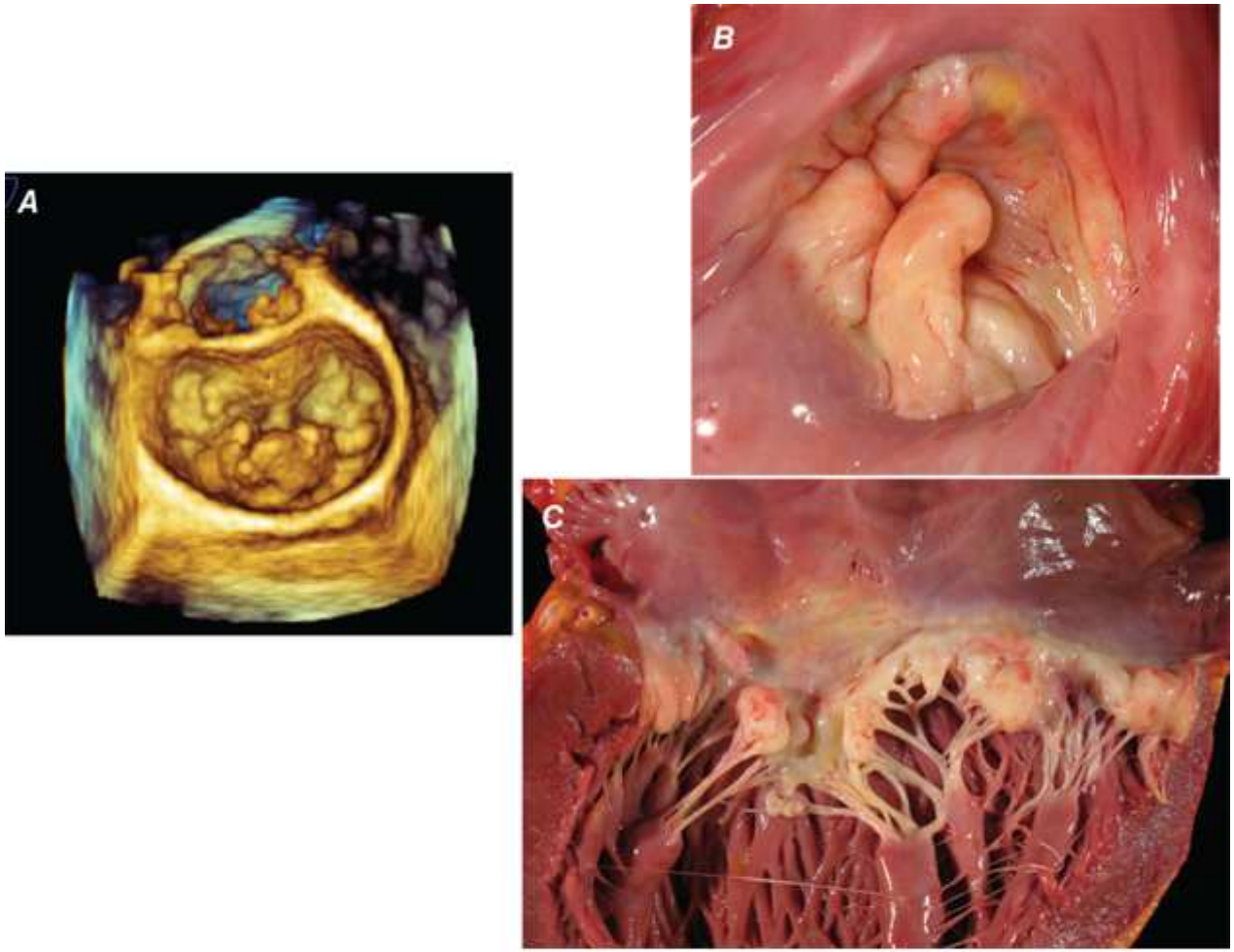
Barlow's disease

- Mitral valve prolapse as part of disease spectrum
- Excess leaflet tissue
- Leaflet thickening and distention
- Diffuse chordal elongation, thickening, and/or rupture.
- Severe annular dilatation with giant valve size
- Additionally, varying degrees of annular calcification are often observed
- Presents in younger women

Barlow's disease

- Myxomatous degeneration of valve (dermatan sulfate)
- Fibrosis of valve a later development
- May be secondary to ischemic dysfunction
- Thrombotic plaques may be found at the site of atrial-valve contact (Lambl excrescences)
- A mid-systolic non-ejection sound (click) occurs in mitral valve prolapse and is followed by a late systolic murmur that crescendos to S_2.

TTE



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

Mitral valve prolapse

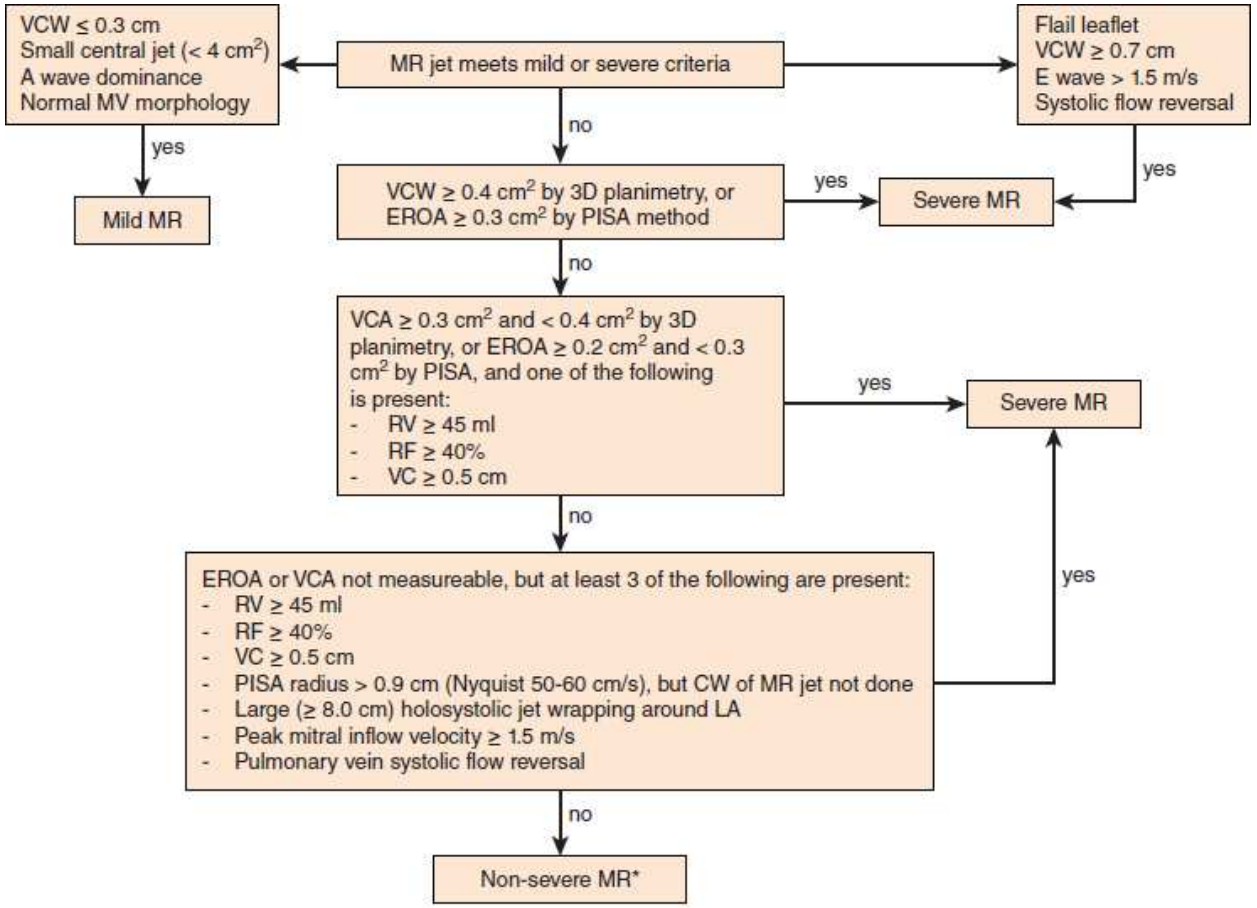
- Standing decreases venous return
- Heart becomes smaller
- Mid-systolic click moves closer to S_1
- Murmur of mitral regurgitation has an earlier onset.
- With prompt squatting, venous return increases
- Heart becomes larger
- Mid-systolic click moves toward S_2
- Duration of the murmur shortens.
- Valsalva maneuver also decreases the intensity of the murmur.

Mitral valve prolapse

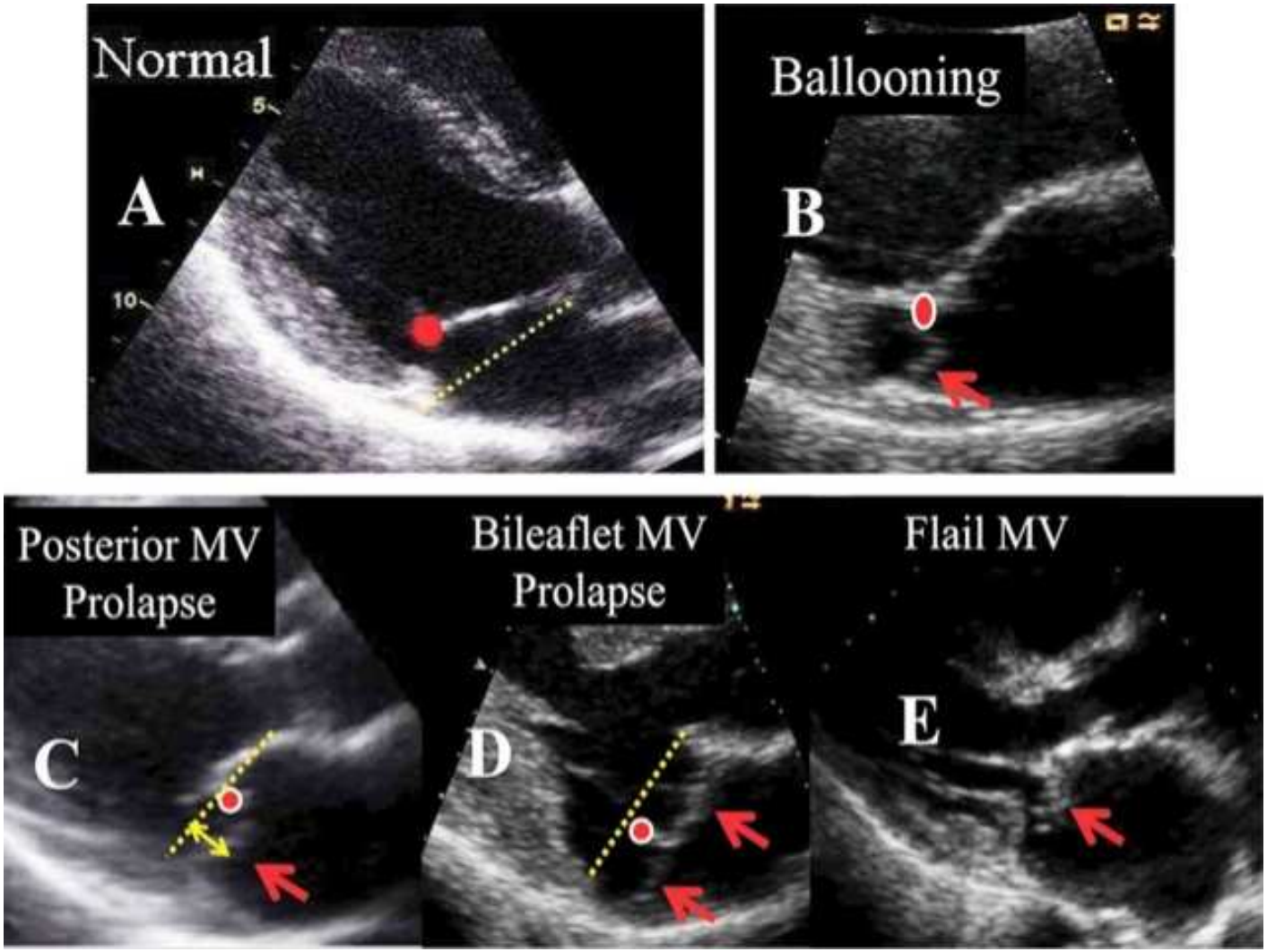
- Presence of a non-ejection click (LR+ 3.8).
- Presence of a systolic murmur with the click
- Associated with long-term complications
- Absence of a murmur and click rules out mitral valve prolapse (LR- 0.04)

Mitral valve prolapse

- Myxomatous degeneration of the valve predisposes to severe regurgitation and chordal rupture, and is a frequent indication for mitral valve repair or replacement.
- 3% develop serious complications
- Endocarditis prophylaxis.
- ASA if a history of embolic disease.
- β-blocker only if symptomatic with non-anginal chest pain, anxiety, or arrhythmia
- Significant mitral valve regurgitation may develop



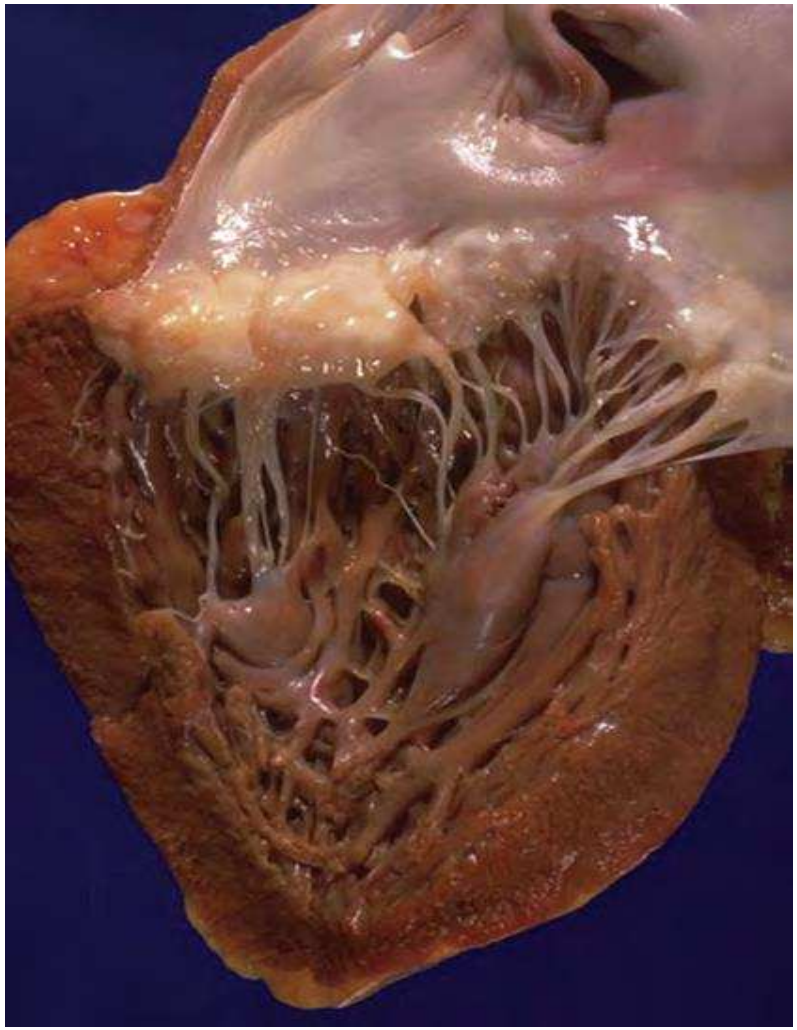
Source: Valentin Fuster, Robert A. Harrington, Jagat Narula, Zubin J. Eapen: Hurst's The Heart, Fourteenth Edition: www.accessmedicine.com



http://image.slidesharecdn.com/mrecho-150211075734-conversion-gate01/95/echocardiographic-evaluation-of-mitral-valve-disease-mitral-regurgitation-19-638.jpg?cb=1423663330

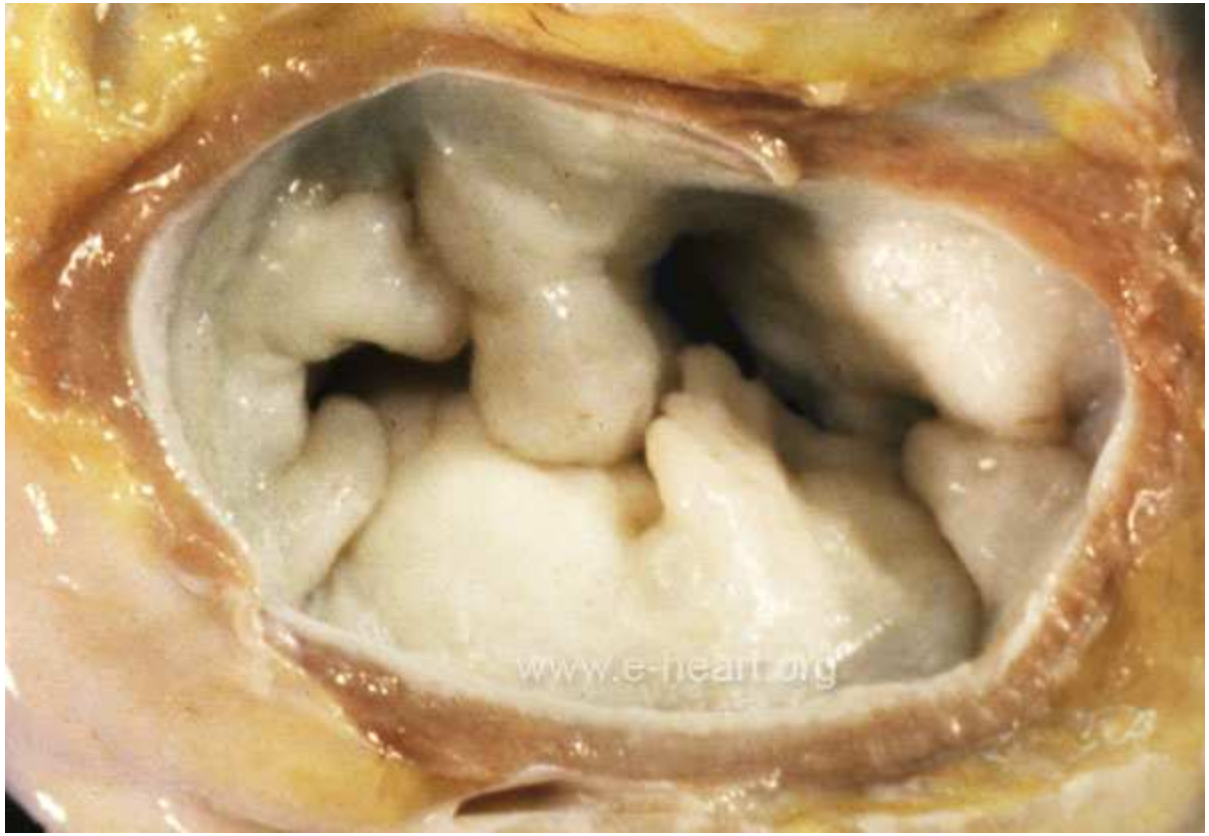
Accessed 12/07/2019

Myxomatous mitral valve (prolapse)

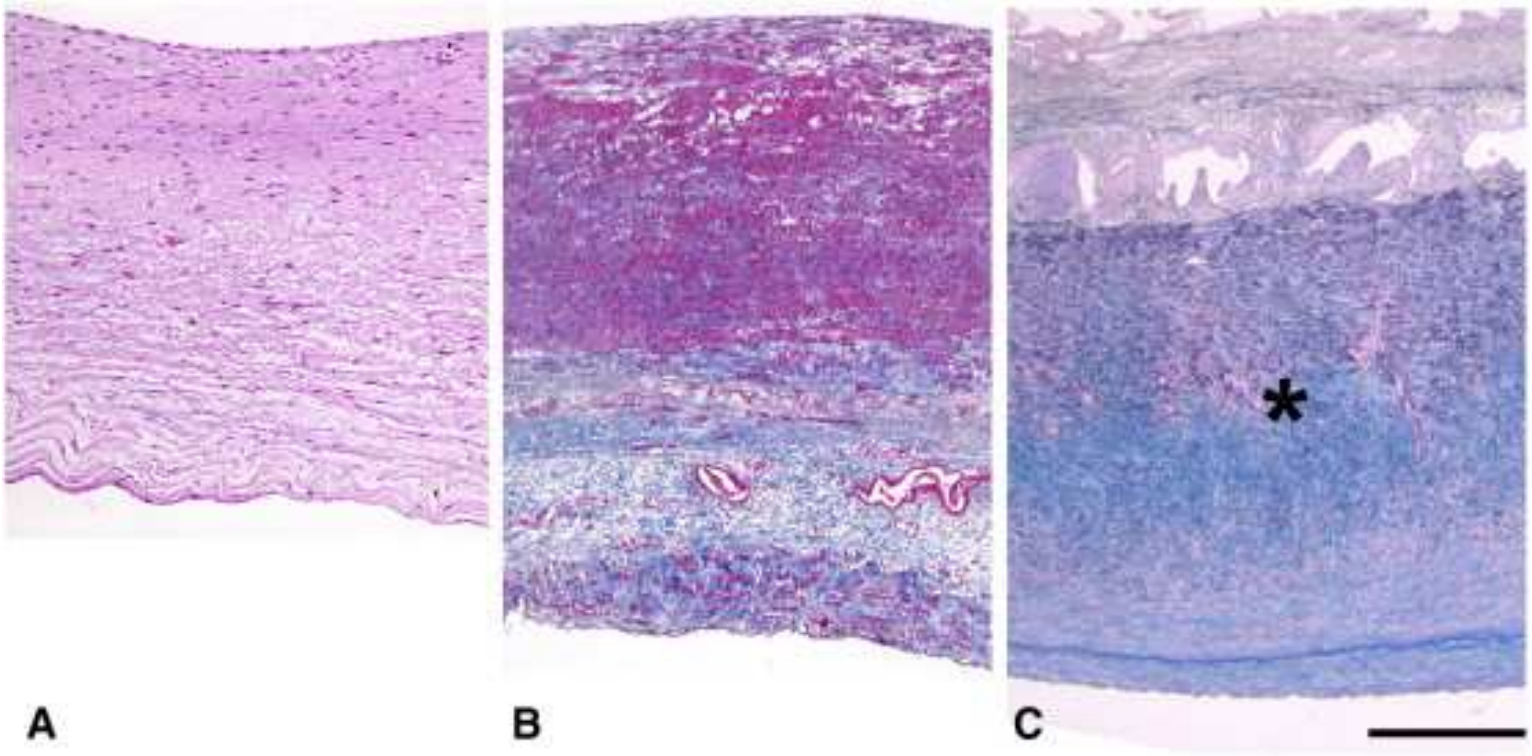


Klatt, EC, Robbins and Cotran Color Atlas of Pathology. (2015) Elsevier. Philadelphia. Fig. 2-46

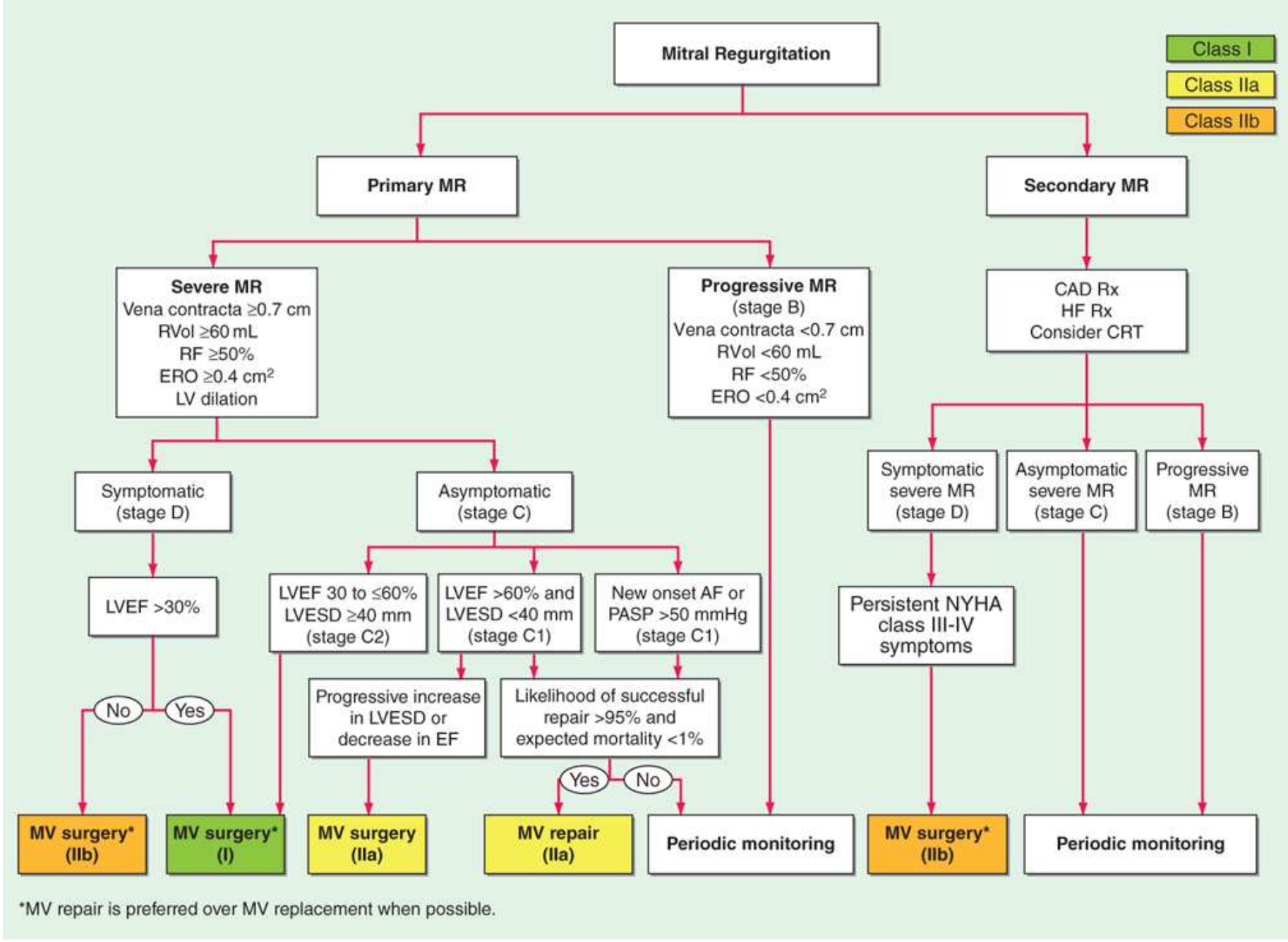
Marfan’s syndrome



Mitral valve prolapse



Prunotto, M, Caimmi, PP, Bongiovanni, M, “Cellular pathology of mitral valve prolapse,” Cardiovascular Pathology (2010) 19: e113-117 https://doi.org/10.1016/j.carpath.2009.03.002 Accessed 12/10/2019



*MV repair is preferred over MV replacement when possible.

Treatment

- Even isolated secondary mitral regurgitation is associated with increased mortality
- Treat valve early as results better than medical management alone
- Alfara stitch to minimize mitral valve area leads to beneficial left ventricular remodeling
- Mitra clip if dilatation secondary to left ventricular disease
- Placement via left atrium
- If 5-10mm dilatation, no benefit with minimal approach
- Repair, if possible, preferred to valve replacement

Pressure-volume relationship

- Aortic stenosis is characterized by increased after-load.
- Both systolic and diastolic pressures rise.
- Pulse pressure widens.
- Mitral stenosis is characterized by decreased pre-load.
- Pulse pressure unchanged.

Pressure-volume relationship

- Aortic insufficiency is characterized by increased preload.
- Systolic pressure rises while diastolic pressure lags
- Wide pulse pressure
- Mitral insufficiency is characterized by decreased afterload.
- Systolic pressure falls
- Pulse pressure narrows.

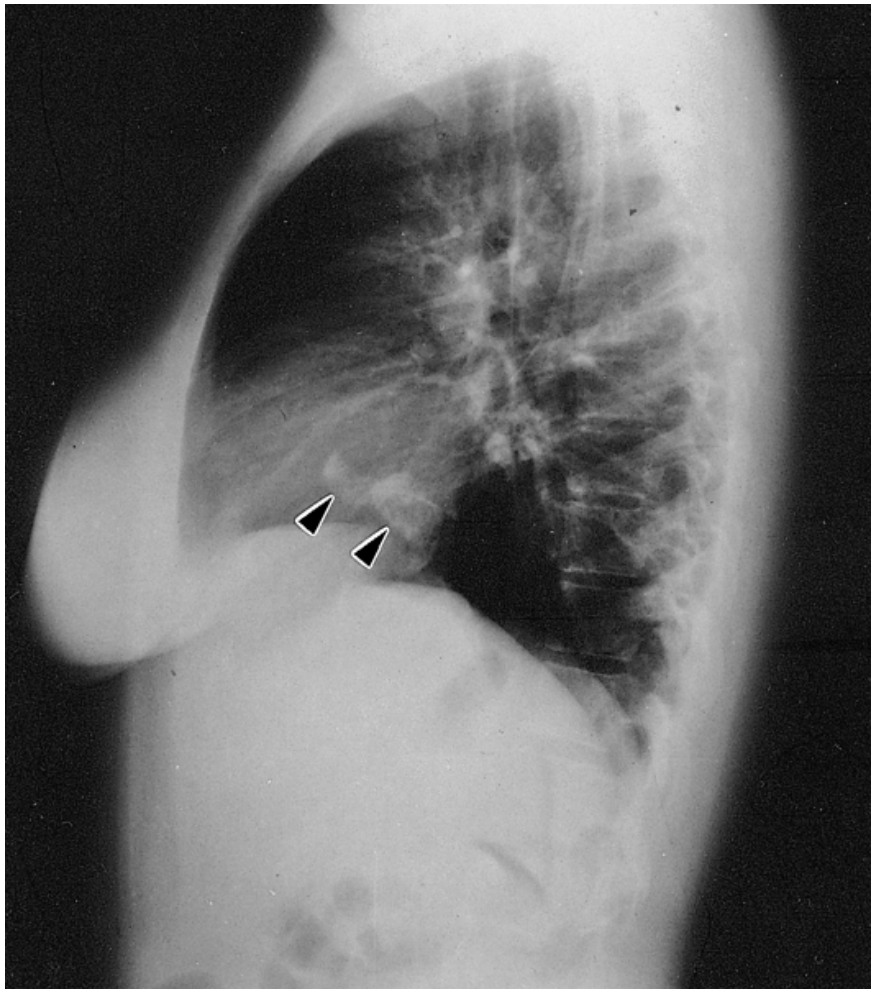
Atrial myxoma

- 30-50% of primary tumors of the adult heart
- Middle aged women
- 90% arise in the atria
- 4:1 preponderance on left.
- Arises near fossa ovalis.
- Space occupying lesion in atrium
- May function as ball-valve if pedunculated
- Composed of stellate cells embedded in an acid mucopolysaccharide ground substance.
- Abortive gland or vessel formation noted.
- Mesenchymal origin

Atrial myxoma

- Familial form (Carney complex)
- 7% of atrial myxomas
- Young age
- Multicentric
- Pigmented nevi
- Fibromyxomatous skin tumors
- Pigmented nodular adrenocortical tumors
- Autosomal dominant
- 70%, PRKAR1A null mutation (cAMP)
- McCune-Albright syndrome (GNAS1 mutation) is not associated with atrial myxoma

Atrial myxoma

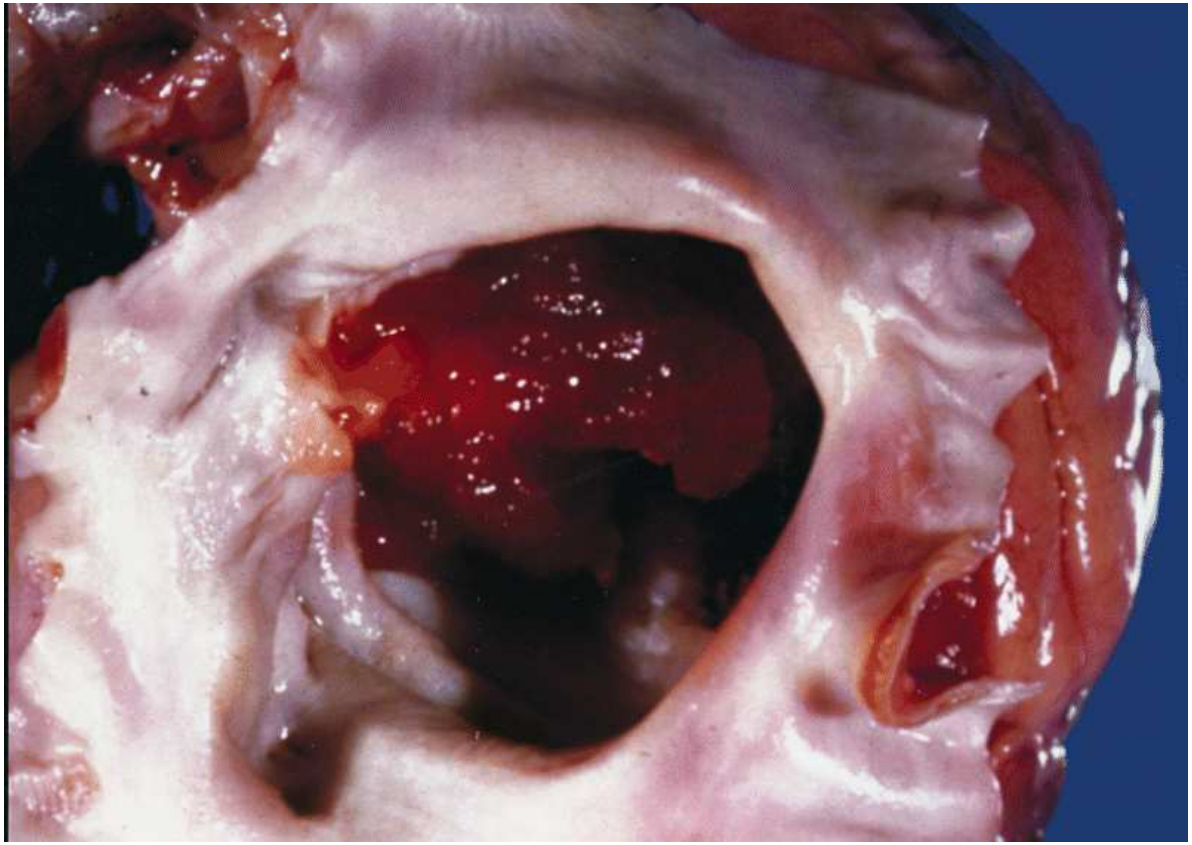


Lateral chest x-ray of a 16-year-old girl with syncope. Two areas of dense calcification (arrowheads) overly the posterior aspect of heart. At surgery a calcified myxoma of the right atrium was removed.

Fig. 2-2

Burke, A, and, Virman, R, "Tumors of the heart and great vessels." Atlas of Tumor Pathology. Third Series. Fascicle 16. Armed Forces Institute of Pathology. Washington, D.C. 1996.

Atrial myxoma

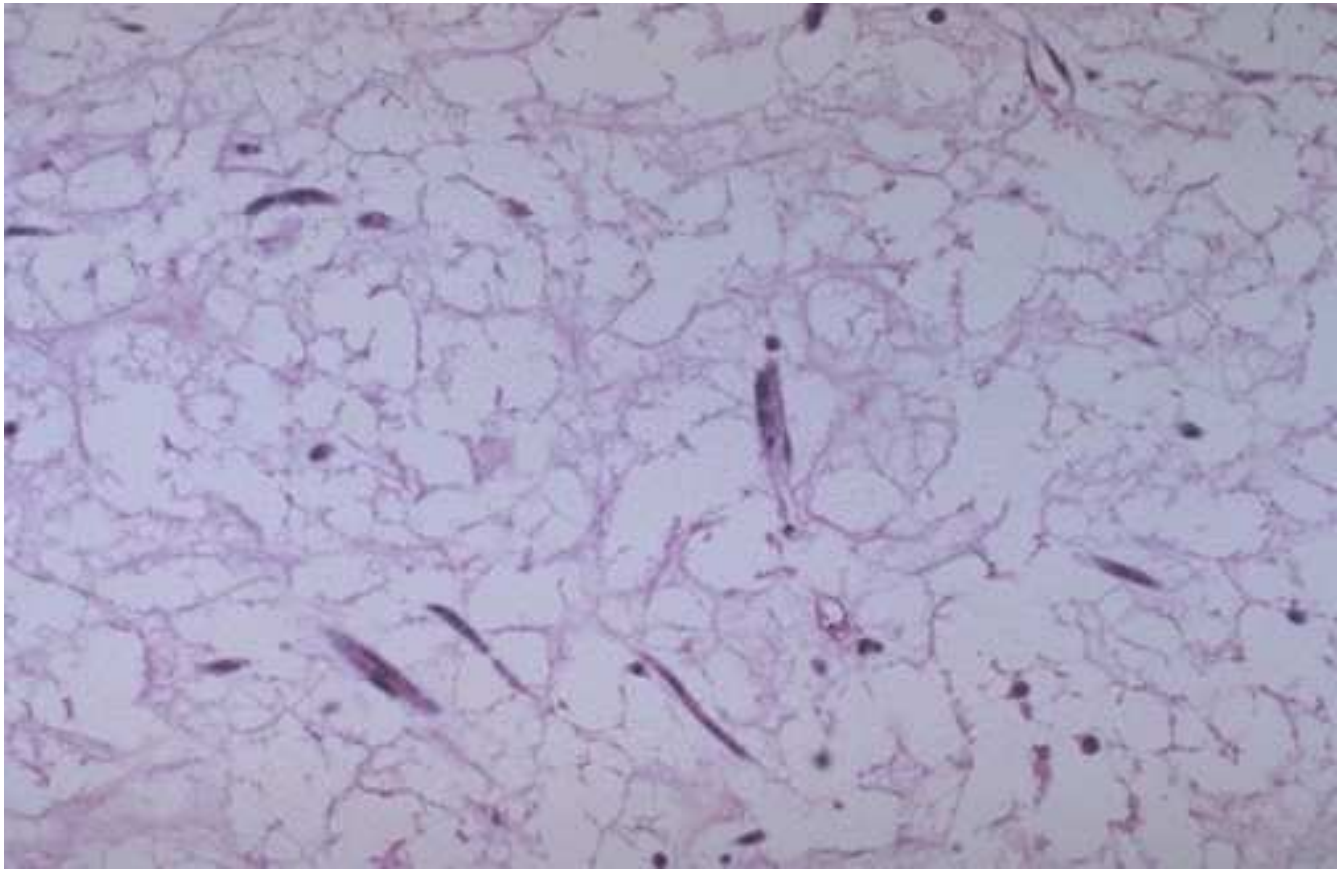


A gelatinous tumor is attached by a narrow pedicle to the atrial septum. The myxoma has an irregular surface and nearly fills the left atrium.

Fig. 3-1

Burke , A, and, Virman, R, "Tumors of the heart and great vessels." Atlas of Tumor Pathology. Third Series. Fascicle 16. Armed Forces Institute of Pathology. Washington, D.C. 1996.

Atrial myxoma



Scattered stellate cells in a myxoid stroma.

https://webpath.med.utah.edu/CVHTML/CV076.html Accessed 12/10/2019

Rhabdomyoma

- Most common pediatric tumor of heart
- >50% associated with Tuberous sclerosis
- Multiple in 90% of cases
- Often asymptomatic
- Predilection for left ventricle and may present with outflow obstruction
- Hamartoma of embryonal myocytes
- Gross Pathology
- Yellow-tan solid, circumscribed, unencapsulated lesions
- Histopathology
- Characteristic spider cell
- large clear cell with glycogen cytoplasmic strands extending to the plasma membrane.

Rhabdomyoma

Firm, white tumor mass fills the ventricle

https://webpath.med.utah.edu/CVHTML/CV076.html Accessed 12/10/2019

Other cardiac tumors

- Benign:
- Fibroma
- Lipoma
- Paraganglioma
- Histiocytoid tumor
- Sarcoma is the primary malignant tumor
- 25% of cardiac tumors
- Metastatic disease usually from breast or lung primary
- 50-65% of melanomas will metastasize to heart

TABLE 262-1

Causes of Pulmonic Valve Disease

Valve Lesion	Etiologies
Pulmonic stenosis	Congenital Carcinoid Tumor Endocarditis
Pulmonic regurgitation	Primary valve disease Congenital Postvalvotomy Endocarditis Carcinoid Annular enlargement Pulmonary hypertension Idiopathic dilation Marfan syndrome

Harrison's Principles of Internal Medicine, 20e > Pulmonic Valve Disease

Pulmonic valve stenosis

- Pulmonic valve stenosis with intact ventricular septum
- Congenital
- Noonan syndrome
- 50% have PTPN1 gene mutation at 12
- RV dysfunction from afterload mismatch occurs earlier in the course of PS and at lower peak systolic pressures
- Usually asymptomatic

Pulmonic valve stenosis

- Ejection click and early systolic murmur
- Ejection click more prominent on expiration
- Pulmonic component of S_2 delayed
- Right ventricular systolic ejection becomes progressively longer
- Increased obstruction to flow.
- As the pulmonic gradient increases
- isometric contraction shortens

Pulmonic valve stenosis

- In severe pulmonic stenosis with concentric hypertrophy
- Decreasing right ventricular compliance
- S_4 appears
- Critical pulmonic valve stenosis
- Newborns
- Present with right heart failure.

- Right sided valvular lesion
- Increased murmur intensity on inspiration

Treatment

- Diuretics can be used to treat symptoms and signs of right heart failure.
- Provided there is less than moderate pulmonic regurgitation (PR), percutaneous pulmonic balloon valvotomy is recommended for symptomatic patients with a domed valve.
- Dysplastic valve requires replacement.

Pulmonic valve regurgitation

- Pulmonic valve regurgitation
- Usually functional (stretching of ring)
- Pulmonary hypertension
- Carcinoid syndrome
- Asymptomatic if mild
- PR is a state of increased preload and afterload
- RV chamber enlargement and eccentric hypertrophy
- Loud S_2 followed by a decrescendo diastolic murmur (Graham-Steel murmur)
- Echocardiography diagnostic

Treatment

- In patients with functional PR due to PA hypertension and annular dilation, efforts to reduce PA vascular resistance and pressure should be optimized.
- Diuretics can be used to treat the manifestations of right heart failure
- Idiopathic PA hypertension, left-sided heart valve disease etiologies managed with vasodilators and surgical intervention
- Surgical valve replacement rarely undertaken
- Transcatheter pulmonic valve replacement if congenital heart disease

Carcinoid syndrome

- Systemic disorder
- Presents with
- Flushing
- Diarrhea
- Bronchoconstriction
- Dermatitis
- Right heart lesions predominate
- Pulmonary vascular bed degrades biogenic amines
- Serotonin levels correlate with cardiac lesion severity
- 5-HIAA metabolite elevated in urine

Carcinoid syndrome

- Gross pathology:
- White intimal plaque-like thickening of endocardial surfaces
- Histopathology:
- Principally smooth muscle cells embedded in an acid mucopolysaccharide matrix
- Causes:
- Agents affecting serotonin metabolism
- Fenfluramine
- Ergotamine and methysergide are metabolized to serotonin in the pulmonary vasculature

Carcinoid syndrome

- Causes:
- Carcinoid tumors
- Bioactive compounds produced by intestinal carcinoids travel via portal vein to liver
- Generally inactivated
- Large metastatic burden in liver associated with syndrome as quantity of bioactive compounds produced exceeds hepatic capacity to metabolize them
- Primary pulmonary carcinoids will act directly on the left side of the heart

Carcinoid syndrome

- Bioactive compounds of rectal carcinoids travel via the inferior vena cava and bypass the liver
- Produce right heart lesions
- Tricuspid insufficiency predominates
- Bioactive compounds of pulmonary carcinoids act directly on the left side of the heart
- Aortic and mitral regurgitation

Causes of Tricuspid Valve Diseases

Valve Lesion	Etiologies
Tricuspid stenosis	Rheumatic
	Congenital
Tricuspid regurgitation	Primary (organic)
	Rheumatic
	Endocarditis
	Myxomatous (TVP)
	Carcinoid
	Radiation
	Congenital (Ebstein's)
	Trauma
	Papillary muscle injury (post-MI)
	Secondary (functional)
	RV and tricuspid annular dilatation due to multiple causes of RV enlargement
	Chronic RV apical pacing

Harrison's Principles of Internal Medicine, 20e > Pulmonic Valve Disease

Tricuspid stenosis

- Tricuspid stenosis with regurgitation
- Rheumatic heart disease is the most common cause of this lesion.
- Usually associated with mitral stenosis
- Carcinoid syndrome
- Staph. aureus infective endocarditis associated with intravenous drug use
- Right ventricle catheter leads
- Anticardiolipin antibody
- Rheumatoid arthritis
- Systemic lupus erythematosus

Tricuspid stenosis

- Because the development of MS generally precedes that of TS, many patients initially have symptoms of pulmonary congestion and fatigue.
- Relatively little dyspnea for the degree of hepatomegaly, ascites, and edema associated with TS
- The jugular veins are distended
- May be giant a waves.
- The v waves are less conspicuous
- There is a slow y descent.
- Systolic murmur along lower left sternal border that increases with inspiration

Tricuspid stenosis

- Opening snap follows P_2
- Diastolic murmur along lower left sternal border and over the xiphoid
- Occurs immediately pre-systole
- Increases with respiration
- The absence of EKG evidence of RV hypertrophy (RVH) in a patient with right-sided heart failure who is believed to have MS should suggest associated tricuspid valve disease.
- Prominent RA and SVC on chest x-ray
- Trans-thoracic echocardiography (TTE) diagnostic

Treatment

- Salt restriction, bed rest, diuretic therapy in pre-operative period to reduce hepatic congestion
- Surgical repair at time of mitral valve surgery
- If repair not possible, valve replacement
- Mechanical valves more prone to thromboembolic complications than at any other site

Tricuspid valve regurgitation

- 80% functional (stretching of ring)
- Usually asymptomatic
- Adults
- Also associated with aortic and mitral regurgitation
- Also associated with Ebstein anomaly
- Blowing holosystolic murmur at the lower left sternal margin.
- Increased on inspiration

Tricuspid valve regurgitation

- RA enlargement and elevation of the RA and jugular venous pressures with prominent c-v waves and rapid y descent
- Pulsatile jugular venous distention
- Pulsatile liver
- Trans-thoracic echocardiography (TTE) diagnostic

Treatment

- Diuretics can be useful for patients with severe TR and signs of right heart failure
- An aldosterone antagonist may be employed because many patients have secondary hyperaldosteronism from marked hepatic congestion
- If secondary to left heart disease, therapy to reduce PA pressure or pulmonary vascular resistance as well as LV pressure
- Surgical repair in severe disease

Strategy

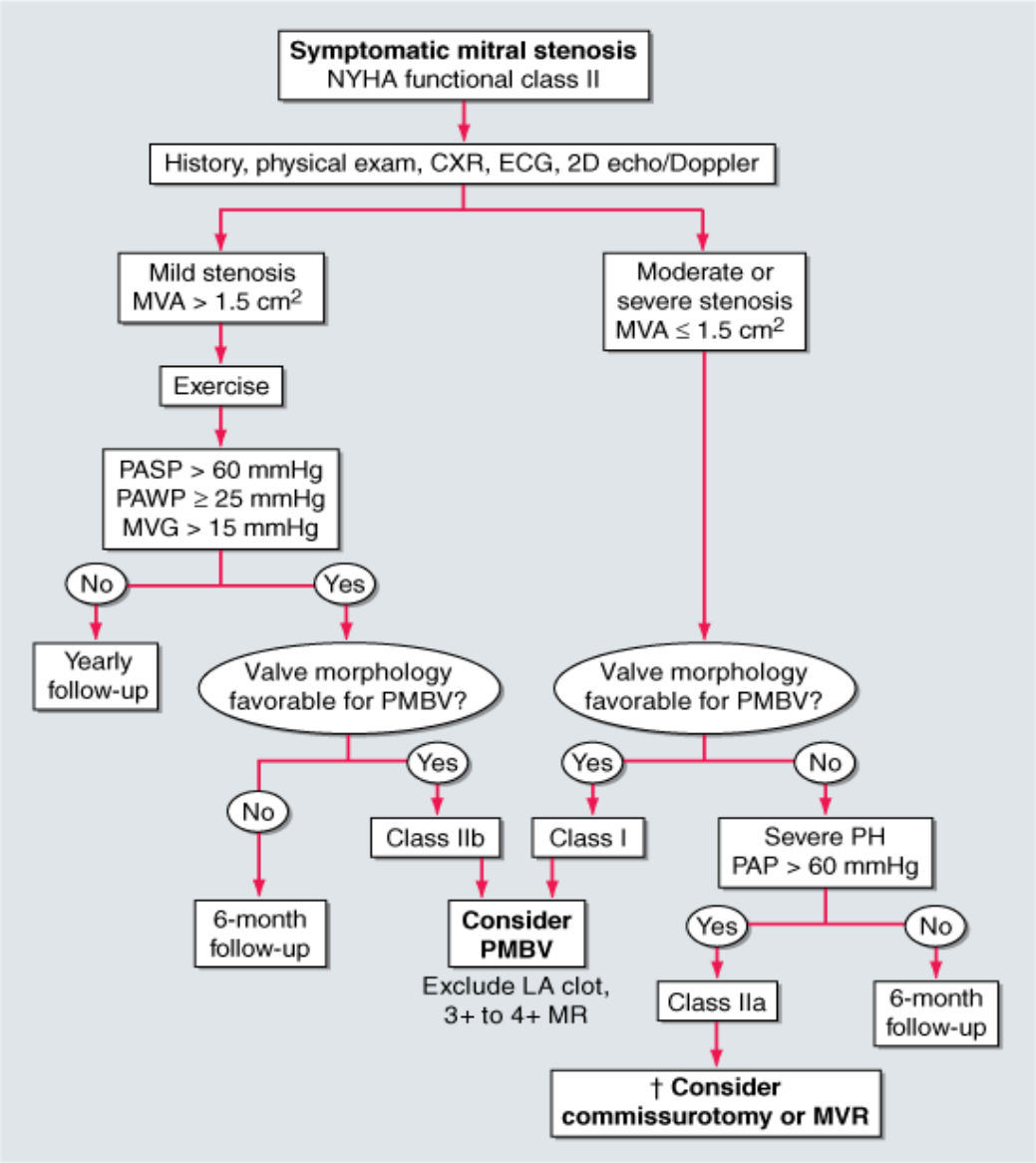


Fig. 230-1 Accessed 03/26/2010

Strategy

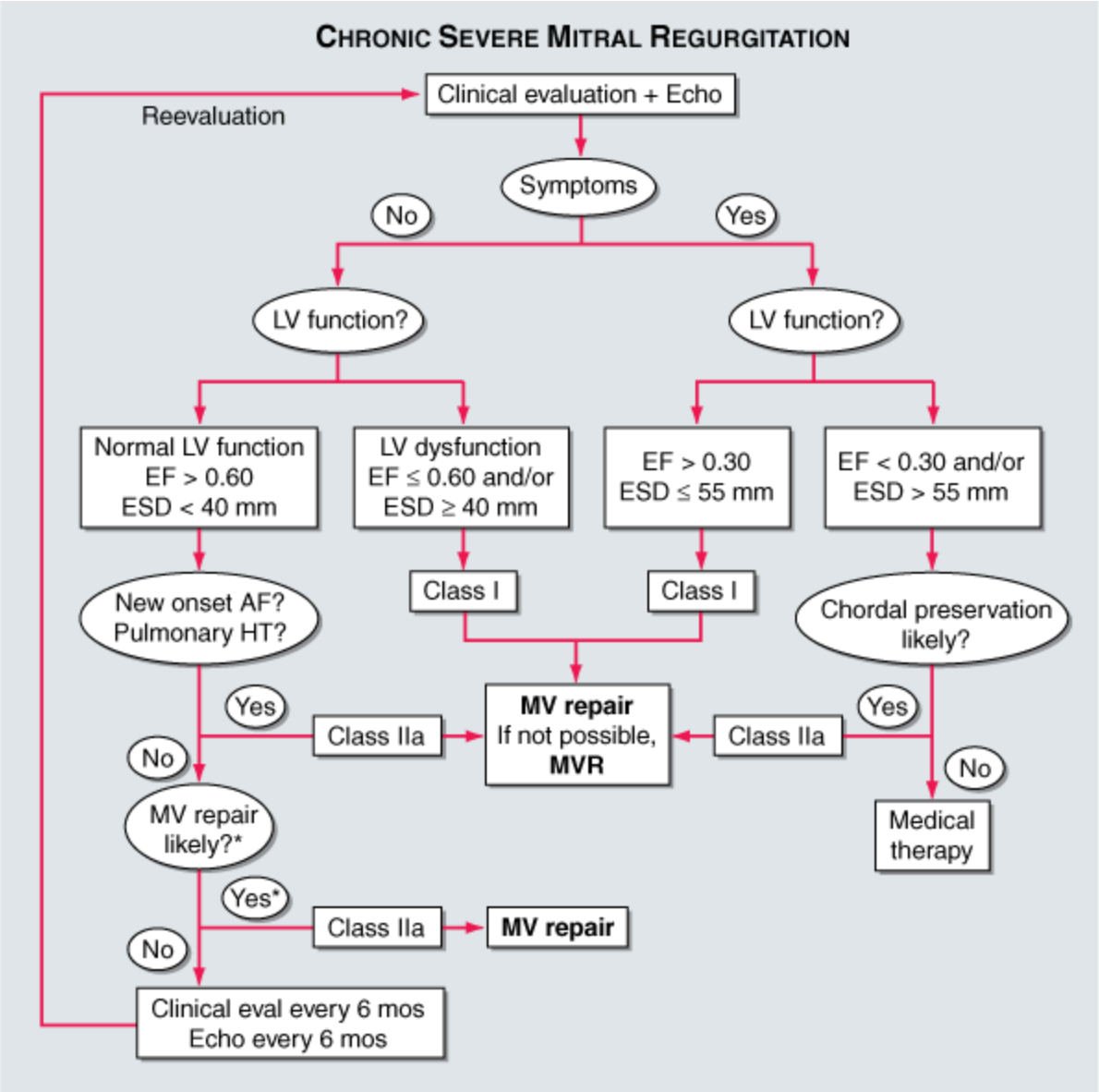


Fig. 230-4 Accessed 03/21/2010

Strategy

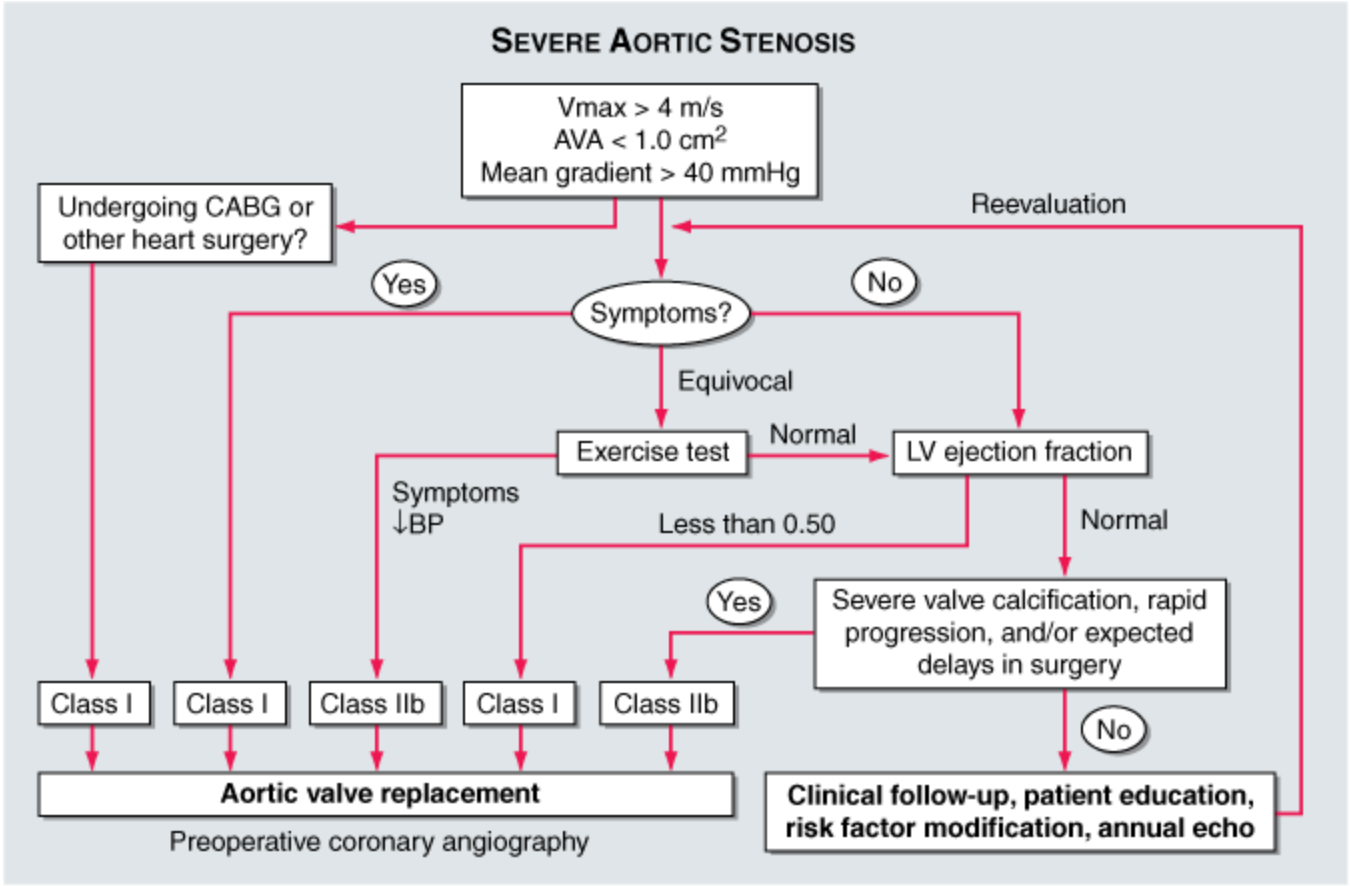
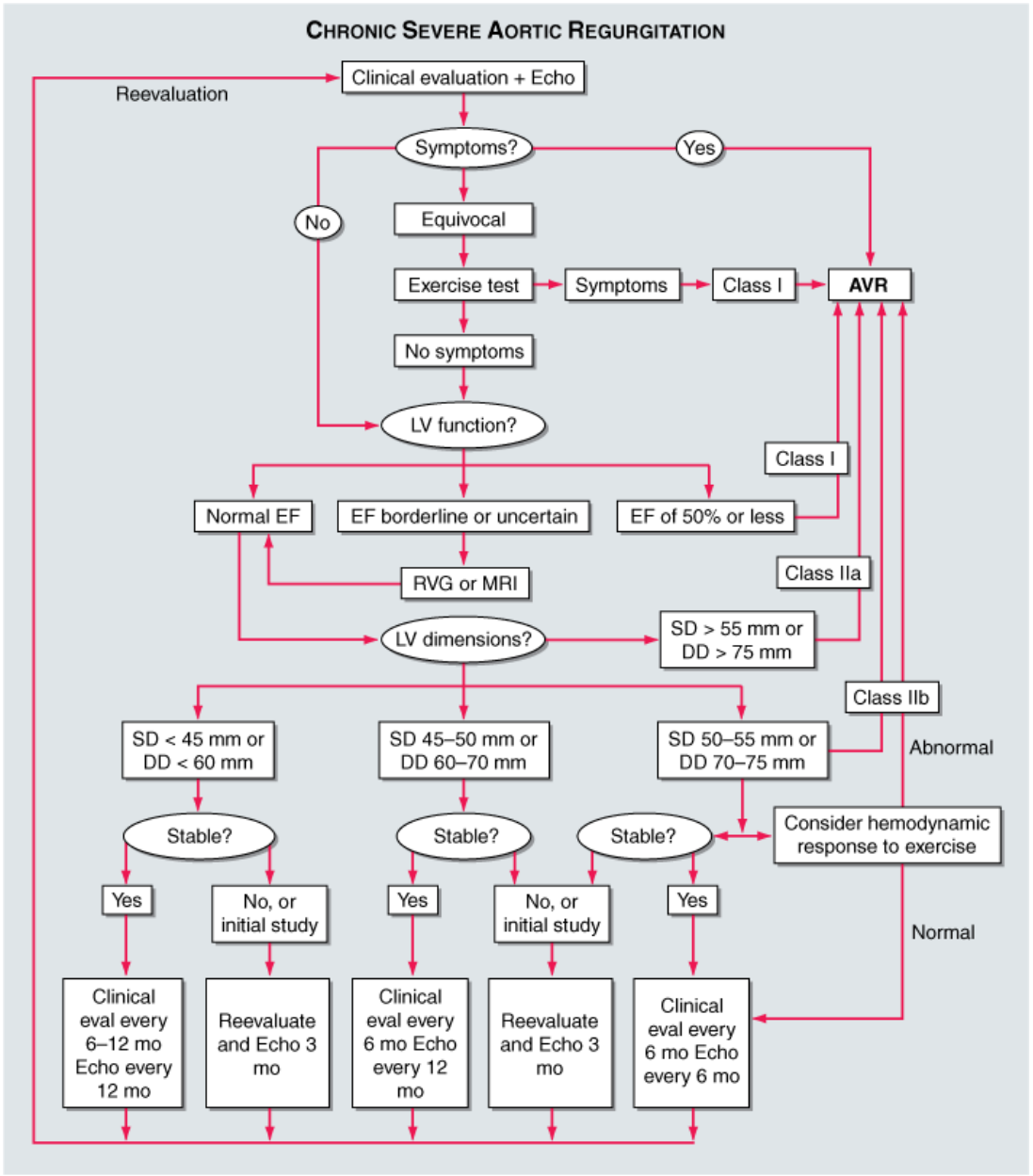


Fig. 230-5 Accessed 03/25/2010

Strategy



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Fig. 230-6 Accessed 03/25/2010

Prosthetic valves

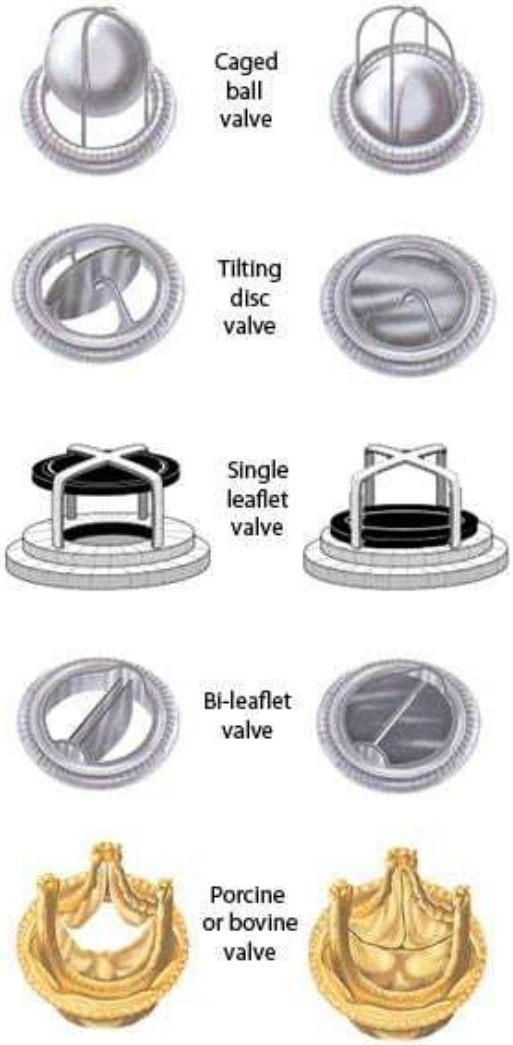
- Bioprosthetic valves
- Xenograft valves favored in those over 65 years of age
- Porcine or bovine
- Human donor grafts are also available.
- 10-20 year valve life
- 10% of bioprosthetic aortic valves require anticoagulation over valve life
- 60% of bioprosthetic mitral valves require anticoagulation over valve life
- Stenosis or calcification as reasons for failure

Mechanical prosthetic valves

- Caged valves and tilting disc valves
- Cavitation mechanics
- 20-30 year lifetime
- Audible click may be disturbing to patient
- The St. Jude Floating bi-leaflet metallic valve
- Pivots about a central axis
- Central blood flow
- Biocompatible
- Fewer complications than other mechanical valves
- Favored in those less than 65 years of age.
- Lifelong anticoagulation

Prosthetic valves

Thrombus formation and infection are the two common reasons for prosthetic valve failure



University of Chicago Surgical Pathology Manual

Infective endocarditis

- 5-15 cases per 100,000 population per year.
- Fourth most common life-threatening infection (after sepsis, pneumonia, intra-abdominal abscess).
- Classification is based on clinical course.
- Clinical signs are due to circulating micro-organisms.

Infective endocarditis

- Acute infective endocarditis is rapidly progressive, fulminant disease (days) associated with valve destruction.
- Both native and diseased valves at risk.
- Subacute infective endocarditis is a less fulminant process (2-3 weeks) associated with valve destruction.
- Diseased valves are at risk.

Predisposing conditions

- Transient Bacteremia
- Intravenous Drug Use
- Indwelling venous catheters
- Dental, surgical, and endoscopic procedures
- Genitourinary manipulation and abortion
- Ulcerative colitis, adenocarcinoma of the colon

Predisposing conditions

- Underlying valvular disease:
- Rheumatic heart disease (principally, mitral valve)
- Mitral Valve Prolapse
- Bicuspid Aortic Valve
- Intracardiac shunts (jet streams)
- Prosthetic Valve

Infective endocarditis

- Fever is the common manifestation.
- Fevers >38.4C are associated with a fulminant course.
- Chills (rigors) may be present when embolic seeding occurs from the diseased valve.
- There is no fixed cycle.
- Often anorexia is described.
- A regurgitant heart murmur is characteristic of valve destruction.
- It may be present in up to 90% of patients.

Infective endocarditis

- The Oslerian triad of sustained bacteremia, acute valvulitis, peripheral emboli, and immune complex phenomena is not often seen today.
- Pleuritic pain followed by hemoptysis may be seen in acute endocardits.
- Dyspnea or even signs of congestive heart failure may develop.
- Heart failure noted in 32% of patients
- Aortic>Mitral>>Tricuspid in incidence

Infective endocarditis

- Immune complexes may deposited in lungs, synovium, and glomeruli.
- Glomerulonephritis with nephritic syndrome may be seen in 60% of patients. Proteinuria, hematuria, red cell casts may be demonstrated in the urine. Rarely does it lead to renal failure.
- Splenomegaly may also be found in 30% of patients and represents long-standing disease.
- Neurologic lesions due to emboli in 15-30% of patients.
- Non-embolic stroke also noted in 17%.

Septic emboli

- Janeway lesions (painless hemorrhagic macules on palms or soles) are found in 40-50% of patients but may be transient;
- Subconjunctival hemorrhages are found in 20% of patients.
- Roth spots (hemorrhages with pale centers in retinal fundus) are found in <5% of patients;
- Splinter hemorrhages in nail beds are found in 10% of patients;
- Osler nodes (painful, on pads of fingers and toes) are found in 5% of patients.

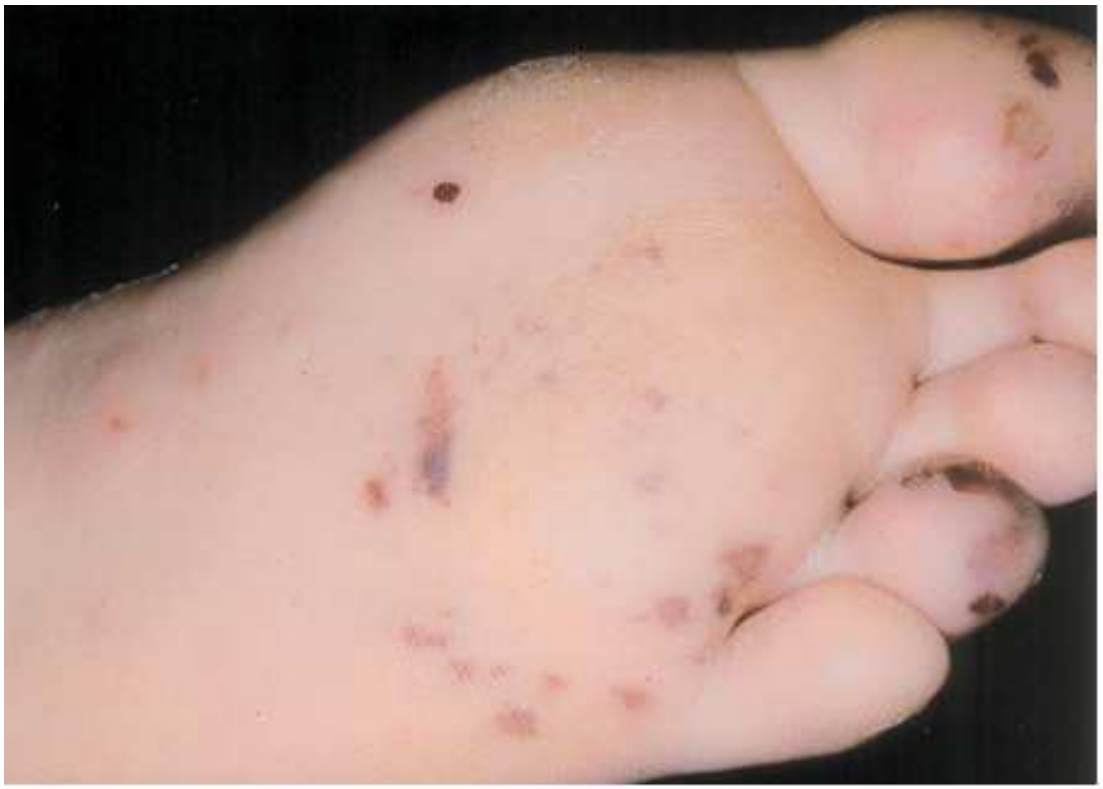
Mycotic aneurysms

- Mycotic aneurysms are microabscesses in arterial walls.
- Cerebral involvement involves the anterior circulation.
- The aneurysms are peripherally located and fusiform in appearance.
- Up to one-third occur before the Circle of Willis.
- CT mutlidetector angiography diagnostic.
- Endovascular or surgical treatment advised if patient otherwise good surgical risk.
- Weak association between size and rupture.

Mycotic aneurysms

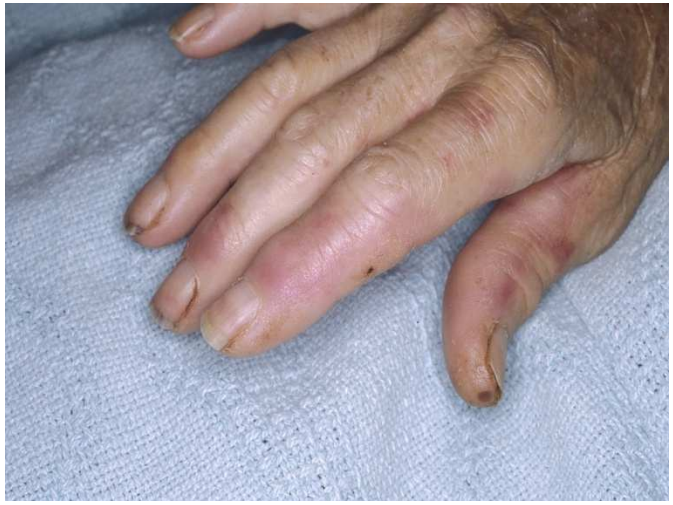
- Frequency in descending order
- Related to entry site
- Aorta
- Peripheral arteries (femoral)
- Cerebral arteries
- Mortality rate 60%; if rupture, 80%
- Visceral arteries (superior mesenteric)

Septic embolus

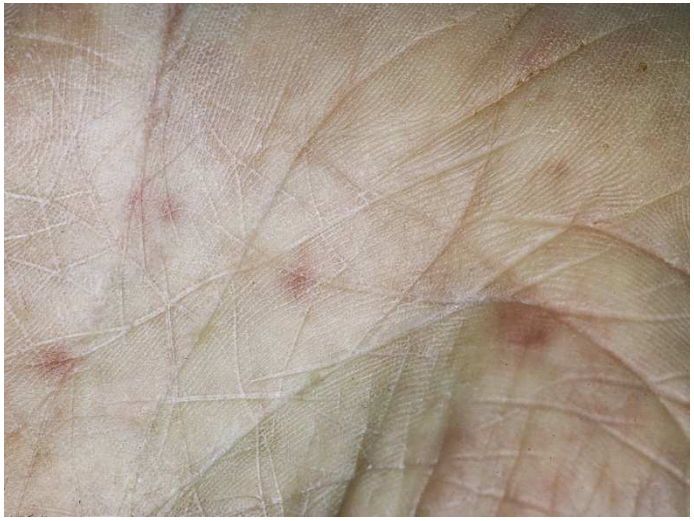


(Courtesy of Lindsey Baden, MD; with permission.)

Septic embolus



Osler node



Janeway lesion

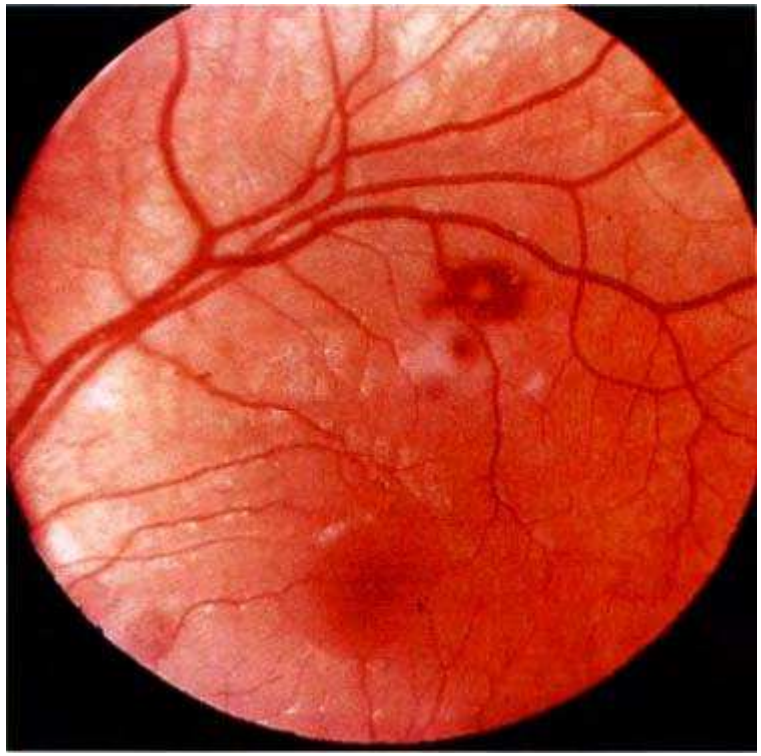
UCSD Catalog of Digital Images. Accessed 09/10/2019

Septic embolus

Splinter hemorrhage

Dermnet NZ Accessed 09/10/2019

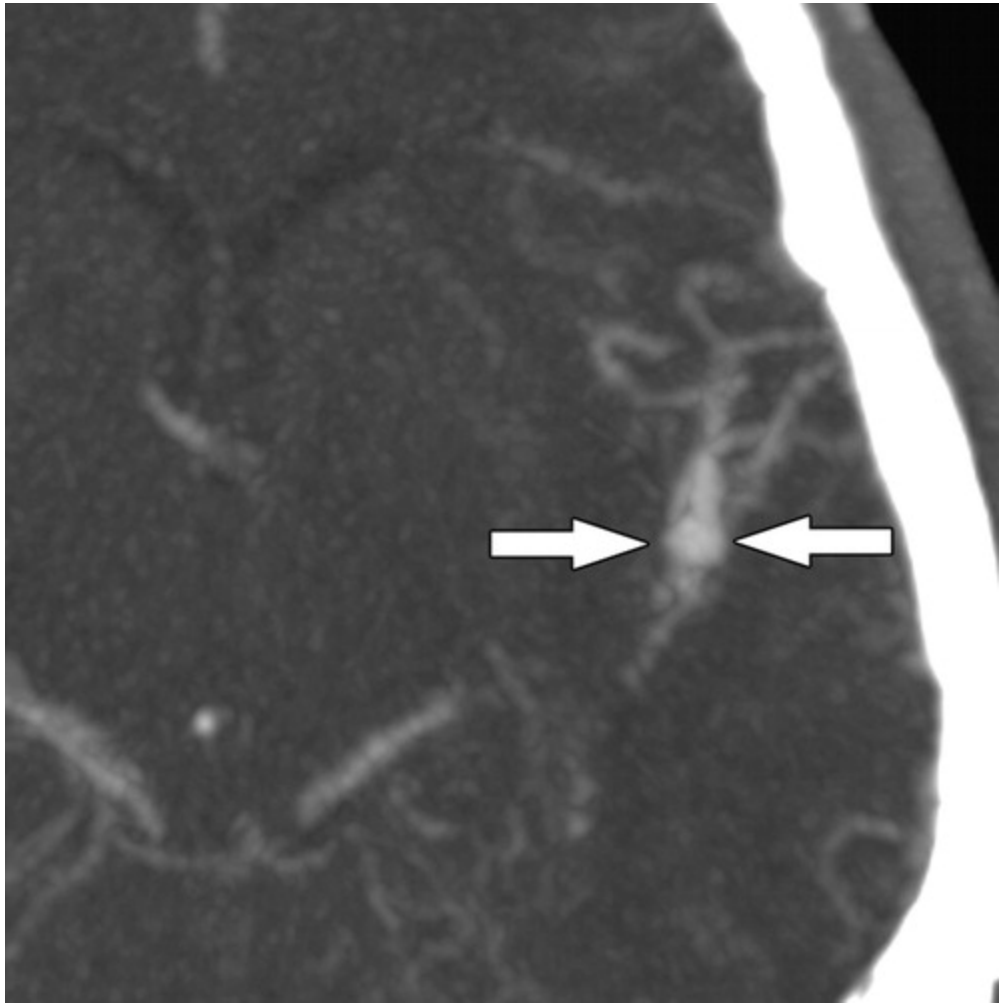
Septic embolus



Roth Spot

Cooke, RA, and Stewart,B, Colour Atlas of Pathology, 3rd edition. (2004) Curchill Livingstone. Edinburgh. Fig. 1-59.

Septic embolism



Mycotic aneurysm

Lee, Wai-Kit, Mossop, Peter J., Little, Andrew F., Fitt, Gregory J, Vrazas, Jhon I., Hoang, Jenny K., Hennessy, Oliver F., Infected (Mycotic) Aneurysms: Spectrum of Imaging Appearances and Management. Radiographics (2008) 28(7): 1853-1868. doi.org/10.1148/rg.287085054
Figure 6b.

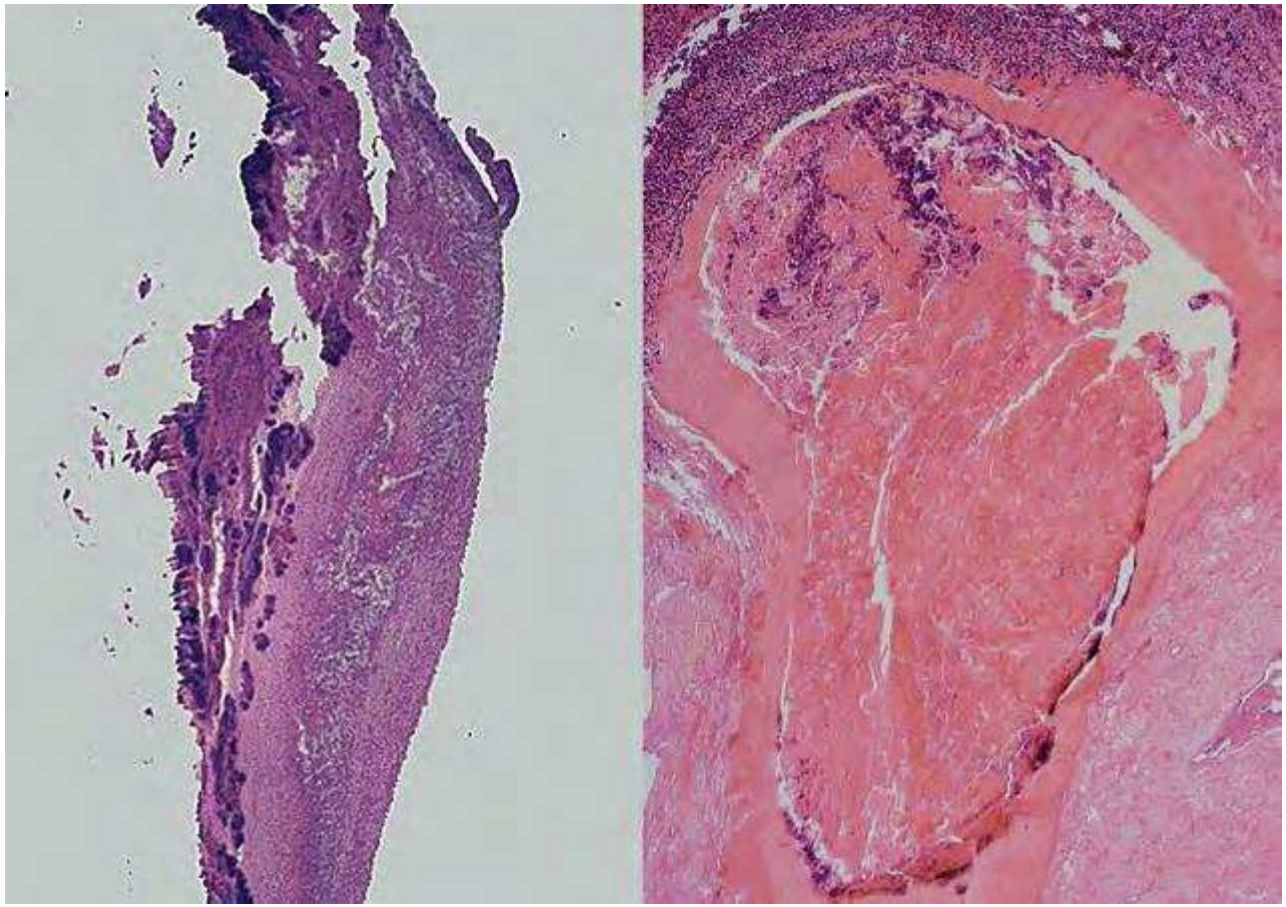
Pathogenesis

- Vegetations on heart valves are characteristic.
- The organisms that commonly cause endocarditis have surface adhesion molecules that adhere to matrix of injured endothelium.
- Fibronectin binding proteins (present on many gram positive organisms) facilitate adherence.
- Platelet adhesion and a local procoagulant response is induced. Inflammation follows.

Pathogenesis

- Valvular murmurs at site of disease as vegetations destroy valve (and chordae tendinae) and lead to valve dysfunction.
- As mitral valve structural abnormalities are more common, the mitral valve is the valve generally affected.

Infective endocarditis

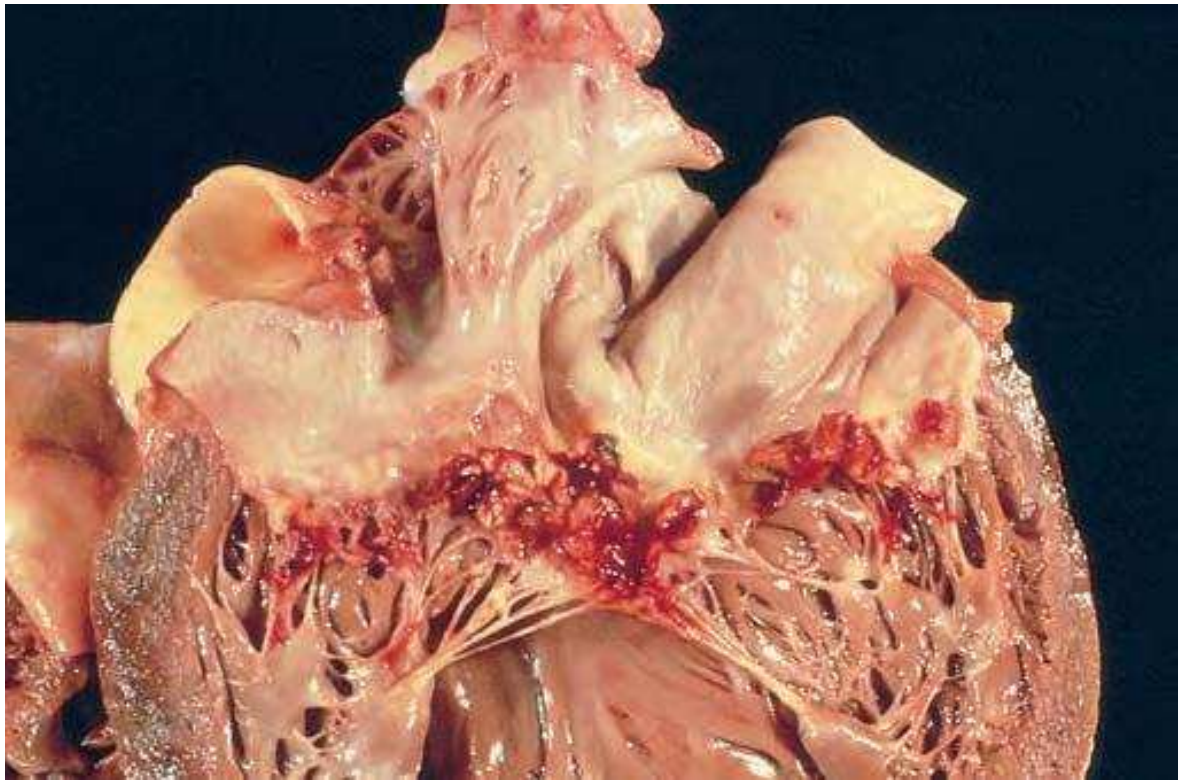


Vegetation

Septic thrombus

Klatt, EC, Robbins and Cotran Color Atlas of Pathology. (2015) Elsevier. Philadelphia. Fig. 2-60

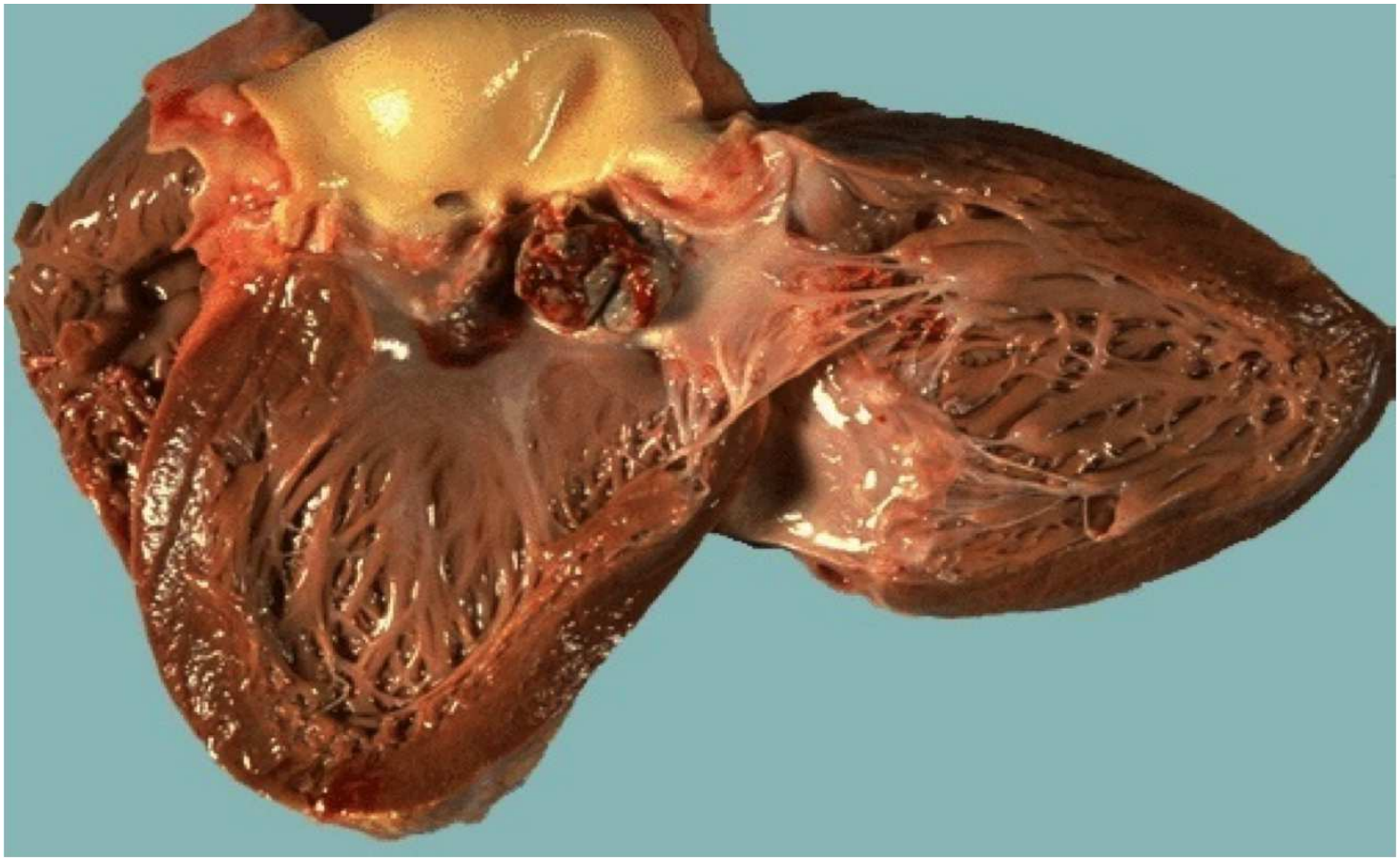
Infective endocarditis



Native mitral valve.

Schoen, and FJ, Mitchell, RN, “Heart”, in Kumar, V, Abbas, AK, Aster, JC (eds.), **Robbins and Cotran Pathologic Basis of Disease**, 9th edition. 2015. Elsevier. Philadelphia. Fig. 12-25A.

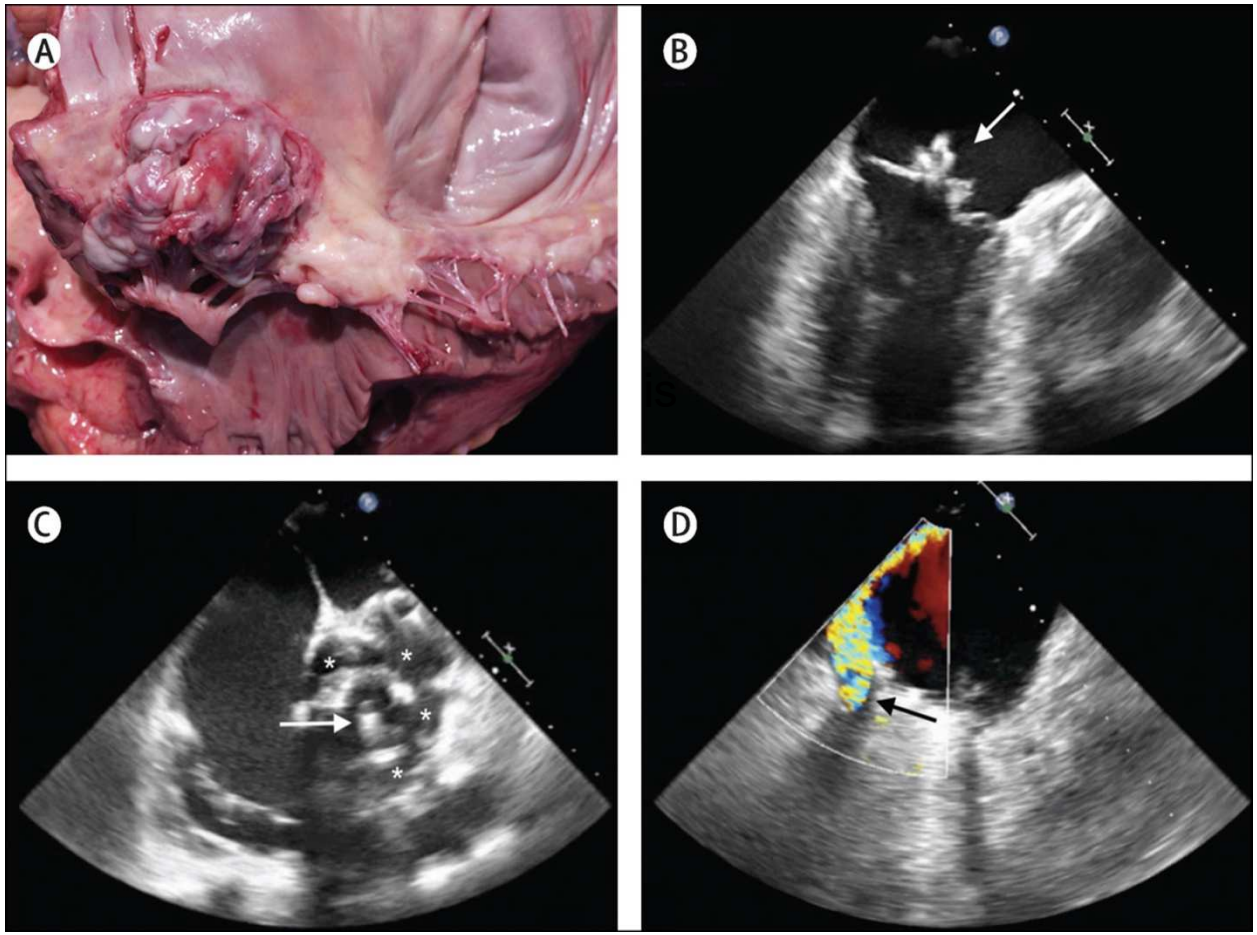
Infective endocarditis



Native aortic valve

Klatt, EC, Robbins and Cotran Color Atlas of Pathology. (2015) Elsevier. Philadelphia. Fig. 2-55

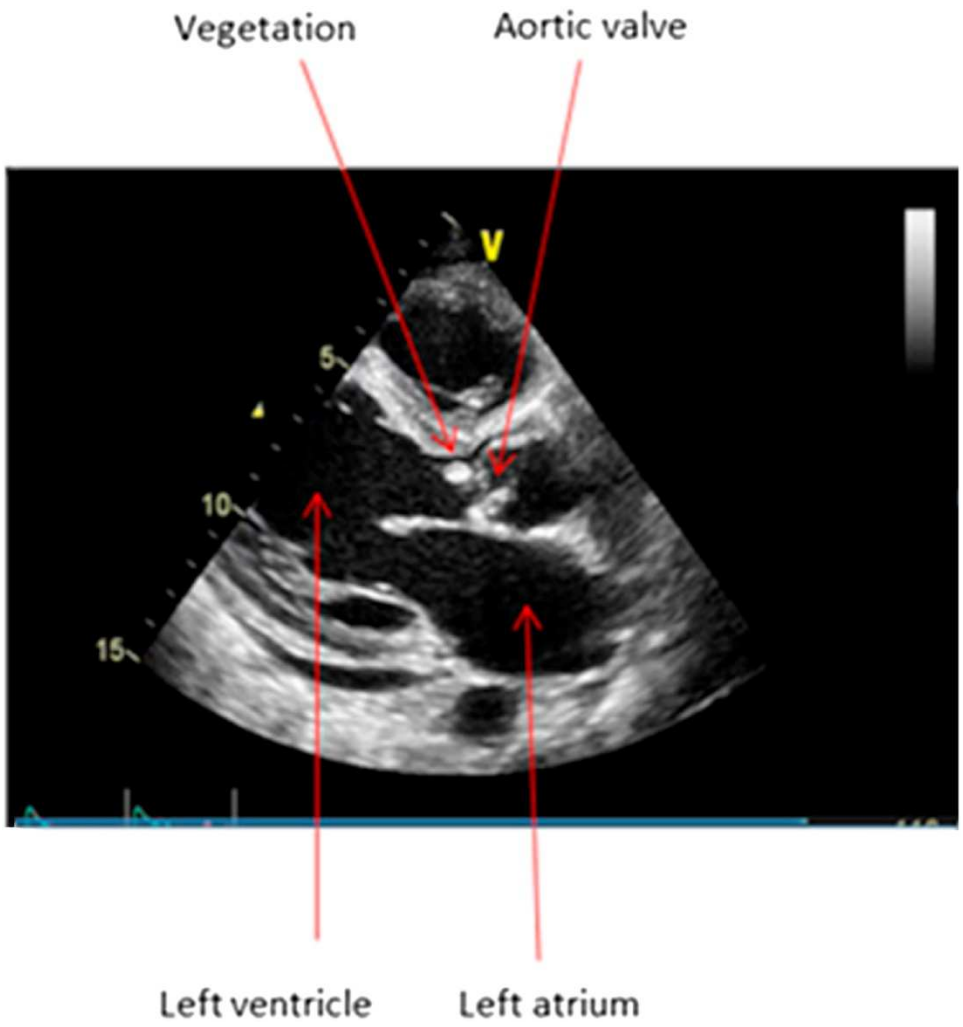
Infective endocarditis



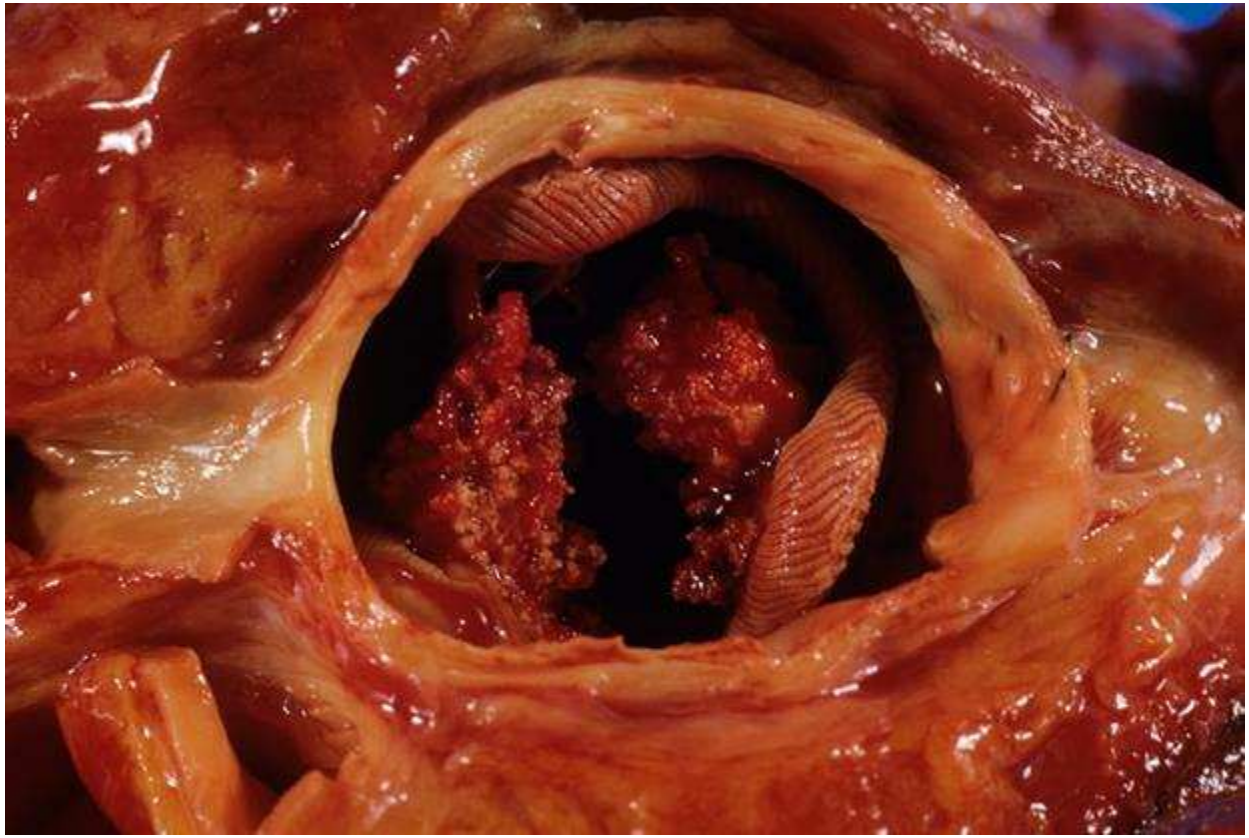
Mitral valve regurgitation

The Lancet

Infective endocarditis



Infective endocarditis



Prosthetic aortic valve

Table 12-9 Diagnostic Criteria for Infective Endocarditis*

Pathologic Criteria
Microorganisms, demonstrated by culture or histologic examination, in a vegetation, embolus from a vegetation, or intracardiac abscess
Histologic confirmation of active endocarditis in vegetation or intracardiac abscess
Clinical Criteria
Major
Blood culture(s) positive for a characteristic organism or persistently positive for an unusual organism
Echocardiographic identification of a valve-related or implant-related mass or abscess, or partial separation of artificial valve
New valvular regurgitation
Minor
Predisposing heart lesion or intravenous drug use
Fever
Vascular lesions, including arterial petechiae, subungual/splinter hemorrhages, emboli, septic infarcts, mycotic aneurysm, intracranial hemorrhage, Janeway lesions†
Immunological phenomena, including glomerulonephritis, Osler nodes,‡ Roth spots,§ rheumatoid factor
Microbiologic evidence, including a single culture positive for an unusual organism
Echocardiographic findings consistent with but not diagnostic of endocarditis, including worsening or changing of a preexistent murmur

*Diagnosis by these guidelines, often called the Duke Criteria, requires either pathologic or clinical criteria; if clinical criteria are used, 2 major, 1 major + 3 minor, or 5 minor criteria are required for diagnosis.

†Janeway lesions are small erythematous or hemorrhagic, macular, nontender lesions on the palms and soles and are the consequence of septic embolic events.

‡Osler nodes are small, tender subcutaneous nodules that develop in the pulp of the digits or occasionally more proximally in the fingers and persist for hours to several days.

§Roth spots are oval retinal hemorrhages with pale centers.

Modified from Durack DT, et al: New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Am J Med, 96:200, 1994, and Karchmer AW: Infective Endocarditis. In Braunwald E, Zipes DP, Libby P (eds): Heart Disease. A Textbook of Cardiovascular Medicine, 6th ed. Philadelphia, WB Saunders, 2001, p 1723.

Blood culture positive

- Typical microorganisms consistent with infective endocarditis
- Viridians streptococci
  - Streptococcus bovis
  - HACEK group
  - Staphylococcus aureus
- Community-acquired enterococci in the absence of a primary focus
- Single positive blood culture for Coxiella burnetii or anti–phase 1 IgG antibody titer ≥1:800
- Single positive blood culture for slow growing pathogen

Blood culture

- Blood cultures must be obtained from different sites
- Optimal sampling time is if rigor is present as is associated with organism showering into blood
- At least 2 positive blood cultures drawn >12 h apart
- OR all 3 positive blood cultures drawn >12 h apart
- OR a majority of ≥4 separate cultures of blood
- with first and last sample drawn at least 1 h apart

Other laboratory tests

- 19 % culture negative usually Coxiella burnetti
- positive laboratory tests (1 of the following)
- positive PCR (or other nucleic acid-based technique) for Coxiella burnetii, Bartonella spp., or Tropheryma whipplei from blood samples
- C. burnetii antiphase I IgG antibody titer > 1:800 or isolated from single blood culture
- indirect immunofluorescence assays for detection of IgM and IgG antibodies to Bartonella henselae or B. quintana with IgG titer > 1:800

Major imaging criteria

- Evidence of subendocardial involvement
- Transthoracic echocardiogram
- Positive for infective endocarditis
- OR rated at least possible infective endocarditis by clinical criteria
- OR complicated infective endocarditis
- [paravalvular abscess]

Paravalvular abscess

- Oscillating Intracardiac mass on valve or supporting structures;
- OR In the path of regurgitant jets;
- OR on implanted material in the absence of an alternative anatomic explanation;
- OR abscess;
- OR new partial dehiscence of prosthetic valve
- or new valvular regurgitation
- Trans esophageal echocardiogram preferred to transthoracic echocardiogram

Minor criteria

- Predisposition, predisposing heart condition, or intravenous drug use
- Fever, temperature >38°C
- Vascular phenomena
- Major arterial emboli
- Septic pulmonary infarcts
- Mycotic aneurysm
- Intracranial hemorrhage
- Conjunctival hemorrhages
- Janeway lesions
- Roth spots

Minor criteria

- Immunological phenomena:
- Glomerulonephritis
- Osler nodes
- Rheumatoid factor present
- Microbiological evidence:

Positive blood culture but does not meet a major criterion as noted above

(excludes single positive cultures for coagulase negative staphylococci and organisms that do not cause endocarditis),

OR serological evidence of active infection with organism consistent with infective endocarditis

Caveat

- Worsening or changing or pre-existing murmur is not a sufficient criterion for diagnosis

Microbiological clues

- Staph. Aureus
- Most commonly found micro-organism in endocarditis in the developed world (reflects health care contact).
- Affects both normal and diseased valves.
- Major cause of tricuspid valve destruction
- Associated with intravenous drug use
- Fulminant disease.

Microbiological clues

- Coagulase negative Staph. (epidermidis)
- Associated with prosthetic valve associated endocarditis.
- Strep. Viridians
- Second most commonly found micro-organism in endocarditis.
- Affects diseased valves.
- Aerobic Gram-negative bacilli (HACEK) include Hemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella.
- Usually associated with poor dental heath.

Epidemiological Clues

- Intravenous drug use
- Staph. aureus, including community-acquired oxacillin-resistant strains
- Coagulase-negative staphylococci
- β-hemolytic streptococci
- Fungi
- Aerobic Gram-negative bacilli, including Pseudomonas aeruginosa
- Polymicrobial

Prosthetic valve clues

- Early (≤1 y) prosthetic valve placement
- Coagulase-negative staphylococci
- Staph. aureus
- Aerobic Gram-negative bacilli
- Fungi
- Corynebacterium species
- Legionella species

Prosthetic valve clues

- Late (>1 y) prosthetic valve placement
- Coagulase-negative staphylococci
- Staph. aureus
- Strep. viridians
- Enterococcus species
- Fungi
- Corynebacterium species

Medical history clues

- Indwelling cardiovascular medical devices
- Staph. aureus
- Coagulase-negative staphylococci
- Fungi
- Aerobic Gram-negative bacilli
- Corynebacterium species

- Poor dental health, dental procedures
- Strep. viridians
- Nutritionally variant streptococci (Abiotrophia defectiva, Granulicatella species, Gemella species)
- HACEK organisms

Medical history clues

- Genitourinary disorders, infection, and manipulation, including pregnancy, delivery, and abortion
- Enterococcus species
- Group B streptococci (Strep. agalactiae)
- Listeria monocytogenes
- Aerobic Gram-negative bacilli
- Neisseria gonorrheae

- Gastrointestinal lesions
- Strep. gallolyticus (bovis)
- Enterococcus species
- Clostridium septicum

Medical history clues

- Chronic skin disorders, including recurrent infections
- Staph. aureus
- β-hemolytic streptococci

- Burn
- Staph. aureus
- Aerobic Gram-negative bacilli, including
- P. aeruginosa
- Fungi

Medical history clues

- AIDS
- Salmonella species
- Strep. pneumoniae
- Staph. Aureus

- Pneumonia, meningitis
- Strep. Pneumoniae

- Solid organ transplantation
- Staph. aureus
- Aspergillus fumigatus
- Enterococcus species
- Candida species

Medical history clues

- Diabetes mellitus
- Staph. aureus
- β-hemolytic streptococci
- Strep. Pneumoniae

- Alcoholism, cirrhosis
- Bartonella species
- Aeromonas species
- Listeria species
- Strep. pneumoniae
- β-hemolytic streptococci

Medical history clues

- Dog or cat exposure
- Bartonella species
- Pasteurella species
- Capnocytophaga species

- Contact with contaminated milk or infected farm animals
- Brucella species
- Coxiella burnetii
- Erysipelothrix species

- Body lice
- Bartonella species

Most common organisms

- Staphylococcus aureus, and S. lugdunensis
- Enterococcus faecalis
- all streptococcal species except for Streptococcal pneumoniae and S. pyogenes
- Granulicatella spp.
- Abiotrophia spp.
- Gemella spp.
- HACEK group (Haemophilus spp., Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae)

Most common organisms

- Additional pathogens considered typical in the setting of intracardiac prostheses include
- coagulase negative staphylococci
- Corynebacterium striatum and C. jeikeium
- Serratia marcescens
- Pseudomonas aeruginosa
- Cutibacterium acnes
- non-tuberculous mycobacteria (especially Myobacterium chimaerae)
- Candida spp.

Treatment guides

- Drug selection is initially guided by Gram-stain until definitive identification antibiotic sensitivities are available.
- If an acute presentation (days), native valve, treat for Staph. aureus, β-hemolytic Strep., and aerobic Gram-negative bacilli until culture results available.
- Consider vancomycin (target trough concentration of 15-20 mcg/mL) plus cefepime 2 g IV every 8 hours.

Treatment guides

- Drug selection is initially guided by Gram-stain until definitive identification antibiotic sensitivities are available.
- If a subacute presentation (weeks), native valve, treat for Staph. aureus, Strep. viridians, HACEK, and Enterococcus until culture results available.
- Consider consider vancomycin (target trough concentration of 15-20 mcg/mL) plus ampicillin-sulbactam 3 g IV every 6 hours.

Treatment guides

- If prosthetic valve and <1yr has passed since placement, treat for Staph., Enterococcus, and aerobic Gram-negative bacilli until culture results available.
- Consider vancomycin (target trough concentration of 15-20 mcg/mL) plus gentamicin 1 mg/kg IV every 8 hours and cefepime 2 g IV every 8 hours
- If staphylococcal prosthetic valve endocarditis is identified, rifampin can be added 3-5 days after culture clearance

Treatment guides

- If prosthetic valve and >1yr has passed since placement, treat for Staph., Strep. Viridians, and Enterococcus until culture results available.
- Consider vancomycin (target trough concentration of 15-20 mcg/mL) plus ceftriaxone 2 g IV every 24 hours

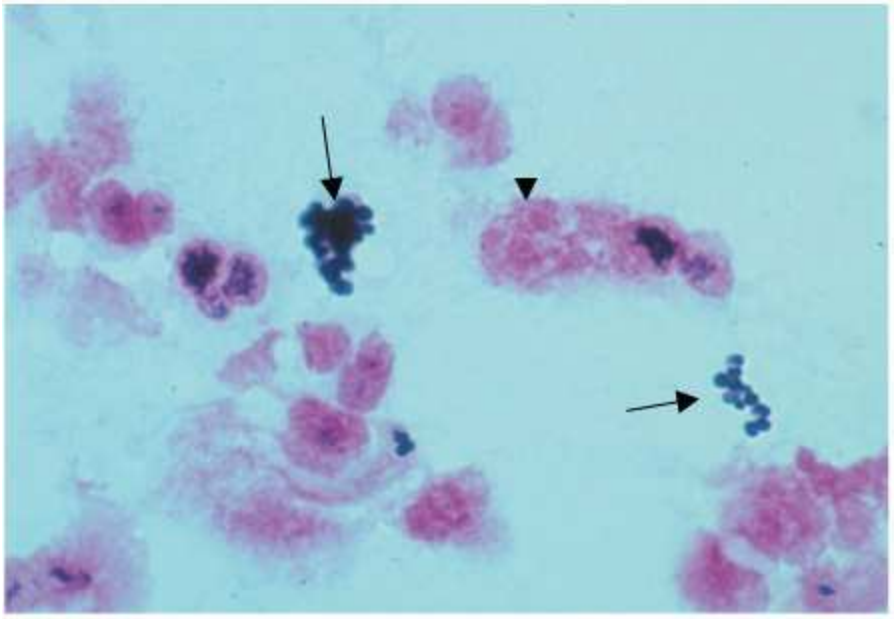
- Antifungal therapy is generally not started empirically.

- No routine anticoagulation

Treatment guides

- Indications for surgery
- Heart failure due to valvular dysfunction
- Left-sided endocarditis due to *Staphylococcus aureus*, fungi or highly resistant organisms
- Persistent bacteremia despite therapy
- Cardiac complications such as annular or aortic abscess and heart block.

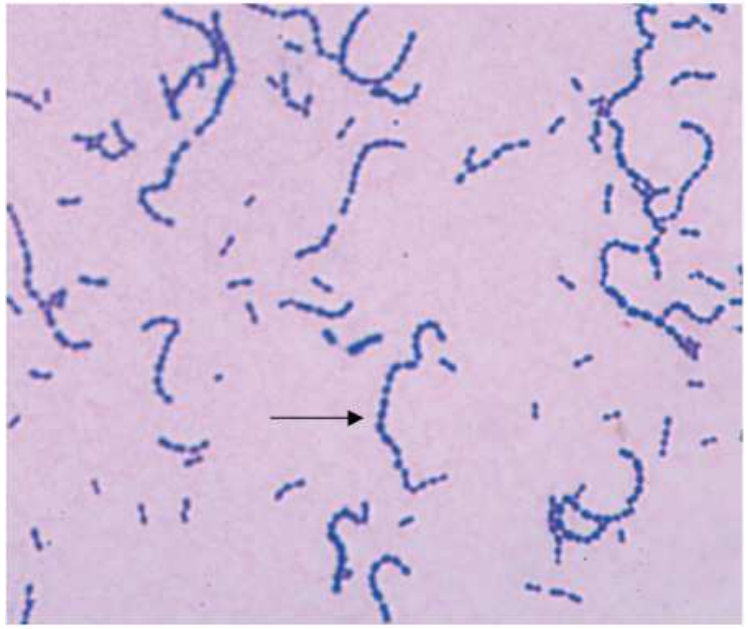
Gram positive cocci



Source: Levinson W: *Review of Medical Microbiology and Immunology*, 10th Edition: http://www.accessmedicine.com

In clusters. Staphylococcus.

Color plate 1 Accessed 07/01/2010

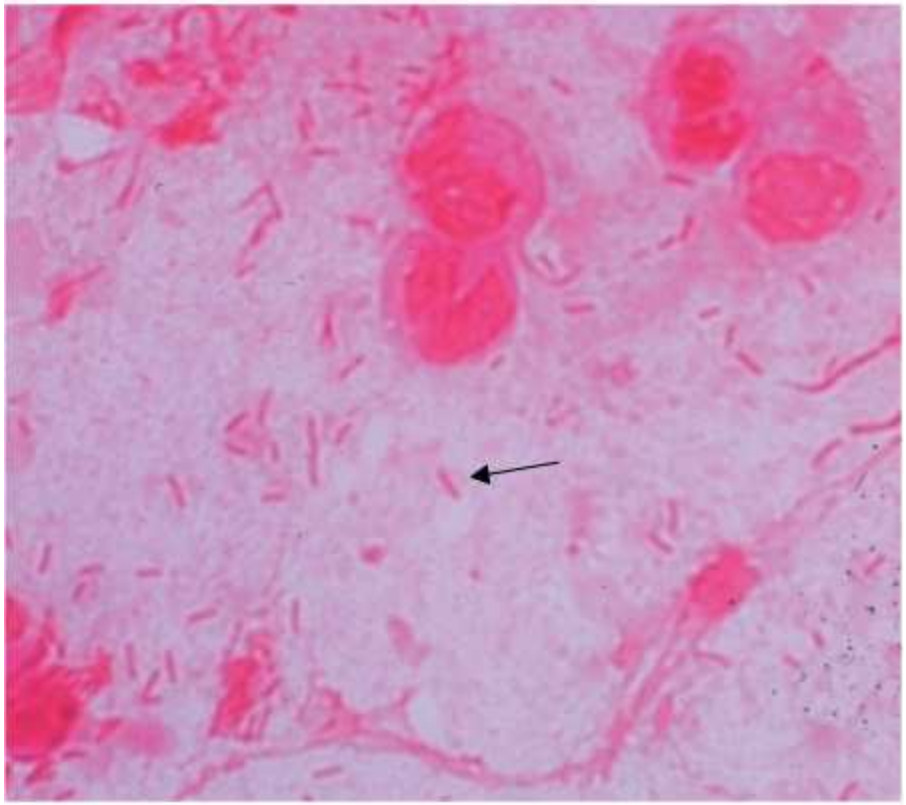


Source: Levinson W: *Review of Medical Microbiology and Immunology*, 10th Edition: http://www.accessmedicine.com

In chains. Streptococcus.

Color plate 2 Accessed 07/01/2010

Gram-negative bacilli



Source: Levinson W: *Review of Medical Microbiology and Immunology*, 10th Edition: http://www.accessmedicine.com

Arrow points to a gram-negative rod.

Provider: Professor Shirley Lowe, University of California, San Francisco School of Medicine. With permission.

Color plate 8 Accessed 08/01/2010

Treatment

- Native valve endocarditis (Strep. viridians or Strep. Bovis)
- 4 weeks therapy as minimum
- Penicillin G or Ceftriaxone
- If rapidly resolving and no renal disease is present, gentamicin may be added and the duration of therapy may be shortened to 2 weeks.
- Vancomycin is substituted for those who cannot tolerate penicillin or ceftriaxone.

Treatment

- Native valve endocarditis (Methicillin sensitive Staph. Aureus) is best treated with a β-lactam antibiotic.
- Six weeks of therapy
- Nafcillin is preferred to cefazolin if:
- Brain abscess present
- Complicated right sided endocarditis.
- Cefazolin is acceptable for those with non-anaphylactoid reactions to penicillin.
- Neither rifampin nor clindamycin should be used as associated with higher levels of relapse.

Treatment

- Methicillin resistant Staph. aureus left sided endocarditis
- 6 weeks therapy
- Vancomycin with daptomycin
- OR daptomycin
- Surgical intervention is generally avoided in cases of intravenous drug use.

Treatment

- In the presence of prosthetic valves or other prosthetic material
- 6 weeks of therapy
- vancomycin and rifampin
- with gentamycin limited to the first two weeks
- Effective for coagulase negative Staph. as well as Staph. Aureus.

Treatment

- E. fecails is generally the enterococcus isolated.
- Frequently it is resistant to aminoglycosides.
- Ceftriaxone with ampicillin for six weeks is effective therapy.
- Ceftriaxone therapy for 4 weeks is effective for treating HACEK organisms; 6 weeks, if prosthetic valve.

Treatment

- Non-HACEK Gram-negative bacilli
- 6 weeks treatment
- β-lactam antibiotic and an aminoglycoside
- OR fluoroquinolone
- Surgical removal of the valve is often required.

Indications for Surgical Intervention

Fifty percent of infected valves are replaced to both control the infection and restore function.

- Vegetation
- Persistent vegetation after systemic embolization
- Anterior mitral leaflet vegetation, particularly with size >10 mm
- ≥1 Embolic events during first 2 wk of antimicrobial therapy
- Increase in vegetation size despite appropriate antimicrobial therapy

Indications for surgical intervention

- Valvular dysfunction
- Acute aortic or mitral insufficiency with signs of ventricular failure
- Heart failure unresponsive to medical therapy
- Valve perforation or rupture
- Perivalvular extension
- Valvular dehiscence, rupture, or fistula
- New heart block

- Large abscess or extension of abscess despite appropriate antimicrobial therapy

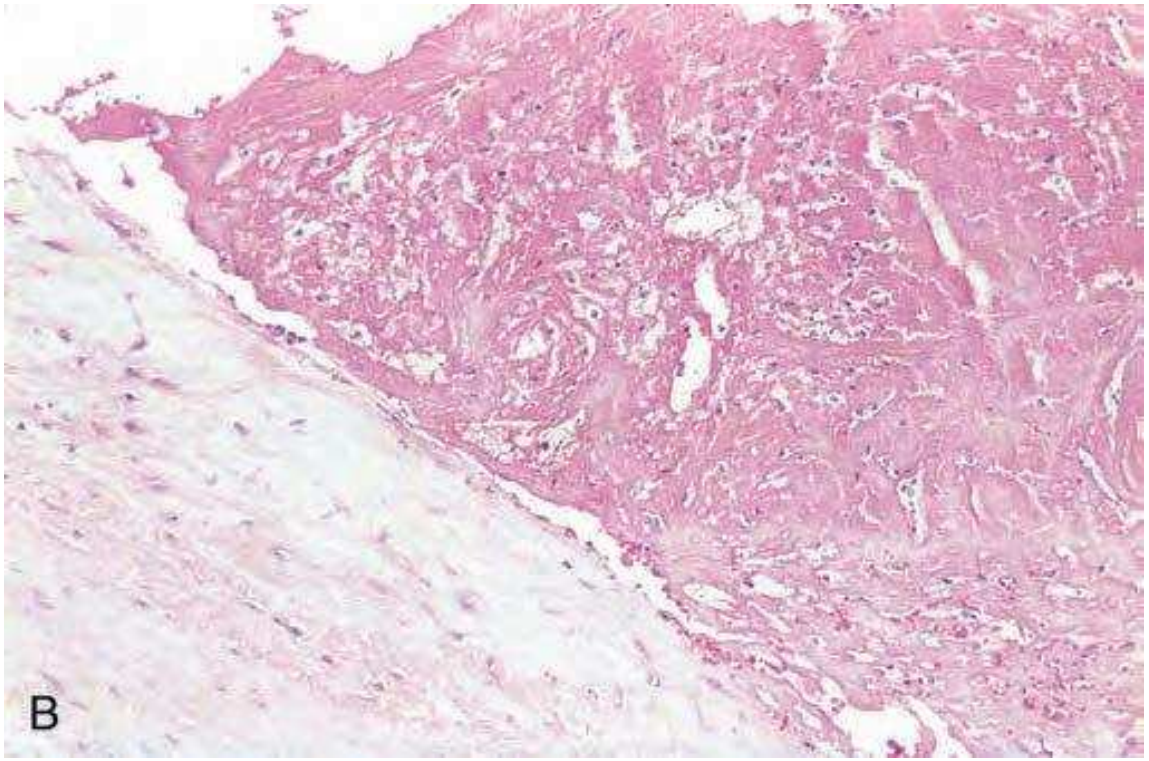
Monitor therapy

- Two sets of blood cultures are drawn every 24-48 hours until bloodstream infection clears.
- If operative tissue cultures are positive, follow with an entire course of antibiotic therapy.
- Anticoagulation is problematic.
- Life-long endocarditis prophylaxis before any minor surgical procedure.
- Life-long azole therapy if treated fungemia.

Non-thrombotic bacterial (marantic) endocarditis

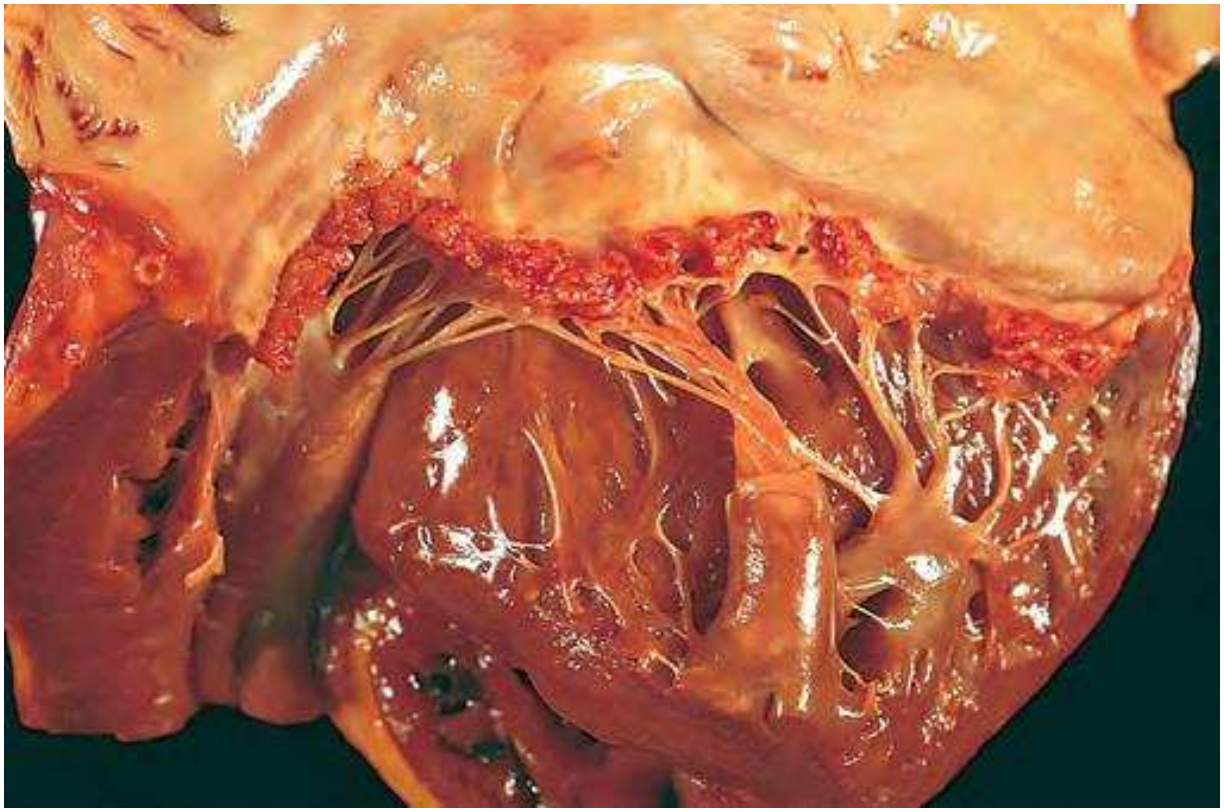
- Sterile verrucous vegetations (thrombus cap)
- No inflammatory infiltrate in tissue
- Frequently occurs concomitantly with deep venous thromboses or pulmonary emboli (hypercoagulable state)
- Procoagulant effect of circulating mucin from mucinous adenocarcinomas. (Trousseau syndrome)
- Similar lesions are seen in antiphospholipid syndrome.
- Indwelling vascular catheters also associated with similar changes on heart valves
- Rarely embolize.

Non-thrombotic bacterial (Marantic) endocarditis



Schoen, and FJ, Mitchell, RN, “Heart”, in Kumar, V, Abbas, AK, Aster, JC (eds.), Robbins and Cotran Pathologic Basis of Disease, 9th edition. 2015. Elsevier. Philadelphia. Fig. 12-26B.

Non-thrombotic bacterial (Marantic) endocarditis

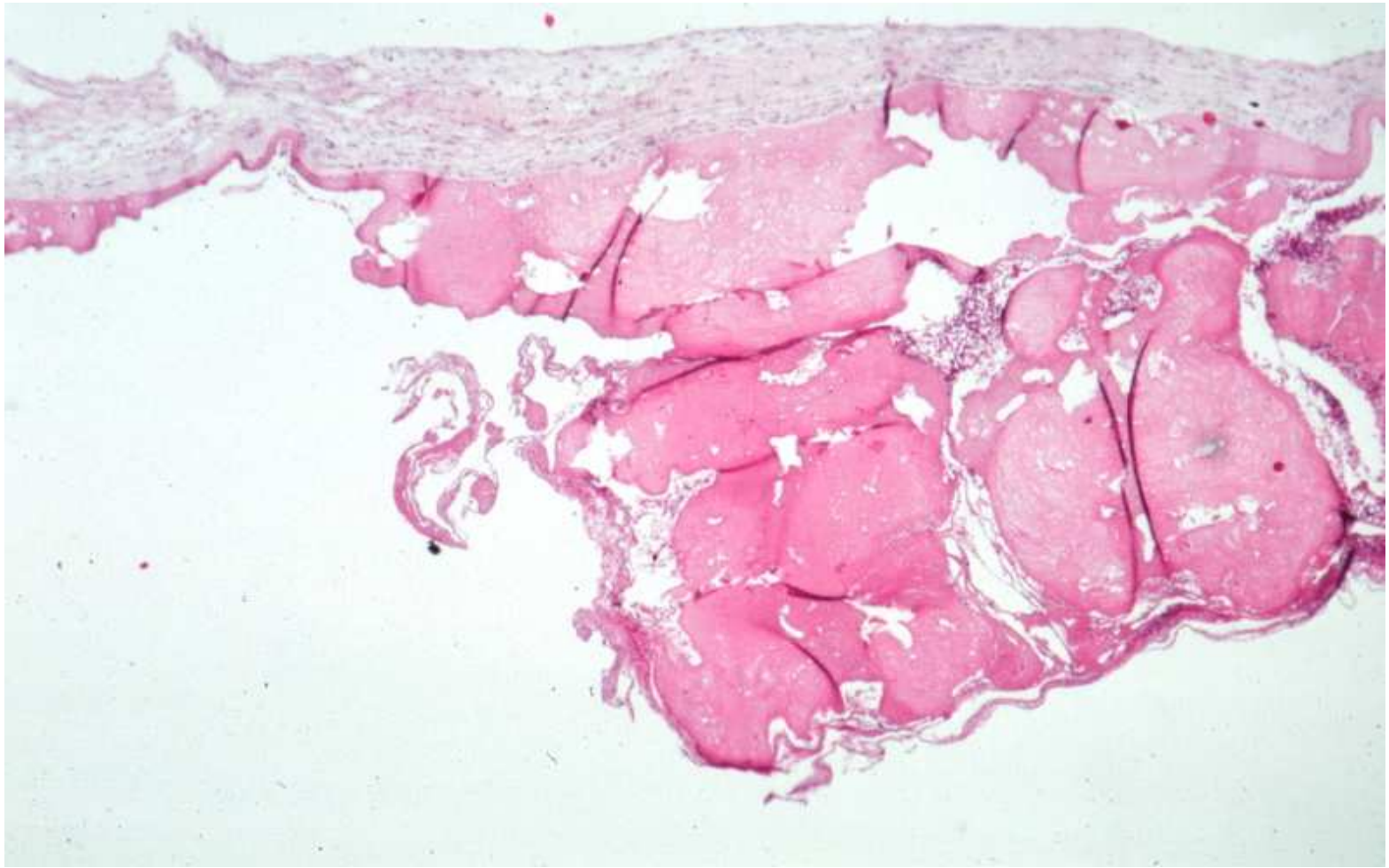


Schoen, and FJ, Mitchell, RN, “Heart”, in Kumar, V, Abbas, AK, Aster, JC (eds.), Robbins and Cotran Pathologic Basis of Disease, 9th edition. 2015. Elsevier. Philadelphia. Fig. 12-26A.

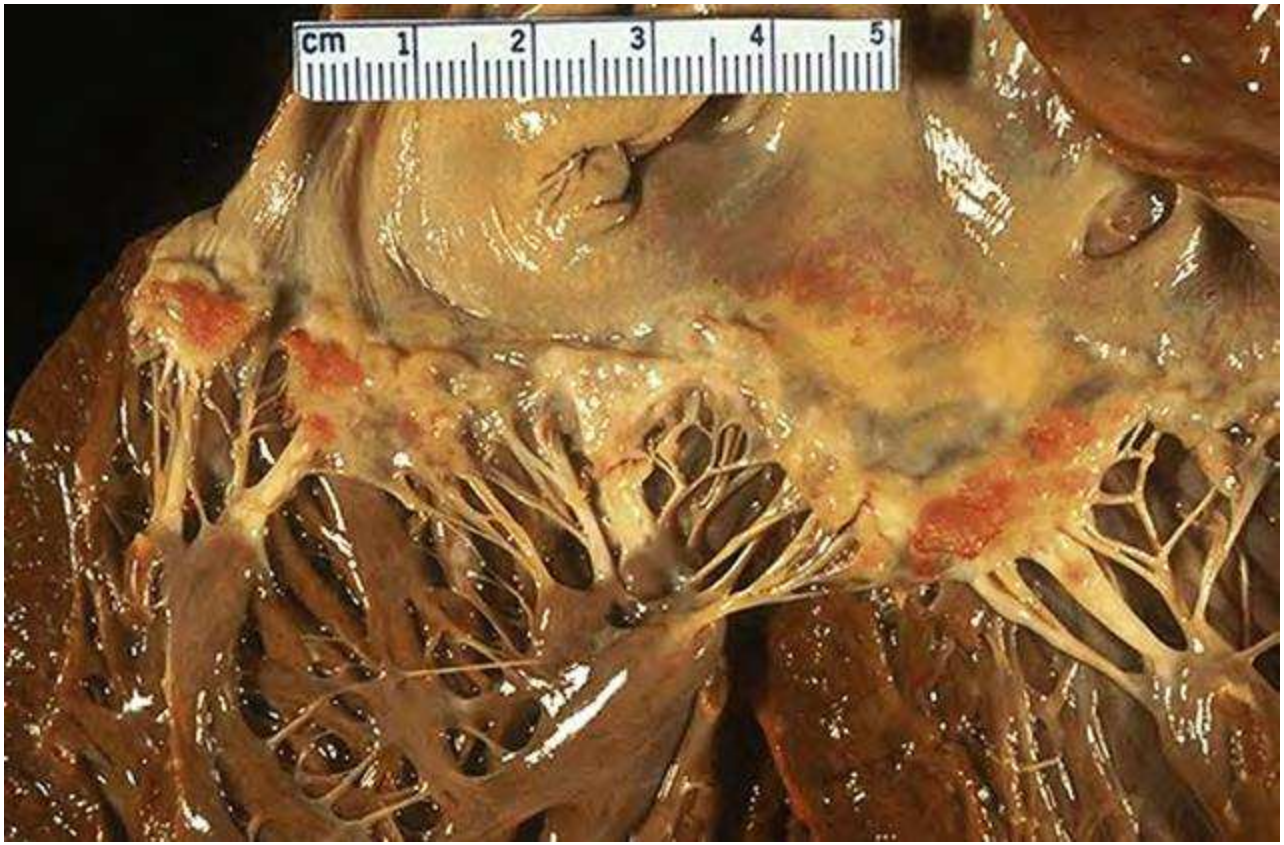
Liebman-Sacks endocarditis

- Small, sterile vegetations
- Fibrinoid necrosis along undersurface of mitral and tricuspid valves, chordae tendinae, valvular or mural endocardium
- There is a valvulitis present.
- Fc-receptor-bearing cells are recruited in the inflammatory response.
- Do not embolize.
- May lead to mitral regurgitation; however, are often not clinically important.
- Occur in up to 25% of patients with Systemic Lupus Erythematosus (seropositive).

Liebman-Sacks endocarditis



Liebman-Sacks endocarditis

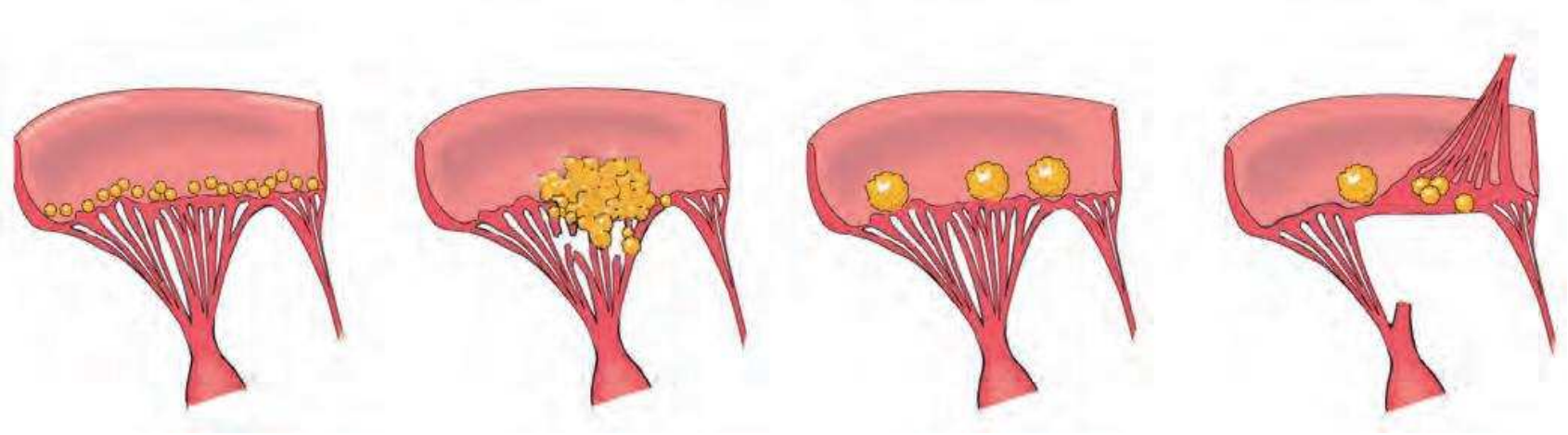


Klatt, EC, Robbins and Cotran Color Atlas of Pathology. (2015) Elsevier. Philadelphia. Fig. 2-64

Rheumatic heart disease

- Rheumatic phase
- Immune complexes circulating
- Small, verrucous lesions may be found all along the mitral valve as well.
- Sterile

Vegetation distribution



RHD **IE** **NTBE** **LSE**

Schoen, and FJ, Mitchell, RN, “Heart”, in Kumar, V, Abbas, AK, Aster, JC (eds.), Robbins and Cotran Pathologic Basis of Disease, 9th edition. 2015. Elsevier. Philadelphia. Fig. 12-24.