Cardiovascular System

Pathology of rheumatic fever, endocarditis and heart

Objectives:

At the end of this lecture, the students should be able to:

- → Understands the clinicopathological features of rheumatic heart disease, which is a major cause of acquired mitral and aortic valve diseases in the Kingdom of Saudi Arabia.
- → Know the pathological causes and pathophysiological consequences of stenosis and incompetence of all the cardiac valves but particularly the mitral and aortic valves.
- → Understands the pathology of infective endocarditis so as to be able to identify patients at risk and when appropriate ensure prophylactic treatment is given.

المحاضرة مربوطة بمعلومات في محاضرة المناعة والمايكرو فذاكروها قبلها

Key principles to be discussed:

(1) Pathology and manifestations of rheumatic heart disease as a major cause of valvular diseases in the Middle East and Saudi Arabia.

(2) Complications of rheumatic heart disease including atrial fibrillation, valvular and atrial thrombus formation with systemic embolism, cardiac failure and infective endocarditis.

(3) Infective endocarditis: predisposing factors, clinical acute and subacute forms, common pathogenic bacteria in IE and complications including valve perforation, thrombosis and septic embolization of the vegetations.

(4) Causes and consequences of valvular heart disease with special emphasis on aortic and mitral valve including "floppy or prolapsed" mitral valve.

Rheumatic fever:

- **Introduction:**

  Rheumatic heart disease is a heart disease caused by rheumatic fever. It could be an **acute** or **chronic** rheumatic heart disease.

  (Also called as acute rheumatic heart disease or acute rheumatic carditis/pancarditis)

  Rheumatic fever (RF) is a major health problem in 3rd world countries and in crowded, low socioeconomic urban areas.

  - Occurs in only ***3%*** of patients with **group A streptococcal pharyngitis**
  - Seen mainly in children, **5 to 15 years** of age.
  - Fortunately, the incidence and mortality of RF has declined over the past 30 years (due to improved socioeconomic condition and rapid diagnosis and treatment of strep. pharyngitis). But the disease is still very common in the Middle East and Saudi Arabia.

- **Definition:**

  RF is an acute, **immune mediated**, multi-system inflammatory disease that occurs a few weeks after, group A-beta hemolytic streptococcal infection. It's a **non-suppurative**[1] inflammatory disease with cardiac and extracardiac manifestations.

  - The inflammation is mainly in the heart, CNS, joints and skin.

- **Pathogenesis:**

  - It is linked to streptococcal infection.
  - Disease occurs 1 to 5 weeks **after** pharyngeal infection by ***Group A beta -Hemolytic Streptococcus,*** ***(***An elevated titer of antistreptolysin O (ASO) is evidence of a recent streptococcal infection.) however, the pathogenesis of RF remains unclear.
  - It is most likely **immune mediated** in which the causative organisms (streptococci) result in the formation of **antibodies.**
  - Those antibodies **cross react** with certain antigens in the heart and joints (because they are similar to streptococcal antigen, i.e. **M-protein**) by activating **Th - CD4 cells.**

    باختصار البكتريا تحتوي على الـ(M-protein) فلما تدخل الجسم لأول مرة، الجسم راح ينتج أجسام مضادة لهذا البروتين، لكن هذا البروتين موجود في جسم الإنسان بصورة طبيعية، فبالتالي الأجسام المضادة راح تهاجم الأعضاء اللي فيها البروتين وتسبب مشاكل فيها.

    تبدأ المشكلة من المناعة وتهاجم أكثر من عضو الى أن تؤدي الى تغيرات في القلب

  - The mechanism of its damage to the heart is not yet understood.
  - Repeated attacks or a single severe first attack can cause **chronic rheumatic heart disease** leading to **congestive cardiac failure.**

[1] Pertaining to inflammation without the production of pus

Cardiac Manifestations of Rheumatic Fever:

We can say there's pancarditis when the inflammation includes all three layers of the heart (endocardium, myocardium and pericardium).

- **Pericarditis:**
  - → Fibrinous or serofibrinous secretion in the pericardium.
  - → These secretions collect between the visceral and parietal pericardium like butter between two slices bread and therefore also called "bread and butter" pericarditis.
  - → May result in pericardial, pleural or other serous effusions.

- **Myocarditis:**
  1. We can see many Aschoff bodies.
  2. May lead to cardiac failure and is the cause of most deaths occurring during the early stages of acute rheumatic fever.

- **Endocarditis:**
  - Rheumatic endocarditis usually occurs in areas subject to greatest hemodynamic stress, such as the points of valve closure and the posterior wall of the left atrium, resulting in the formation of the so-called MacCallum plaque.
  - The mitral and aortic valves, which are subjected to much greater pressure and turbulence, are more likely to be affected than are the tricuspid and pulmonary valves.
  - Inflammation of the endocardium including the heart valves (valvulitis) and chordae tendineae.
  - It results in fibrin deposition on valve leaflets forming tiny, pale thrombi along lines of closure called rheumatic vegetations.
  - Mitral and aortic valve are mainly involved.
  - Aschoff bodies/nodules are uncommon in the valves.
  - This acute inflammation may:
    - Resolve completely.
    - Progress to scarring with development of chronic fibrotic deformities of the heart valves and chordae tendineae leading to chronic rheumatic heart disease many years later.

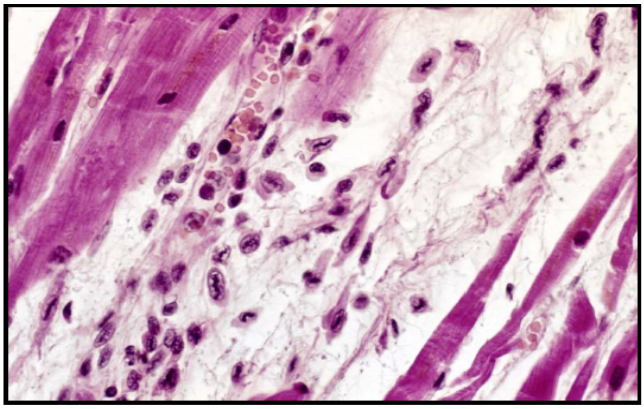
- **Subendocardial Lesions:**
  Can also be seen, commonly in the left atrium called as MacCallum plaques.

Morphology and Biopsy Findings:

- Acute rheumatic fever: is characterized by discrete inflammatory foci within a variety of tissues.

Aschoff Bodies: These myocardial inflammatory lesions (classic lesion of rheumatic fever.) are collections of:

- Lymphocytes (primarily T cells)
- Scattered plasma cells
- Plump activated macrophages (Anitschkow cells).
- A focus of eosinophilic collagen (representing the site of antibody-antigen reaction)
- Chronic inflammation.



Aschoff Bodies

1. They are situated next to small arteries and are characteristically seen in the myocardium (rheumatic myocarditis).
2. They ultimately "heal" by fibrosis resulting in a nodule of scar tissue.
3. They appear in a late stage of the disease.

Another term: Aschoff nodules: are collection of chronic inflammatory cells (especially macrophages -histiocytes-). They are large, have a lot of cytoplasm & central wavy nucleus. They are surrounded by lymphocytes, plasma cells, giant cells and collagen necrosis.

Aschoff nodules Mostly found in hemodynamic areas where blood is always flowing:

- Can be found in all 3 layers of the heart (pericardium, myocardium and endocardium).
- The cusps of the valves.
- Posterior wall of the left atrium (MacCallum Plaque).

Rheumatic vegetations:

1. Tiny (size of a pin's head), sessile arranged in a row and firmly fixed with the underlying tissue.
2. These are situated in the valve cusp, a few millimeters away from the free margin (this is the most traumatized area).

- Chronic rheumatic heart disease:

Characterized by organization of the acute inflammation and subsequent scarring.

What happens here?

- Aschoff bodies are replaced by fibrous scar
- The mitral valves exhibit:

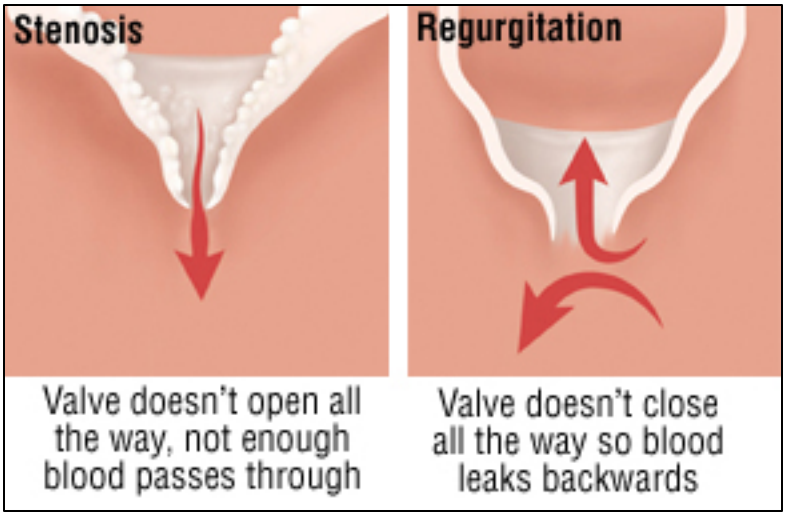
A. Leaflet thickening.
B. Commissural fusion and shortening.
C. Thickening fusion of the chordae tendineae.

- Fibrous bridging across the valvular commissures and calcification create "fish- mouth" or "buttonhole" stenoses.

The most important functional consequence of rheumatic heart disease is **valvular stenosis and regurgitation**.

As a result, fibrosis causes two conditions:

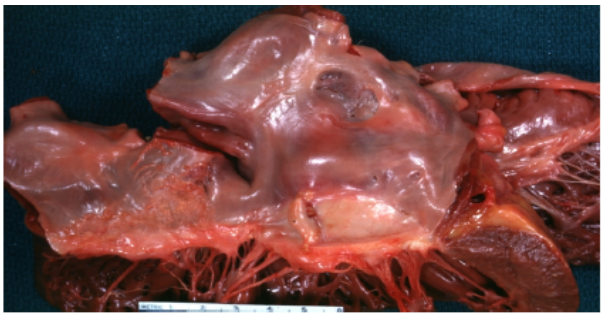
A. **Stenosis** of the valves.
B. **Regurgitation**:
    - **Mitral valve** → Blood will flow back from ventricle to atrium during contraction.
    - **Aortic valve** → Aortic regurgitation towards the left ventricle.



- The mitral valve alone is involved in 70% of cases.
- Combined mitral and aortic disease in another 25% of the cases.
- The tricuspid valve usually is less frequently (and less severely) involved (5%).
- The pulmonic valve almost always escapes injury.

In the findings of biopsy:

- **The pericardium** exhibits a **fibrinous exudate**, which generally resolves without sequelae.
- **The myocardial** scattered **Aschoff bodies** within the interstitial connective tissue.
- **Valve involvement** results in **fibrinoid necrosis** and **fibrin deposition** along the lines of closure vegetations that cause little disturbance in cardiac function.
- **Subendocardial lesions** can also be seen, commonly in left atrium called as MacCallum plaques



MacCallum plaques

Clinical Features:

- Manifests years or decades after the initial episode of rheumatic fever.
- Signs and symptoms depend on the valve(s) involved: cardiac murmurs, hypertrophy, dilation, congestive heart failure, arrhythmia, thromboembolism and infective endocarditis.
- Treatment may require valve surgery.

Diagnosis of rheumatic fever:

- Checking the joints for signs of inflammation.
- Checking for fever.
- Examining the skin for nodules under the skin or a rash.
- Listening to the heart for abnormal rhythms, murmurs or muffled sounds that may indicate inflammation of the heart.
- Conducting a series of simple movement tests to detect indirect evidence of inflammation of the central nervous system.
- Stethoscope → Murmur caused by stenotic valve (fish mouth orifice).
- Echocardiogram → uses sound waves to produce live-action images of the heart.
- X-ray or CT-scan → Hypertrophy in left atrium & ventricle.
- Neurologically → might find thrombus caused by atrial fibrillation.
- Serum titers show elevation in streptolysin O.

Jone's criteria:

It is used for the diagnosis of rheumatic fever. Divided into major and minor criteria. If the patient got one major & two minor **or** two major and zero minor then he has the disease.

Minor criteria:

- History of fever and arthralgia (joint pain without clinically evident inflammation.)
- Leukocytosis (increase neutrophils count).
- Laboratory finding increase in (ESR, CRP (C-Reactive protein)).
- ECG changes (prolongation of PR segment).
- Previous rheumatic fever or rheumatic heart diseases.

Major criteria:

- **Pancarditis:**

  Which means (Pericarditis, Myocarditis, Endocarditis). The valves are affected because they are covered by endocardium, so they are part of endocarditis.

- **Migratory polyarthritis**:

  It's "fleeting arthritis" in the large joints e.g. wrist, knee, ankle, elbow, etc. It is self-limiting with no chronic deformities. Aschoff bodies may be present in the synovial membrane, joint capsule, ligament etc. with joint effusion.

- **Sydenham chorea ((St. Vitus' dance)**:

  The CNS is affected by the immunological reaction - especially the basal ganglion - → causes involuntary movements of the musculoskeletal system, behavioral and personality changes. (This occurs late in the disease.)

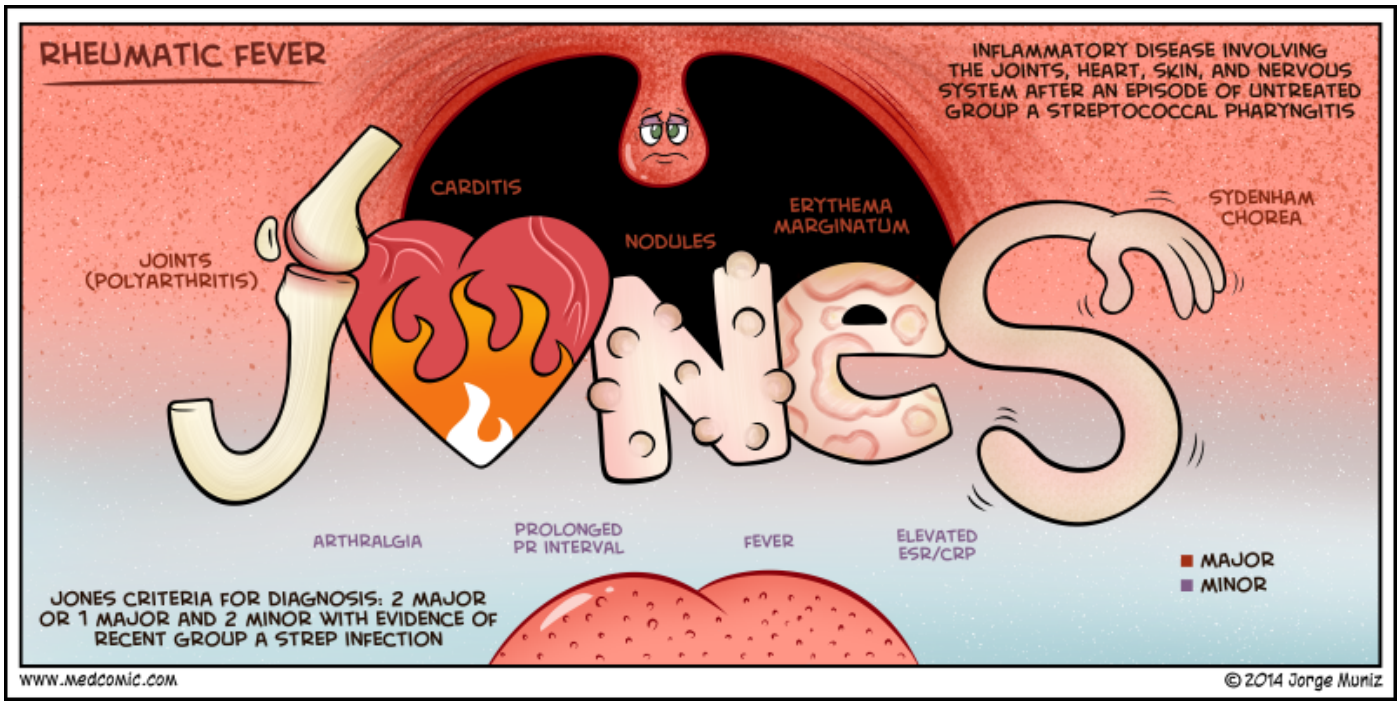
- **Erythema marginatum**:

  A distinctive skin rash characteristic of rheumatic fever, often involving the trunk and extremities.

- **Subcutaneous Nodules (Rheumatic nodules)**:

  Small painless swelling usually over bony prominences

Summary of Jone's Criteria:



Complications of Rheumatic Fever:

- → **Valve regurgitation:**

  This condition is a leak in the valve, which allows blood to flow in the wrong direction.

- → **Damage to heart muscle**.

  The inflammation associated with rheumatic fever can weaken the heart muscle, resulting in poor pumping function.

- → **Heart failure**: an inability of the heart to pump enough blood to the body
- → **Left atrium hypertrophy** causes atrial fibrillation → stagnation of blood → forming blood clot (thrombus) → could cause brain stroke or heart failure.
- → **Rheumatic fever can cause senile calcific aortic stenosis**.
- → **Bacterial infective endocarditis:**

  The scarred valves of rheumatic heart disease provide an attractive environment for bacteria to grow.

- → **Adhesive pericarditis.**

Infective Endocarditis

It's an infection of the cardiac valves or mural surface (الجدار السطحي) of the endocardium. Resulting in the formation of an adherent mass of thrombotic debris and microorganisms.

Infective endocarditis is very hard to treat because of the avascular nature of the heart valves.
(صعب يوصله أي شي تذكر العظام الصغيرة في اليد اذا كسرت ما تنشفي بسرعة لنفس السبب)

Infective endocarditis is divided based on the tempo (progression) and severity, into 2 major groups:

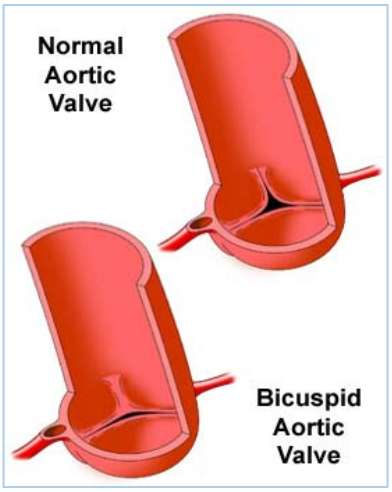
- **Acute Endocarditis:**
  - It's a very rare disease and is caused by **highly virulent organisms** (staphylococcus aureus).
  - It's often secondary to infection occurring elsewhere in the body such as bronchiectasis or brain abscess.
  - Because it is highly virulent, it has a high progression rate and can infect even healthy valves. (It also has little local host reaction because of its high progression)
  - Capable of causing substantial morbidity and mortality even with appropriate antibiotic therapy and/or surgery.

  Quick summary of acute endocarditis:
  1-Caused by **highly virulent organisms** (staphylococcus aureus).
  2-Has high progression rate.
  3-Infects healthy valves.

- **Subacute Endocarditis:**
  - Refers to infections by organisms of low virulence involving a previously abnormal heart, especially deformed valves.
  - Streptococcus viridans is the underlying cause in 50-60% of the cases.
  - In both acute and subacute forms, there are friable bulky and potentially destructive vegetation (composed of fibrin, inflammatory cells and microorganisms) on the heart valves.
  - Progresses slowly, unlike the acute form.
  - As mentioned before, subacute form usually happens due to a predisposing cause, like:
    1- Congenital heart disease.
    2- Rheumatic fever (most common).
    3- Prosthetic valves.

Predisposing Factors:

Infective endocarditis can develop on previously normal valves, but cardiac abnormalities predispose to such infections:



- Congenital heart disease: in children.
- Bicuspid aortic valve:

  It is a congential abnormality of the aortic valve where the two of the aortic valvular leaflets fuse during development resulting in bicuspid instead of tricuspid valve.
- Rheumatic heart disease.
- Mitral valve prolapse. (Most common site for IE)
- Atrial septal defect:

  A hole in the wall between the two upper chambers of the heart (atria) it is a congenital cardiac anomalies presenting in adulthood.
- The elderly due to degenration of heart valves (e.g. calcific aortic stenosis), diabetics and pregnant women are at increased risk.
- Prosthetic heart valves:

  It's in 10% of all cases, caused commonly by coagulase-negative staphylococci (e.g. S.epidermidis)
- Intravenous drug abusers:

  Commonly caused by S.aureus (common to skin), they may inject microorganisms intravenously when taking the injection under non-sterilizing conditions that may cause endothelial damage.
  - The tricuspid valve is infected in half of cases.
- Transient bacteremia:

  From any procedure may lead to infective endocarditis (e.g. Dental procedures, urinary catheterization, infected indwelling vascular catheters gastrointestinal endoscopy, and obstetric procedures).

  Remember the difference between bacteremia and septicemia?

  Bacteremia: is the presence of the bacteria in the blood.

  Septicemia: is the presence and multiplication of the bacteria in the blood.
- The causative organisms differ depending on the underlying risk factors. 50-60% of all cases occurring in damaged or deformed valves are caused by streptococcus viridans; UNLIKE the more virulent S.aureus that can infect the damaged valves as well as the healthy and its responsible of 10% of all cases.

Complications:

- Valve ulceration and perforation, rupture of chordae tendineae,
- Arrhythmias, valvular regurgitation and congestive heart failure (due to destruction of a valve).
- Septicemia or septic systemic embolization of infected vegetations which travel to multiple sites, causing infarcts or abscesses in many organs (e.g. Neurologic deficits due to embolization to the brain or infarcts of the myocardium due to embolization to the coronary artery),
- Pulmonary emboli is seen in tricuspid valve/ right sided endocarditis e.g. Iv drug addicts.
- Mycotic/infected aneurysms of vessels.
- Renal failure the renal glomeruli may be site of focal glomerulonephritis (focal necrotizing glomerulitis) caused by immune complex disease or by septic emboli.

Other types of Endocarditis:

1. Non-Bacterial Thrombotic Endocarditis (NBTE) – Marantic endocarditis

It's a paraneoplastic syndrome which causes sterile vegetations on the valves as a result of ↑ coagulability secondary to ↑ mucin production.

Characterized by the deposition of small masses of fibrin, platelets, and other blood components on the leaflets of the cardiac valves (sterile). There is no infective organism. It is aseptic. Aortic valve is the most common site. The fibrin deposits are randomly arranged. May embolize to different parts of the body including brain, but the emboli are sterile.

Complications:

- Chordae tendineae rupture.
- Emboli.
- Glomerulonephritis.
- Suppurative pericarditis.

NOTE: "MARANTIC" DERIVES FROM "MARASUMUS" WASTING ASSOCIATED WITH CANCER

Pathogenesis/ association:

- Subtle endothelial abnormalities.
- Hypercoagulability.
- Association with malignancy (50%) and other debilitating diseases.
- This form of endocarditis associated with debilitating disorders, such as metastatic cancer and other wasting conditions.
- Characteristics include small, sterile fibrin deposits randomly arranged along the line of closure of the valve leaflets.

Risk factors:

- Mucinous adenocarcinomas "Cancer".
- Immunocompromised.
- Advanced chronic diseases.

Treatment:

Anticoagulant therapy, but cardiac vegetations may require surgical intervention in rare instances.

2. Libman-Sacks endocarditis (LSE) Less common, noninfective,
   Sterile vegetations caused by systemic lupus erythematous (SLE).
   Usually asymptomatic but mitral regurgitation murmur can be heard.
   The lesions probably develop as a consequence of immune complex deposition and thus exhibit associated inflammation, often with fibrinoid necrosis of the valve substance adjacent to the vegetation.

   Dystrophic Calcification:
   It's calcification of necrotic tissue associated with normal calcium level and caused by local inflammation.

   Complications:
   - Fibrosis causes retraction of chordae tendineae → causes incompetence → uncontrolled blood flow → heart failure.
     يعني: يتسبب في انكماش وانقباض في الاوتار اللي تمسك ال CUSPS > يؤدي الى عدم اغلاق كامل للصمام > تدفق دم غير منتظم > فشل في القلب
   - Because these vegetation are very friable, they shoot septic emboli → could cause brain abscess.
     ممكن الحبيبات (vegetation) تنطلق في الدم وتصل الى الدماغ مما يسبب ال Brain Abscess

3. Endocarditis of carcinoid syndrome:
   - Secretory products of carcinoid syndrome, especially 5-hydroxytryptamine can cause endocarditis.
   - The valves on the left side of the heart are rarely involved, because serotonin and other carcinoid secretory products are detoxified in the lung.
   - This form of endocarditis results in thickened endocardial plaques characteristically involving the mural endocardium or **the valvular cusps of the right side of the heart.**

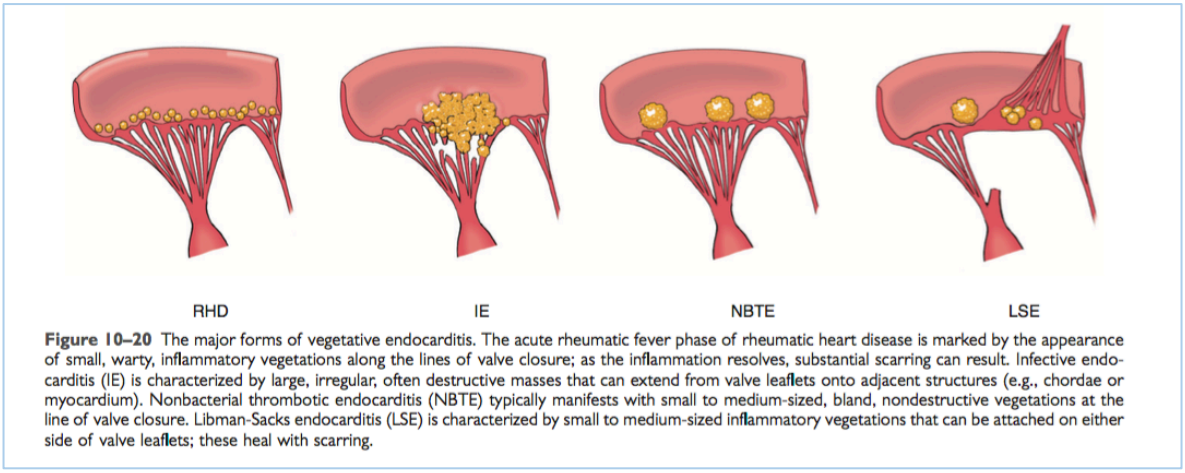


Figure 10–20 The major forms of vegetative endocarditis. The acute rheumatic fever phase of rheumatic heart disease is marked by the appearance of small, warty, inflammatory vegetations along the lines of valve closure; as the inflammation resolves, substantial scarring can result. Infective endocarditis (IE) is characterized by large, irregular, often destructive masses that can extend from valve leaflets onto adjacent structures (e.g., chordae or myocardium). Nonbacterial thrombotic endocarditis (NBTE) typically manifests with small to medium-sized, bland, nondestructive vegetations at the line of valve closure. Libman-Sacks endocarditis (LSE) is characterized by small to medium-sized inflammatory vegetations that can be attached on either side of valve leaflets; these heal with scarring.

THE MAIN DIFFERENCES BETWEEN RHEUMATIC FEVER AND THE ENDOCARDITIS IS:

RHEUMATIC FEVER	ENDOCARDITIS
STERILE (IMMUNE REACTION)	NON-STERILE (SEPTICEMIA)
VEGETATION NEAR THE LINES OF CLOSURE (سطحي)	VEGETATION IS DEEP & INVOLVING THE WHOLE CUSP (إلى الداخل)

Valvular Heart Diseases:

Definition:

It's the damage or defect in one or more of the four heart valves. Most commonly affected are mitral and aortic valves, rare in tricuspid valve, and almost never in the pulmonary valve

Heart Valves Diseases Has Two Main Types:

(1) Stenosis: failure of the valve to open completely.
Valvular stenosis is almost always due to a primary cuspal abnormality and is virtually always a chronic process (e.g., calcification or valve scarring).

(2) Regurgitation (backflow) (incompetence, insufficiency): failure of the valve to close completely
Valvular insufficiency can result from:

- Either intrinsic disease of the valve cusps (e.g., endocarditis)
- Or disruption of the supporting structures (e.g., the aorta, mitral annulus, tendinous cords, papillary muscles, or ventricular free wall) without primary cuspal injury.

Stenosis or regurgitation can occur alone or together in the same valve.

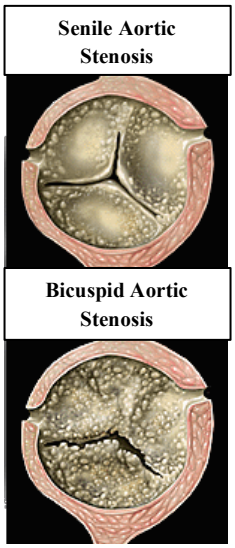
Causes:

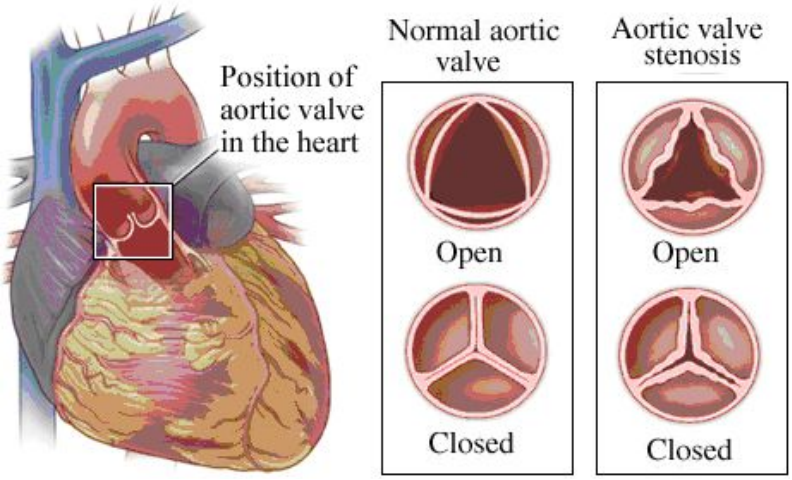
- Congenital (during embryo development). Most common congenital valvular lesion is a bicuspid aortic valve, containing only two functional cusps instead of the normal three.
- Secondary to thrombus and other diseases like infective endocarditis.
- Degeneration of the valve with age.
- Post inflammatory scarring (most common cause): A scar that occurs secondary or after an inflammatory process e.g. as a late result of rheumatic fever.
- Can occur even with prosthetic cardiac valves. Which are subject to physical deterioration or can be the site of thrombus formation or infectious endocarditis. They can also cause mechanical disruption of red blood cells resulting in hemolytic anemia with schistocyte formation.

Aortic Valve Diseases:

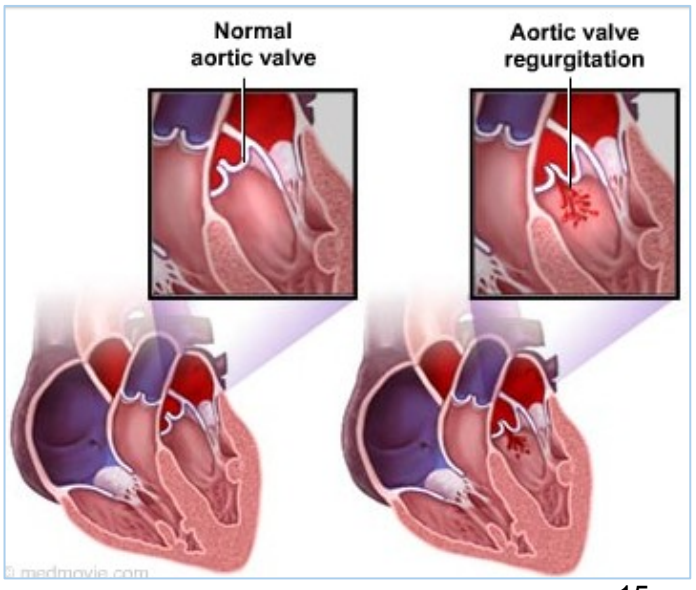
This valve along with mitral valve are frequently involved in RHD and infective endocarditis.

1) Aortic stenosis: (the valve not opening properly)
   Caused by calcification and normally seen in old patients (senile) thus sometimes called senile calcific aortic stenosis.
   What can calcific aortic stenosis also affect?
   - Normal aortic valve as part of the aging degenerative process seen in persons older than 60 years of age. It typically begins to manifest when patients reach their 70s and 80s
   - Congenital bicuspid aortic valve causing congenital aortic valvular disease. The onset with bicuspid aortic valves is at a much earlier age (often 40 to 50 years).
   - Valve affected and scarred by rheumatic heart disease. In this case, scarring may be evidence by fusion of the valve commissures.



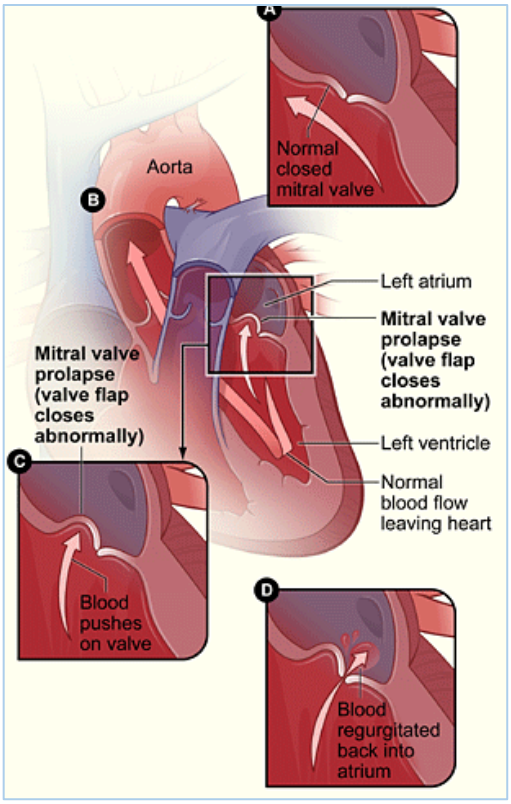


2) Aortic regurgitation: (the valve not closing properly thus allowing the leakage of blood from the ventricle) can be caused by:
   - RHD
   - Infective endocarditis
   - Non-dissecting aortic aneurysm. (Resulting from cystic medial necrosis.)
   - Syphilitic (luetic) aortitis (rare) with dilation of the aortic valve ring.

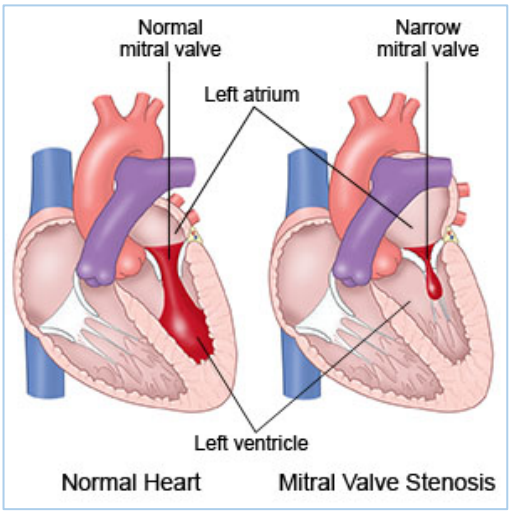


Mitral Valve Diseases:

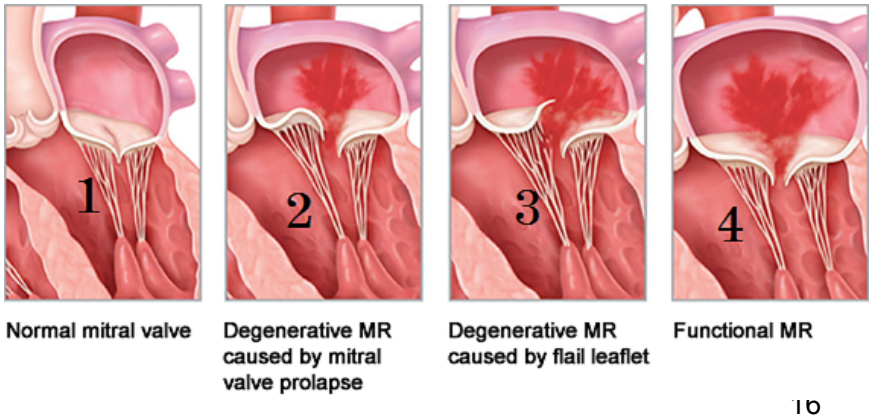
1) Mitral valve prolapse (also called myxomatous mitral valve) most commonly seen in developed countries it happens when one or more leaflets are floppy.
   - Unknown pathogenesis but can be associated with Marfan syndrome (very tall very thin) seen in young women.
   - Most patients are asymptomatic but can result in mitral insufficiency and arrhythmias. There is myxoid/mucoid degeneration of the valve, which causes ballooning of mitral valves (floppy cusp) results in stretching of the mitral valve, producing a parachute deformity of the cusp with prolapse of the cusp into the atrium during systole (they balloon back into the left atrium during systole).
   - These changes produce a characteristic systolic murmur. With a midsystolic click.



2) Mitral valve stenosis : (MORE COMMON THAN REGURGITATION)
Most commonly due to rheumatic heart disease.
Mitral stenosis leads to:
   - Leaflets become thickened, fibrotic and fused leading to fish mouth/ button hole deformity (stenosed valve looks like fish's mouth or button hole)
   - Increased pressure & dilatation and hypertrophy of the left atrium
   - Secondary Ca++ deposition.
   - Pulmonary hypertension and lungs are firm and heavy (chronic passive congestion).
   - May affect the right heart later (right ventricular hypertrophy)



3) Mitral valve regurgitation is usually a result of RHD, mitral valve prolapse, damage of the papillary muscle caused by myocardial infarction and Infective endocarditis.
Leads to left ventricular hypertrophy and dilatation. Stretching of the mitral valve ring.



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نايف الهادي	سمر العتيبي
ريان منيف	فرح مندوزا
فارس إبراهيم الورهي	منيرة العمري
قصي عبدالباقي عجلان	نوف العبدالكريم
أحمد طه الخياري	
زياد عبدالعزيز السالم	
مشعل الحازمي	

قال صلى الله عليه وسلم: من سلك طريقًا يلتمس فيه علمًا سهّل الله له به طريقًا إلى الجنة

دعواتنَا لكم بالتوفيق.