Congenital and acquired valve defects

Atherosclerosis

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Congenital Heart Disease (CHD) *Definition and importance*

- structural or functional abnormalities of the heart and great vessels
- arising during embryonic development
- present at birth (not always clinically apparent immediately)
  - **Incidence:** ~8–10 per 1,000 live births
  - most common congenital malformations/developmental defects
- Thanks to cardiac surgery and intensive care, **most patients now survive into adulthood** → a growing **GUCH** population (*grown-up congenital heart disease*).


Symptoms and Signs of Congenital Heart Defects
Heart murmur
Cyanosis

Congenital Heart Disease (CHD)

- **Influence of genetics vs. environmental factors** (e.g., TORCH infections, smoking, alcohol, etc.)
- **Variable degree of clinical significance**
  - from clinically silent to life-threatening conditions
- **Most common CHD:**
  - ventricular septal defect (**35.6%**), atrial septal defect (**15.4%**), patent ductus arteriosus (**10.2%**)
  - tetralogy of Fallot (**4.4%**), transposition of the great arteries (TGA; **3.9%**), tricuspid atresia (approx. **1–2%**)

TORCH *= group of congenital infections (Toxoplasmosis, Others, Rubella, Cytomegalovirus, Herpes simplex).*

Congenital Heart Disease (CHD) — Classification

Acyanotic

Without shunt

- Aortic stenosis
- Pulmonary artery stenosis*
- Coarctation of the aorta
- Abnormal position of the heart (*ectopia cordis* and *dextrocardia*)

Left-to-right shunt

- Ventricular septal defect (VSD)
- Atrial septal defect (ASD)
- Patent ductus arteriosus (PDA; ductus arteriosus Botalli)
- Atrioventricular septal defect (AVSD)
- Partial anomalous pulmonary venous return (PAPVR)
- Lutembacher syndrome

* usually acyanotic, but in severe cases may lead to cyanosis (if there is an atrial septal defect)

Congenital Heart Disease (CHD) — Classification

Cyanotic

Right-to-left shunt

- Tetralogy of Fallot
- Transposition of the great arteries (TGA)
- Ebstein anomaly
- Hypoplastic left heart syndrome
- Pulmonary atresia
- Truncus arteriosus

Other cyanotic lesions

- Tricuspid valve atresia
- Single functional ventricle
- Interrupted aortic arch
- Eisenmenger syndrome**

** usually not a congenital anomaly, but included here because of the shunt mechanism

Congenital and acquired valve defects

Goals

- distinguish **stenosis vs. regurgitation** as the two basic hemodynamic valve problems,
- explain **compensation** (hypertrophy/dilation) and the **mechanisms of decompensation**,
- understand the pathophysiology of the most common valve lesions: **AS, AR, MS, MR** (+ right-sided lesions),
- distinguish typical etiologies of **congenital vs. acquired** disease (degenerative, rheumatic, infectious, functional),
- name complications relevant also to dentistry: **heart failure, atrial fibrillation, pulmonary hypertension, thromboembolism, infective endocarditis**.

Introduction

- Valve defects are relevant for dental practice for two reasons:

1) **they change the patient's hemodynamic reserve:** some patients tolerate stress, pain, tachycardia or hypotension significantly worse (typically severe aortic stenosis, decompensated regurgitation)
2) **some valve conditions are associated with an increased risk of infective endocarditis** - the mechanism is pathophysiological: damaged endothelium on the valve + turbulent flow → susceptibility to colonization in case of bacteremia

Classification

- by disorder: stenosis (forward flow obstruction) vs. regurgitation/insufficiency (backflow),
- by location: aortic, mitral, tricuspid, pulmonary,
- by etiology: congenital (e.g. bicuspid aortic valve, Ebstein anomaly) vs. acquired (degenerative calcification, rheumatic disease, endocarditis, ischemic/functional insufficiency)

Basic terms and classification

Congenital valvular diseases

- A structural defect of a valve or of sub-/supravalvular components present from birth:
- leaflet dysplasia, commissural fusion, abnormal number of leaflets,
- abnormalities of the chordae tendineae/papillary muscles,
- malposition/“apical displacement” (tricuspid valve in Ebstein anomaly),
- supravalvular/subvalvular stenoses.

Inherited valvular diseases (genetic predisposition)

- monogenic connective tissue syndromes (→ dilation of the aortic root, secondary aortic regurgitation, myxomatous degeneration),
- familial occurrence of **BAV** and **MVP**,
- chromosomal/syndromic conditions with typical valvular lesions.
- **Practical note:** a large proportion of “congenital” lesions has a genetic background; the difference is whether it is an isolated defect or part of a syndrome.

- **BAV** = bicuspid aortic valve; **MVP** = mitral valve prolapse.

Hemodynamic principles

- Valve failure is primarily a problem of flow and pressure.
- In stenosis, a pressure gradient is created across the valve; in regurgitation, a volume load is created on the compartment.

Stenosis = pressure overload (afterload ↑)

- the ventricle generates higher pressure to overcome the gradient,
- **concentric hypertrophy** develops (especially in **AS**, **PS**),
- diastolic dysfunction, subendocardial ischemia (especially in AS),
- reduced systolic reserve during exertion.

Regurgitation = volume overload (preload ↑)

- part of the stroke volume flows back,
- the ventricle dilates (**eccentric hypertrophy**),
- long-term remodeling → systolic dysfunction,
- in acute regurgitation (congenital less often), a dramatic rise in filling pressures.

Clinical translation

- stenoses: “fixed” cardiac output → syncope/angina/dyspnea,
- regurgitations: a “silent” compensated phase → later dilation and heart failure.

4 key concepts:

1. **Preload** (filling volume/pressure): what the ventricle receives at the beginning of systole.
2. **Afterload** (load against ejection): the resistance against which the ventricle ejects blood.
3. **Compliance** (distensibility): determines how rapidly pressure rises as volume increases.
4. **Frank–Starling mechanism:** up to a point, higher preload → higher output; once reserve is exceeded → congestion and failure.

Link to valve disease:

- **Stenosis = pressure overload** (the ventricle must generate higher pressure).
- **Regurgitation = volume overload** (the ventricle/atrium carries an extra volume).

Pressure–volume loops (didactic, without drawing):

- **Aortic stenosis** → shift to higher systolic LV pressure, lower stroke volume, hypertrophy.
- **Mitral/aortic regurgitation** → higher EDV, dilation, progressive EF decline with decompensation.

Pathophysiology of stenosis: “fixed obstruction” and pressure overload

- In stenosis, the problem is that forward flow must pass through a narrowed orifice.
- **The result is:**
  - **turbulent flow** (murmur),
  - a **pressure gradient** across the valve,
  - **reduced stroke volume**, especially during exertion (when output should increase).

Pathophysiology of stenosis: “fixed obstruction” and pressure overload

Compensation:

- **Pressure overload → concentric hypertrophy** (most typical in aortic stenosis),
- hypertrophy temporarily reduces wall stress, but worsens diastolic relaxation → **diastolic dysfunction**.

Decompensation mechanisms:

- rising filling pressures → **pulmonary congestion**,
- relative subendocardial ischemia (especially in AS): the myocardium thickens and needs more O_2, but coronary perfusion may be limited (low diastolic pressure, high LVEDP),
- **“fixed cardiac output”**: the patient tolerates tachycardia, vasodilation, and hypotension poorly.

Pathophysiology of regurgitation: volume overload, dilation, remodeling

- Regurgitation means that part of the systolic (or diastolic) volume flows back. Two parameters are key:
  - regurgitant volume and regurgitant fraction,
  - rate of onset: acute vs. chronic regurgitation.

Pathophysiology of regurgitation: volume overload, dilation, remodeling

Chronic regurgitation (compensated phase):

- volume overload → **eccentric hypertrophy/dilatation**,
- the ventricle can maintain forward output for a long time by increasing total stroke volume (**forward + regurgitant**).

Why may the patient have no symptoms for a long time?

Because the body "remodels" the geometry of the ventricle and atrium. The cost, however, is increasing volumes, wall stress, and gradual contractile fatigue.

Acute regurgitation (critical):

- there is no time for dilatation and adaptation to develop,
- pressure rises abruptly in the atrium or ventricle → sudden pulmonary congestion and shock (typically acute MR with papillary muscle rupture; acute AR with endocarditis or aortic dissection).

Left-sided lesions I

Aortic stenosis

- **Narrowing of the aortic valve orifice** due to an anatomic abnormality or an inflammatory process.
- **Causes**
  - **Altered number of valve cusps (congenital)** – **bicuspid** (approx. **0.5–1.4%** of the population), **unicuspid**
  - **Acquired** – **rheumatic fever** (developing countries), **systemic lupus erythematosus**, **hyperuricemia**, **infections**
  - **Other** – **Paget disease**, **Fabry disease**
- **Epidemiology and statistics**
  - **6/1000 births** (more common in boys)
  - About **5%** of the population **>65 years** (exponential increase with age: **0.2** (50–59 years) vs **9.8** (80–89 years))

Left-sided lesions I: Aortic stenosis (AS) and aortic regurgitation (AR)

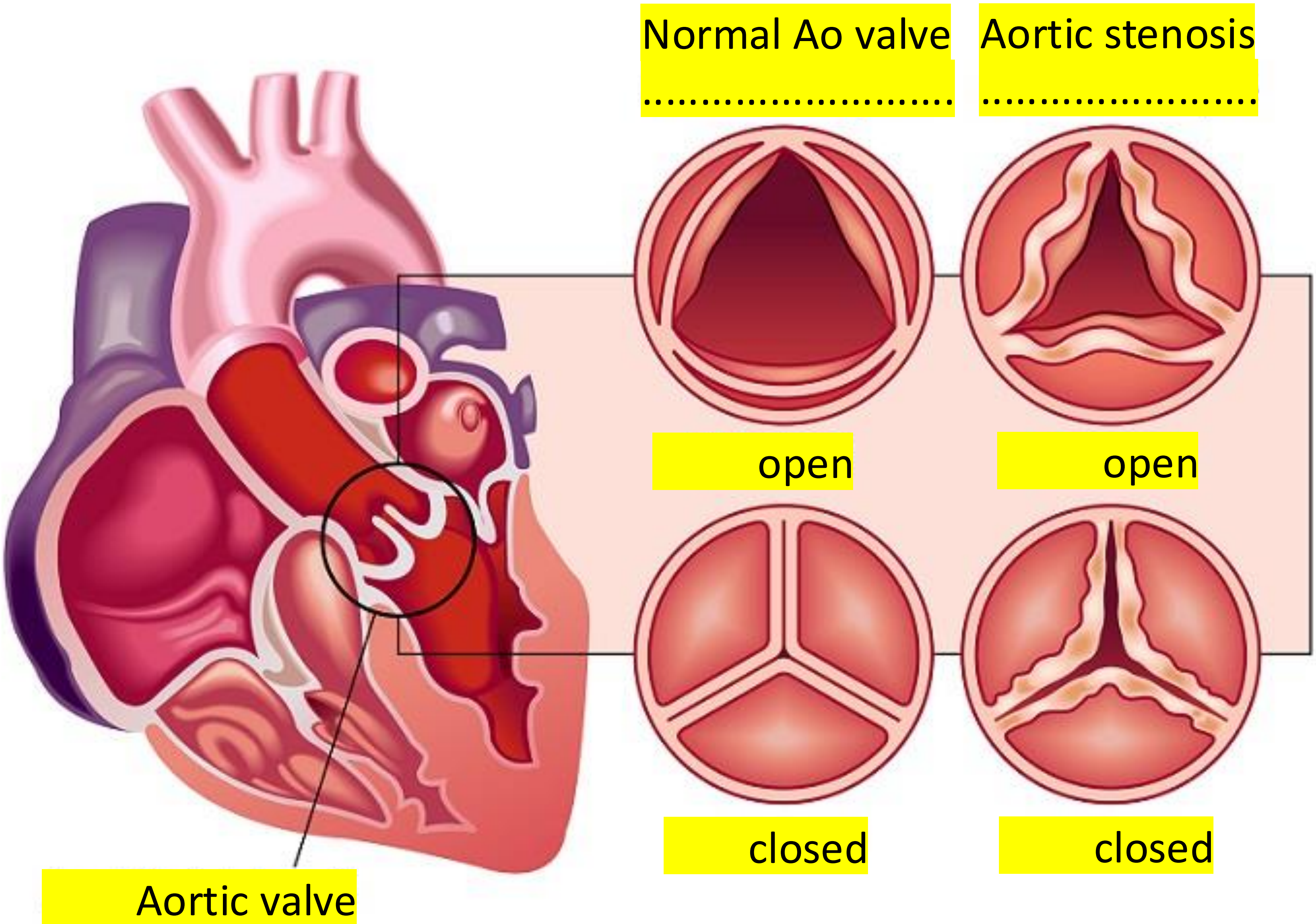
A) Aortic stenosis

Etiology:

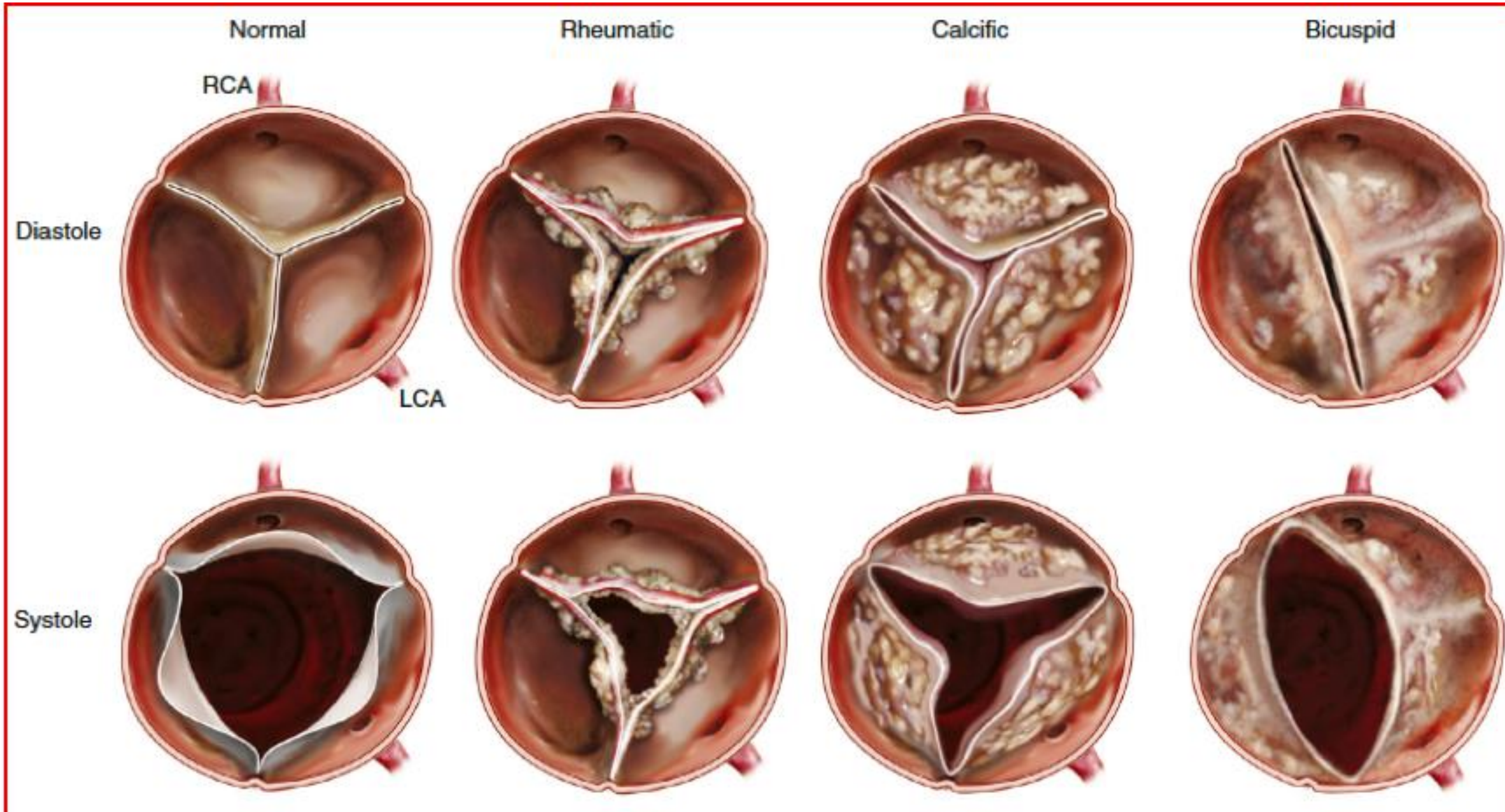
- acquired: **degenerative calcification** (most common in older patients),
- congenital: **bicuspid aortic valve** → earlier calcification/stenosis.

Pathophysiology:

- stenosis → the **LV must generate high systolic pressure** → **concentric hypertrophy**,
- hypertrophy → **diastolic dysfunction** → **sensitivity to tachycardia** (shortened diastole),
- with exertion, cardiac output cannot rise adequately → **syncope / angina / dyspnea** (mechanisms: **fixed output** + **ischemic mismatch**).



Normal Ao valve
……………………………
Aortic stenosis
…………………………
open
open
closed
closed
Aortic valve



Aortic stenosis etiology: morphology of calcific AS, bicuspid valve, and rheumatic AS (Adapted from C. Otto, Principles of Echocardiography, 2017).

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Aortic stenosis – classification

1. Valvular stenosis

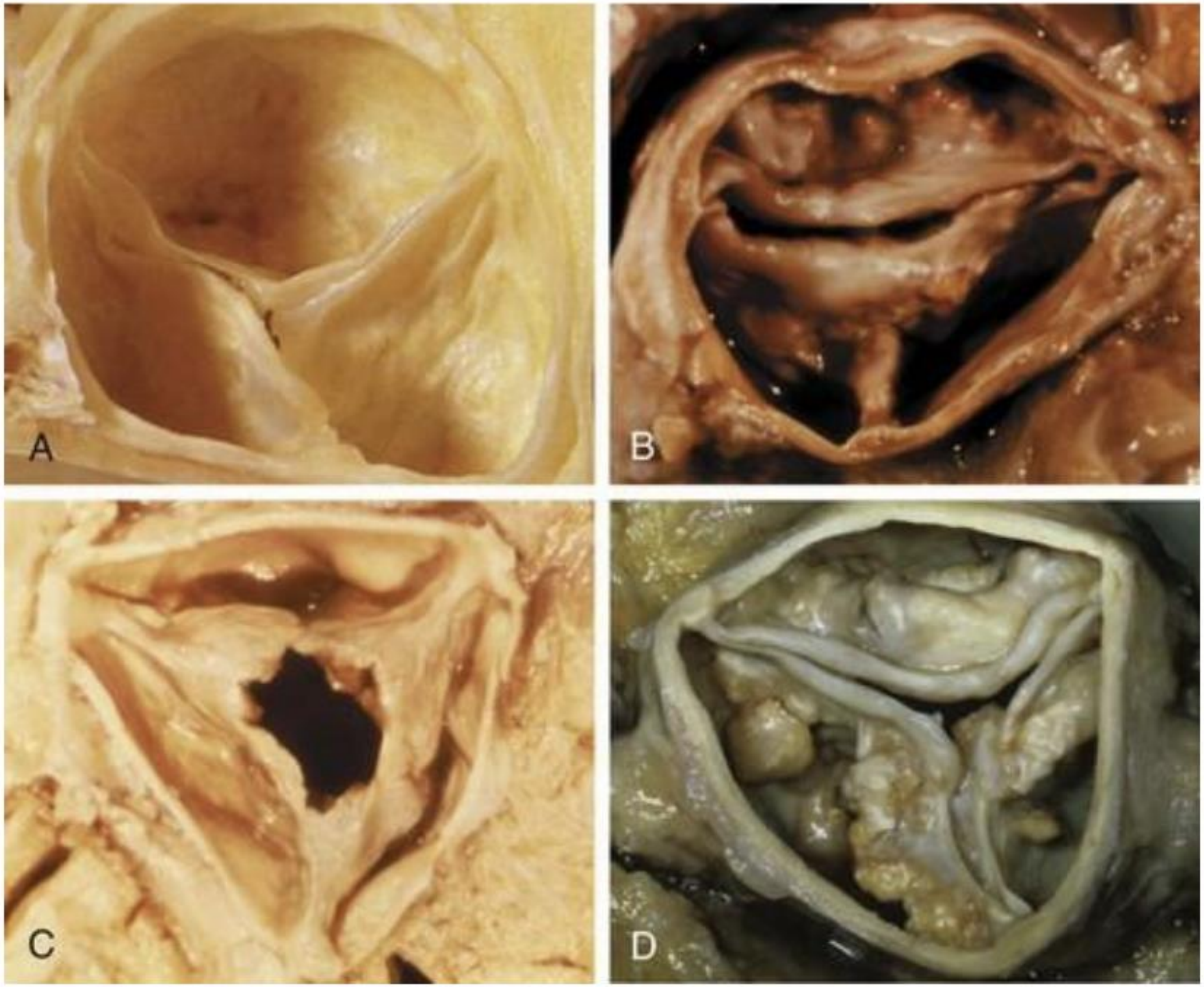
- **Rheumatic fever**
- **Degenerative valve disease**
  - Presence of a **bicuspid** (rarely **unicuspid**) valve
  - **Calcification of a tricuspid** valve (age-associated damage, cumulative process)
- **Valvular thrombosis**

2. Subvalvular stenosis

- **Fixed obstruction** – e.g., a **discrete fibrous subaortic membrane**
- **Dynamic obstruction** – e.g., **hypertrophic cardiomyopathy** → **left ventricular outflow tract obstruction (LVOTO)**

3. Supravalvular stenosis

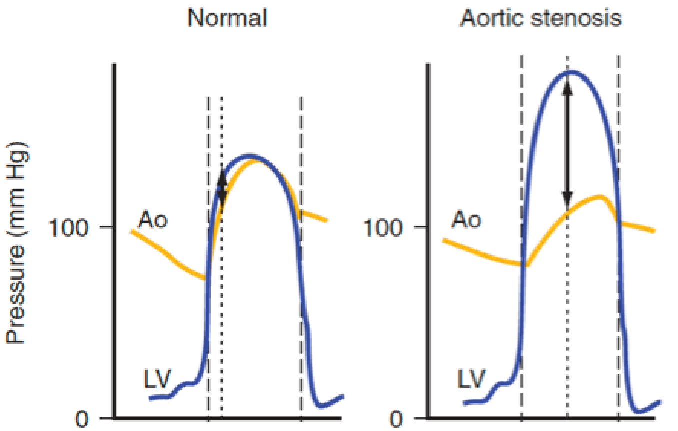
- **Rare** – **systemic elastin arteriopathy** → **"hourglass" variant** → an **annular ring at the upper margin of the sinuses of Valsalva**



Normal Ao valve (A), bicuspid with raphe (B), Ao stenosis post-rheumatic (C), Ao stenosis degenerative (D)

Consequences of aortic stenosis - adaptation

- ↑ Afterload → left ventricular remodeling → concentric hypertrophy → diastolic dysfunction
- Stenosis leads to an ↑ transvalvular pressure gradient
- Long-term preservation of ejection fraction → asymptomatic phase
- Progressive hypertrophy leads to maladaptation:
  - ↓ **coronary perfusion** (due to ↑ **LVEDP** and **shortened diastole – tachycardia**)
  - ↓ coronary flow reserve
  - ↑ oxygen (O_2) demand
- Development of myocardial ischemia



Illustrating the transvalvular pressure gradient in normal and severe aortic stenosis. Aortic pressure changes is represented as yellow curve, and left ventricular pressure as blue curve. The maximum pressure gradient (double-headed arrow) is increased in aortic stenosis. Ao, aorta; LV, left ventricle.

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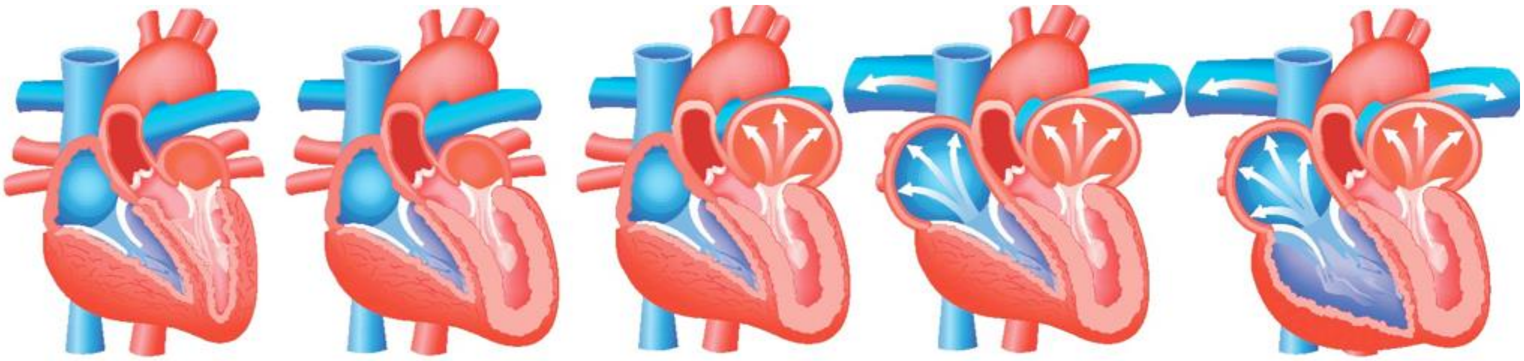
Consequences of aortic stenosis - maladaptation

- **Need for continual increases in preload to maintain cardiac function**

1. **Diastolic dysfunction**
    - **Ventricular remodeling → concentric hypertrophy**
        - **Secondary mitral regurgitation** → transmission of pressure to the atrium → **atrial dilation → atrial fibrillation**
        - **Pulmonary hypertension type II → ↑ PCWP → right ventricular dysfunction** (*cor translatum*)
2. **Systolic dysfunction**
    - **Prolonged exposure to high intraventricular pressure → left ventricular fibrosis**
    - Development of **subendocardial ischemia → ↓ ATP** for myocardial contraction, **ion pump dysfunction**

PCWP – pulmonary capillary wedge pressure (pulmonary artery wedge pressure)



Stages/Criteria	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Damage	LV Damage	LA or Mitral Damage	Pulmonary Vasculature or Tricuspid Damage	RV Damage
Echocardiogram		Increased LV Mass Index >115 g/m² (Male) >95 g/m² (Female)	Indexed left atrial volume >34mL/m²	Systolic Pulmonary hypertension ≥60 mmhg	Moderate-Severe right ventricular dysfunction
		E/e' >14	Moderate-Severe mitral regurgitation	Moderate-Severe tricuspid regurgitation	
		LV Ejection Fraction <50%	Atrial Fibrillation		

Cardiac stratification of aortic stenosis based on the extent of cardiac damage. LA, left atrial; LV, left ventricular; RV, right ventricular. PMID: 29020232

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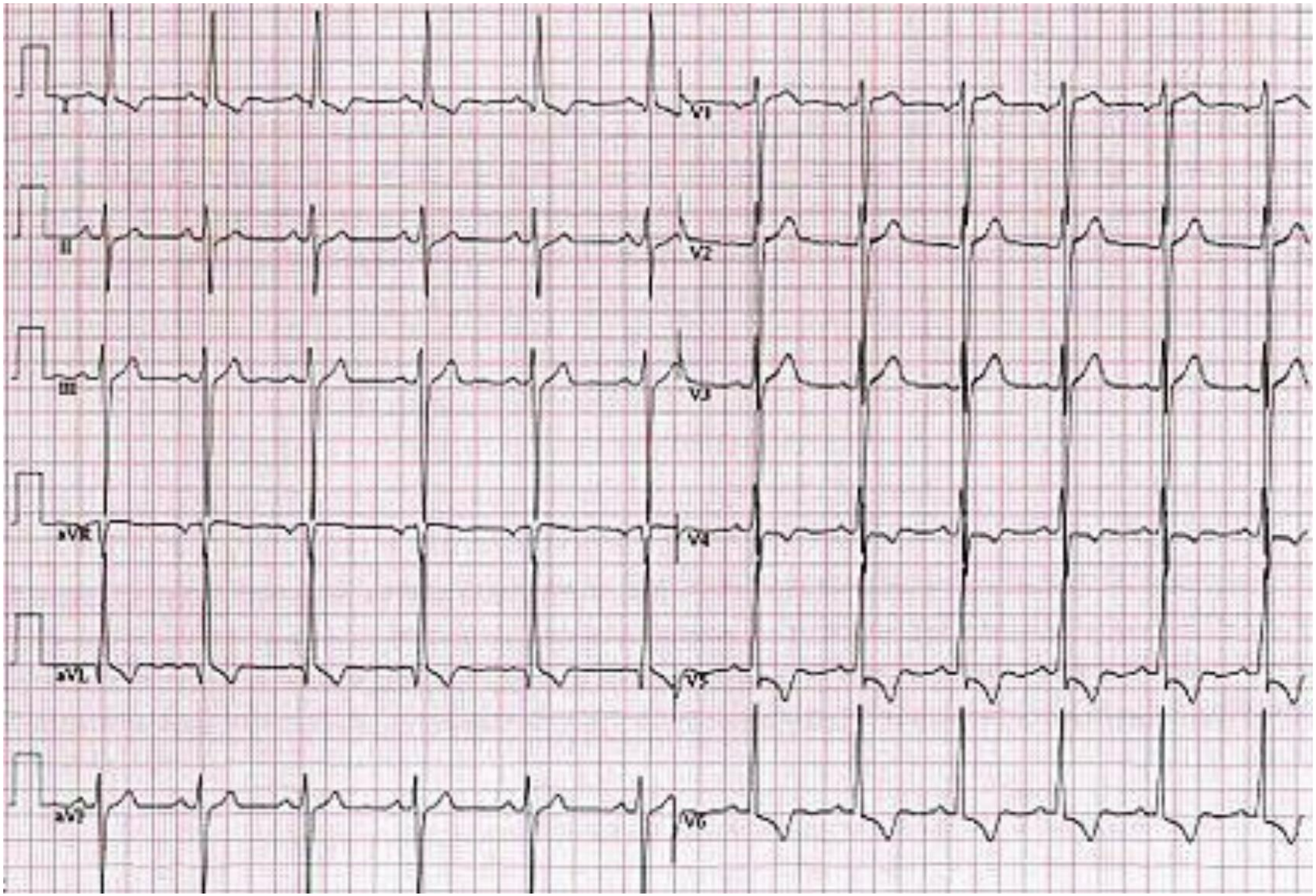
Manifestation of aortic stenosis

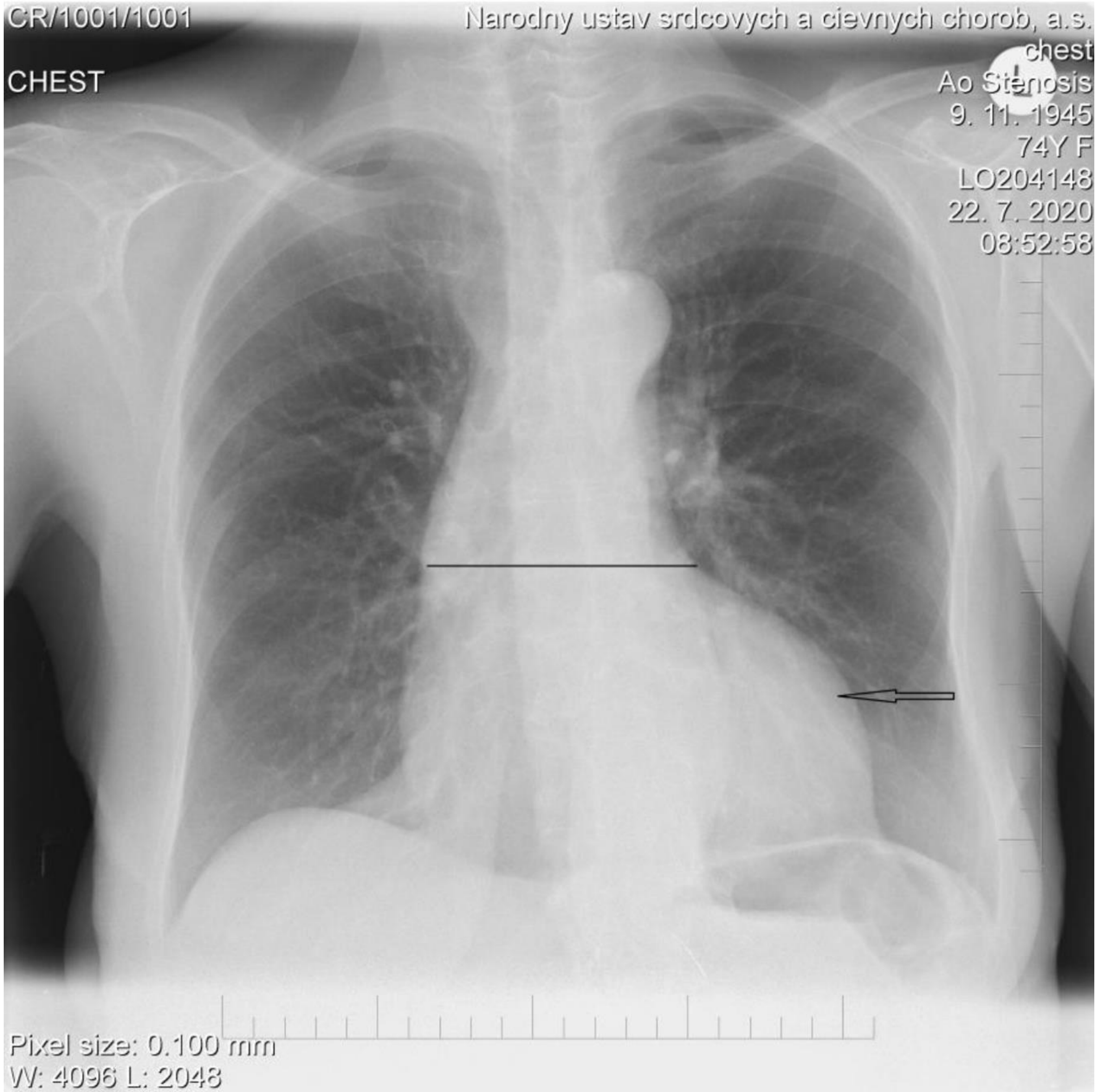
- **Long asymptomatic period → decompensation triggered by another disease/condition**
  - Acute **MI**, arrhythmia (**atrial fibrillation**), systemic infection/**sepsis**, **hypovolemia**, **GI bleeding**, uncontrolled hypertension, **infective endocarditis**, **pulmonary embolism**
- **Gold standard of diagnosis → echocardiography**
  - **ECG** → left ventricular hypertrophy
  - **BNP testing is not recommended** (echo is more accurate)

- **Clinical presentation**
  - **Exertional dyspnea**
  - **Presyncope/syncope**
  - **Chest pain**
  - **Systolic murmur** → radiation to the **carotid arteries**
  - **Pulsus parvus et tardus** (small, delayed pulse)
  - Signs of **hemolytic anemia** → **↓ Hb**, **↑ LDH** (from RBC hemolysis)
  - **Troponin T and I** → sign of **acute coronary syndrome**
  - **AST, ALT** → “shock liver” in low cardiac output states

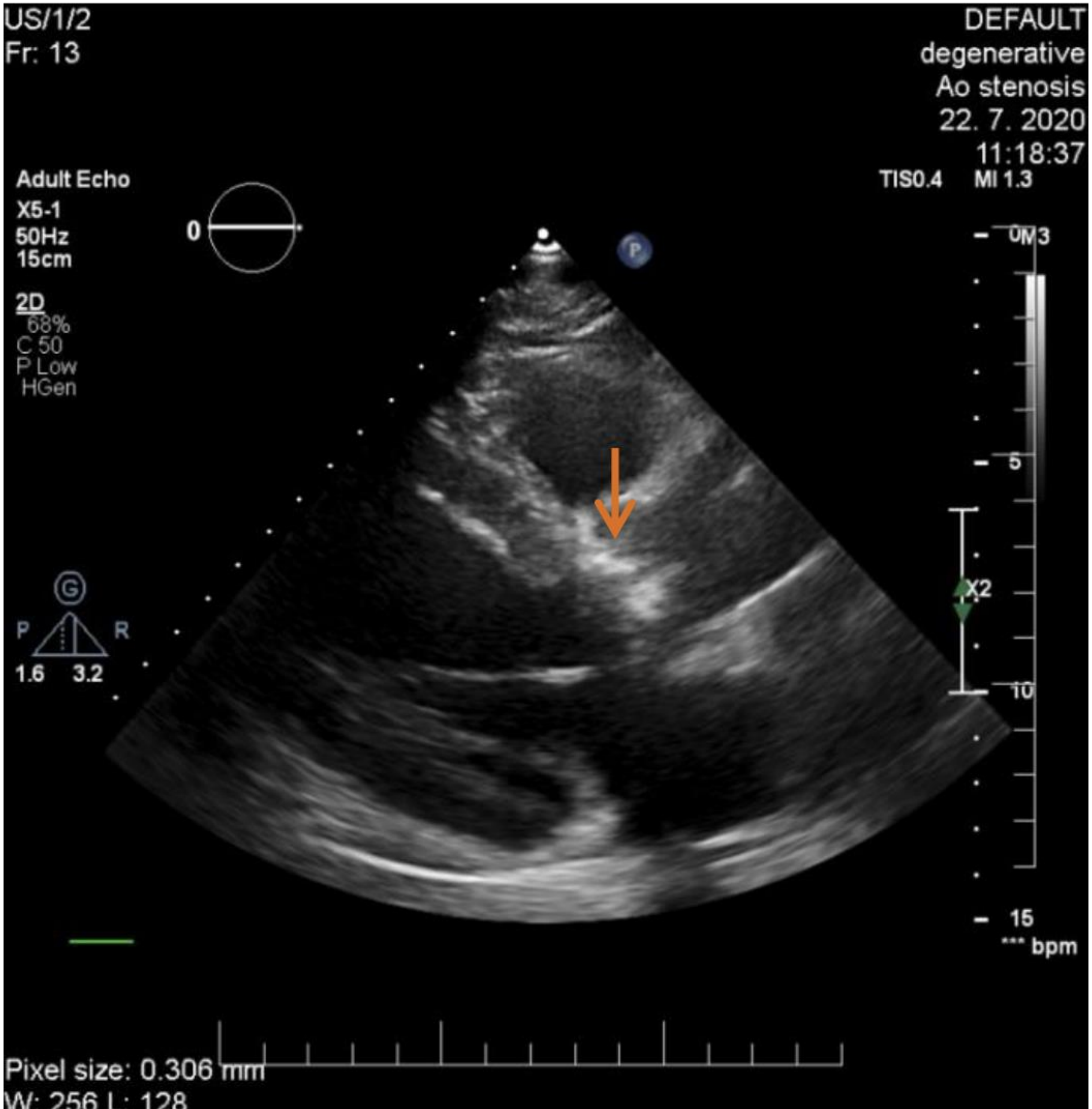
manifestations of hypertrophy and strain of the left ventricle in aortic stenosis

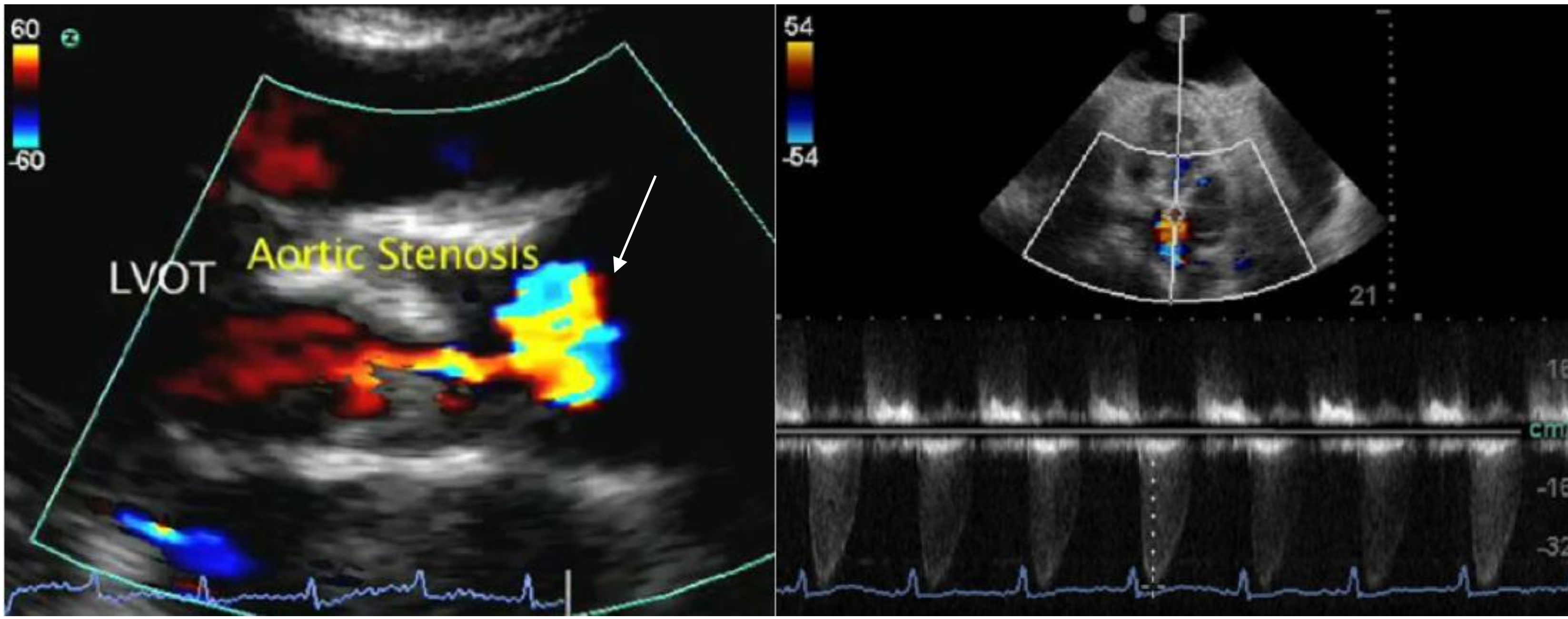


Chest X-ray – the heart shadow may be normal or slightly enlarged to the left (fig. arrow), sometimes a calcified aortic valve can be observed, signs of stasis in the small circulation may be present. In some cases, the aortic shadow is dilated (fig. line)



Hypertrophic left ventricle with heavily calcified aortic valve, arrow.





Echocardiogram of aortic stenosis – behind the narrowed orifice, the flow changes from laminar to turbulent (arrow)

https://recapem.com/wp-content/uploads/2023/07/Severe-aortic-stenosis.png

For dentistry (pathophysiological implication):

- a patient with severe AS poorly tolerates hypotensive episodes, marked tachycardia, and rapid changes in tone

B) Aortic regurgitation

Etiology:

- congenital: **bicuspid valve** (can also lead to AR),
- acquired: **degeneration**, **dilatation of the aortic root**, **endocarditis**; acutely also **aortic dissection**.

Pathophysiology (chronic AR):

- diastolic backflow of blood into the LV → **large EDV** → **eccentric hypertrophy**,
- "**wide pulse pressure**" (high systolic, low diastolic) as a hemodynamic consequence: **large stroke volume + rapid diastolic runoff**,
- later: **systolic dysfunction** due to chronic volume overload.

Acute AR:

- rapid rise in **LVEDP** → **pulmonary edema, hypotension, shock**; **no time for adaptation**.

Left-sided lesions II: Mitral stenosis (MS) and mitral regurgitation (MR)

A) Mitral stenosis

Etiology:

- typically acquired: **rheumatic disease** (in settings where it persists),
- less commonly: **degenerative annular calcification**, **congenital forms**.

Pathophysiology:

- obstruction between the LA and LV → **increased pressure in the left atrium (LA)**,
- pressure transmission to the pulmonary circulation → **pulmonary venous hypertension** → **dyspnea**, **hemoptysis** (in severe cases),
- chronically: **pulmonary hypertension** → **right-sided heart failure**,
- LA dilatation → **atrial fibrillation** → **risk of thromboembolism**.

Key concept: tachycardia worsens MS because it shortens diastole → less time for filling across the narrowed valve → LA pressures rise more rapidly.

B) Mitral regurgitation (MR)

Classification:

- **Primary (organic) MR:** a problem of the leaflets/chordae/papillary muscles (myxomatous degeneration, prolapse, endocarditis).
- **Secondary (functional) MR:** a problem of LV geometry (ischemic dilatation, cardiomyopathy) → traction on the valve apparatus.

Pathophysiology (chronic MR):

- systolic backflow into the LA → volume overload of the LA and LV,
- the LA dilates and increases compliance → a longer asymptomatic phase,
- the LV dilates (eccentric hypertrophy) → maintains forward output, but later contractility declines.

Acute MR (e.g., papillary muscle rupture):

- the LA has no time to adapt → rapid rise in LA pressure → fulminant pulmonary edema.

Right-sided valve disease: TR/TS/PS/PR (and congenital entities)

Tricuspid regurgitation (TR)

- often **functional** (dilatation of the right heart due to **pulmonary hypertension** or **left-sided heart failure),
- **hemodynamics:** volume overload of the **RA/RV** → **systemic venous congestion** (edema, hepatomegaly).

Tricuspid stenosis (TS)

- **rare**; **rheumatic** or **carcinoid**; leads to **venous congestion**.

Pulmonary stenosis (PS)

- often **congenital**; pressure overload of the **RV** → **hypertrophy**, later **heart failure.**

Pulmonary regurgitation (PR)

- after **surgical correction of congenital defects** or in **pulmonary hypertension**; **volume overload** of the **RV**.

Congenital “valvular” defects:

- **Ebstein anomaly (tricuspid valve):** “atrialization” of part of the **RV** → **TR**, arrhythmias.
- **Bicuspid aortic valve:** predisposition to **AS/AR** and **aortopathy**.

Cyanotic congenital heart disease with a right-to-left shunt

Ebstein anomaly

- **Definition** – a rare congenital developmental defect associated with abnormal formation of the **tricuspid valve** and its **apical displacement into the right ventricle**.
- **Causes** – unknown; **15q duplication**, **11q anomalies**, mutations in **MYH7**, **NKX2.5**.
- **Incidence** – **2–7 per 100,000/year** (2024).
- **Pathomechanism**
    - Defective **delamination of the tricuspid valve** from the **interventricular septum** → "**apicalization**" (apical displacement) of the tricuspid valve.
    - The **right ventricle (RV)** is divided into two parts:
        - **"Atrialized" RV** → often myopathy, fibrosis → akinesia, arrhythmias (e.g., **Wolff–Parkinson–White syndrome**).
        - **"Functional" RV** → effect of **tricuspid regurgitation** → RV remodeling (eccentric hypertrophy) → **flattening of the ventricular septum** → **left ventricular dysfunction**.
    - Frequent presence of shunts → e.g., **foramen ovale** → **right-to-left shunt** → **cyanosis** (**20% fetal death in utero, 45% perinatal mortality**).

Bicuspid aortic valve (BAV)

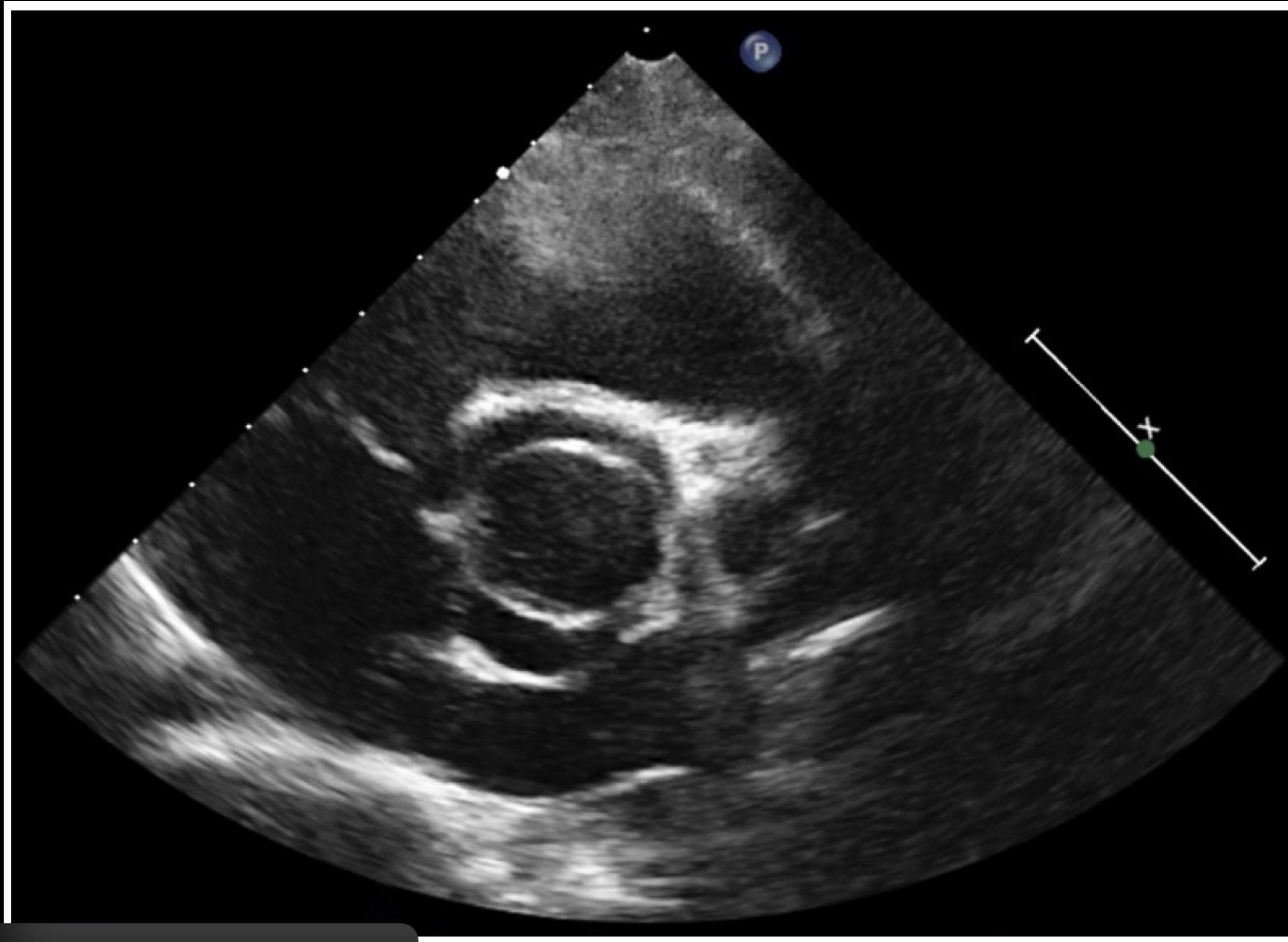
- **the most common congenital valvular anomaly**

Pathophysiology:

- **2 cusps** → abnormal flow (turbulence, shear stress) → accelerated degeneration and calcification → **AS**,
- often associated with **aortopathy** (dilatation of the ascending aorta/root) → risk of aneurysm/dissection; can also lead to **AR** (secondary to dilatation of the annulus/aorta),
- predisposition to endocarditis.

Clinical logic:

- asymptomatic for many years,
- later **AS** (pressure overload of the LV) or **AR** (volume overload of the LV),
- familial occurrence → rationale for echocardiographic screening of first-degree relatives (in clinical practice).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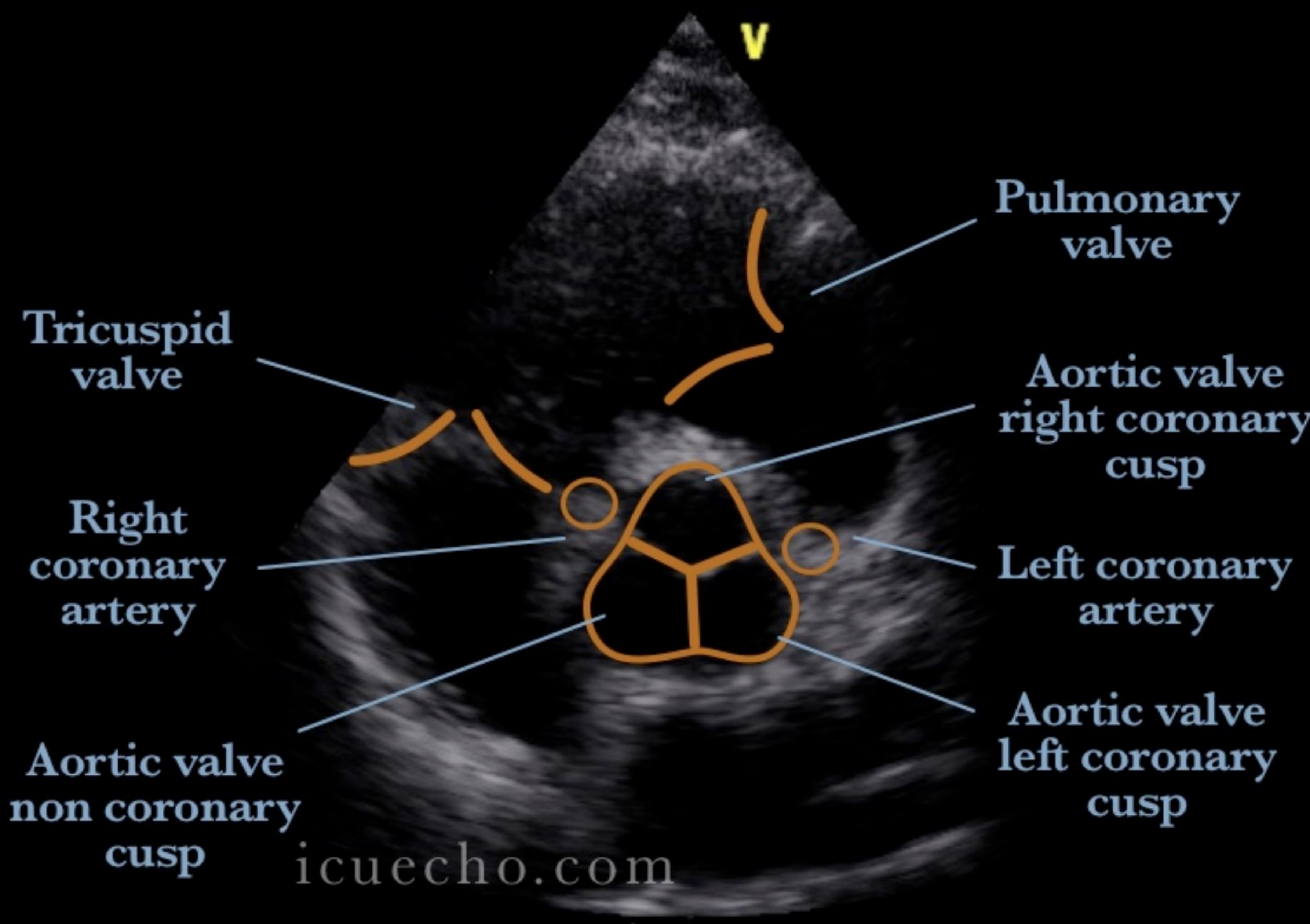

V
Pulmonary valve
Tricuspid valve
Aortic valve right coronary cusp
Right coronary artery
Left coronary artery
Aortic valve non coronary cusp
Aortic valve left coronary cusp
icuecho.com

Lesion (typically congenital/inherited)	Primary defect (anatomy/biology)	Hemodynamic consequence	Typical remodeling	Clinical consequences / risks	ECHO – physiologically key points
Bicuspid aortic valve (BAV)	2 cusps instead of 3; abnormal flow and shear stress; predisposition to calcification and aortopathy	AS, AR, or mixed lesion (often progressive)	In AS: concentric LVH; in AR: LV dilatation	AS: syncope, angina, dyspnea; AR: progressive LV dilatation; aortopathy (ascending aortic dilatation)	AS: peak/mean gradient (flow-dependent), valve area; AR: regurgitation quantification; LV dimensions; **aorta:** diameters (root/ascending)
Congenital valvular aortic stenosis (often uni-/bicuspid)	Dysplastic/thickened cusps, commissural fusion	Fixed LVOT/AV obstruction → pressure overload	Concentric LVH, diastolic dysfunction	Newborn: low output/shock; child: often tolerated initially, later exertional symptoms	Doppler **Vmax** and gradient + LV function assessment; in children always consider flow-dependence
Supravalvular aortic stenosis (SVAS)	Narrowing above the valve (often elastin arteriopathy)	LV pressure overload as in AS, but lesion is “above” the valve	LVH	Angina/dyspnea; may be part of systemic arteriopathy	Localize the stenosis, Doppler profile; assess other vessels as clinically indicated
Mitral valve prolapse (MVP) – myxomatous degeneration	ECM remodeling; “redundant”/elongated leaflet; annular/chordal changes	Primary MR (due to malcoaptation)	LA dilatation (early), then LV dilatation; later systolic dysfunction	Palpitations; AF due to LA dilatation; progressive MR; endocarditis risk (turbulent jets)	MR quantification (vena contracta, regurgitant volume/fraction); LA/LV size; MR mechanism (primary vs secondary)
Congenital mitral valve lesions (e.g., parachute MV, supravalvular ring, cleft)	Abnormal chordae/papillary muscles/ring, or structural leaflet defect	MS (LA pressure overload) or MR (LA/LV volume overload)	MS: ↑LA pressure → pulmonary venous hypertension; MR: LA/LV dilatation	Dyspnea; heart failure in infants (severe forms); later exercise intolerance	In MS: transmitral gradient + consequences of ↑LA pressure; in MR: mechanism + quantification
Ebstein anomaly (tricuspid)	Apical displacement of leaflet + “atrialization” of part of RV; severe TR	TR → RA volume overload, often reduced effective RV output	Marked RA dilatation; RV dysfunction depending on severity	Arrhythmias (substrate + dilatation); cyanosis from R→L shunt (ASD/PFO); right-sided heart failure	Measure leaflet displacement; TR severity; RA/RV size; presence of shunt
Pulmonary stenosis (PS)	Commissural fusion (doming) or dysplastic valve	RV pressure overload	RVH; in severe PS RV failure; post-stenotic pulmonary artery dilatation	Exertional dyspnea; syncope (rare); in severe forms low pulmonary flow	Doppler gradient across PV + RV pressure estimate; RV function; morphology (doming vs dysplasia)

Associated syndromes

- **Marfan / Loeys–Dietz / vascular Ehlers–Danlos:** dilation of the aortic root → **AR**; **MVP/MR**.
- **Turner syndrome:** more frequent **BAV** and aortopathy.
- **Williams syndrome:** supravalvular aortic stenosis.
- **Noonan syndrome: PS** (dysplastic pulmonary valve).
- **22q11.2 deletion syndrome:** conotruncal defects are more frequent; valvular lesions may be part of the spectrum.

Clinical features and diagnosis (what follows directly from pathophysiology)

Symptoms by lesion type:

- **AS/PS:** exercise intolerance, syncope, chest pain (AS), fatigue.
- **MR/AR/TR:** dyspnea, palpitations (AF), fatigue; in advanced stages: signs of heart failure.

Auscultation:

- **Stenosis:** ejection systolic murmur (**AS** radiates to the carotids; **PS** best heard over the pulmonary area).
- **Regurgitation:**
  - **MR/TR:** holosystolic murmur,
  - **AR:** diastolic decrescendo murmur.
- **Murmur intensity ≠ always severity** (with very low flow the murmur may be softer).

Echocardiography is decisive:

- anatomy (number of cusps, dysplasia, prolapse),
- gradients, regurgitant volume, chamber size, function,
- in **BAV**, always assess **aortic dimensions** as well.

Complications and “decompensation triggers”

Most common complications:

- **Heart failure** (left-sided, right-sided, biventricular),
- **Arrhythmias** (especially atrial fibrillation in **MS/MR**),
- **Pulmonary hypertension** (long-term consequence of elevated **LA** pressures),
- **Thromboembolism** (LA dilatation + AF),
- **Infective endocarditis** (especially with damaged valves and turbulent flow),
- **Progressive remodeling with a decline in EF** (especially in chronic regurgitation).

Triggers of decompensation:

- **Infection/fever, anemia, thyrotoxicosis** (increase output demand),
- **Tachyarrhythmia** (especially in MS),
- **Sudden hypertension** (increases regurgitant volume in MR/AR),
- **Hypovolemia or vasodilation** in patients with “fixed output” (**AS**).

Dentistry: practical pathophysiological implications

- **For dental practice, it is important to keep three pathophysiological facts in mind:**

1. **Turbulent flow and damaged valvular endothelium increase susceptibility to colonization during bacteremia →** the mechanistic basis of **endocarditis**.
2. **Some lesions reduce hemodynamic reserve** (severe **AS**, acute **regurgitation**, decompensated **MS/MR**), therefore **control of pain, stress, and abrupt hemodynamic changes** is crucial.
3. **Some patients are on anticoagulant/antiplatelet therapy or have implanted valves**—this is clinically significant; **specific management must follow current guidelines and specialist consultation**.

Infective endocarditis (IE)

Definition and clinical relevance for dentistry

- **Infective endocarditis** is an infectious disease of the **endocardium**, most commonly affecting the **heart valves** or **prosthetic material**.
- For dentistry, it is crucial that a typical trigger is **bacteremia**—often originating from the **oral cavity**—followed by **colonization of predisposed endocardium**.
- The clinical importance of IE lies in the risk of **acute valve failure**, **septic embolization** (brain, spleen, kidneys), and **systemic sepsis**.

Pathophysiologic mechanism

Step 1: Predisposition — a “site for attachment”

IE usually does **not** develop on completely intact endothelium. Predisposing factors include:

- **turbulent flow** (stenoses, regurgitations, congenital shunts),
- **foreign surfaces** (prosthetic valves, annuloplasty rings, patches, occluders, some intracardiac materials),
- **microtrauma of the endocardium** caused by **high-velocity jets**.

Step 2: Nonbacterial thrombotic endocarditis (NBTE)

On damaged endothelium, **platelets and fibrin** are deposited, forming a **“sterile” thrombotic nidus**. This provides a biological **“substrate”** to which microorganisms can subsequently **adhere easily**.

Step 3: Transient bacteremia

During manipulation of the **gingiva**, the **periapical region**, or when bacteria gain access through the **oral mucosa**, bacteria can be released into the bloodstream.

Key concept: bacteremia does **not** occur only during procedures; repeated, smaller episodes of bacteremia also occur during **everyday activities** in patients with **gingival inflammation/periodontitis**.

Step 4: Adhesion and vegetation formation

Microorganisms (typically **oral streptococci**, less often **staphylococci**) attach to the **NBTE**. The vegetation then becomes “coated” with **fibrin and platelets**, which:

- reduces access of immune mechanisms,
- impairs antibiotic penetration,
- enables persistence of the infection.

Step 5: Local destruction and systemic complications

Vegetations can:

- mechanically damage the valve → **acute regurgitation** and **heart failure**,
- form **abscesses** in the **periannular** region,
- embolize → **ischemic/septic emboli** (embolization).

“High-risk dental situations”

“High-risk dental situations” (when clinically relevant bacteremia occurs)

- A higher degree of bacteremia is associated with procedures that disrupt the **gingiva**, **periapical tissues**, or **oral mucosa**.

Typical high-risk situations:

- **tooth extractions**, **periodontal surgery** (incisions, flap surgery),
- **subgingival scaling**, **curettage**, **root planing**,
- **implant procedures** (mucosal incision, flap elevation),
- **endodontic procedures** extending into the **periapical region** or performed in the setting of an **acute infection**,
- **abscess drainage**, manipulation of an **acutely infected focus**.

➤ In patients with **active periodontitis**, the **cumulative exposure** to bacteremias from everyday activities (chewing, toothbrushing with bleeding gums) may be more significant than a single procedure. Therefore, **long-term control of oral inflammation** is essential.

Summary - IE

Summary

- Infective endocarditis (IE) arises especially where there is **endothelial damage** or **foreign material** and **turbulent flow** is present.
- At the damaged site, **NBTE** (*noninfective/nonbacterial thrombotic endocarditis*) forms (**platelets + fibrin**).
- **Transient bacteremia** allows microbes to adhere to the NBTE.
- A **vegetation** forms, which is immunologically "shielded" by **fibrin and platelets**.
- The vegetation leads to **valve destruction** and/or **embolic events**.
- The **highest-risk patient** is one with **prior IE**, a **prosthetic valve/prosthetic material**, or a **complex congenital heart defect with residual turbulence**; high-risk procedures are those involving manipulation of the **gingiva/periapical region/oral mucosa**, especially in the presence of an **active infection**.

Atherosclerosis

Introduction

- In dentistry, you encounter patients with high cardiovascular (CV) risk every day—often even before they come under the care of an internist or cardiologist.
- Your role is not to treat atherosclerosis, but to identify the patient’s risk profile, understand the importance of chronic inflammation, and know how to work safely with a patient who already has atherosclerotic disease—for example after a myocardial infarction, after a stroke, with peripheral arterial disease, or with diabetes.

Lecture objectives

- Explain why atherosclerosis is a **chronic inflammatory process** initiated by **retention of apoB-containing lipoproteins** in the intima.
- Describe the sequence of steps: **endothelial dysfunction → LDL infiltration/retention → immune response → foam cells/necrotic core → fibrous cap → destabilization → thrombosis**.
- Distinguish **stable vs. vulnerable plaque** and the mechanisms of **rupture vs. erosion**.
- Link atherosclerosis with **oral inflammation** (periodontitis, periapical inflammation) as a **systemic pro-inflammatory trigger** (with emphasis on the limits of evidence).
- Derive practical implications for the dentist (**high-risk patient identification, medical history, basic screening**).

Definition

- Atherosclerosis is a chronic disease of the walls of large and medium-sized arteries, in which an **atheromatous plaque** forms in the intima—a structure composed of lipids, immune system cells, smooth muscle cells, and extracellular matrix.
- Clinically, it is important mainly because its complications—**thrombosis after plaque rupture or erosion**—lead to acute ischemic events such as **myocardial infarction** or **ischemic stroke**.
- From a mechanistic perspective, the key point is that this is not passive “fat deposition,” but a process initiated by **retention of atherogenic lipoproteins** and the subsequent **inflammatory response of the vessel wall**.

- Atherosclerosis = a disease of the intima of large and medium-sized arteries
- Trigger: retention of apoB-containing lipoproteins + endothelial dysfunction
- Clinical turning point: thrombosis due to plaque rupture/erosion
- Atherosclerosis as a process, not just “fat deposition.” Today, the core concept is retention of LDL/apoB in the intima and the subsequent chronic immune response.

- **ApoB (apolipoprotein B)** is the main structural protein of **atherogenic lipoproteins** in plasma. Practically: **apoB = "the number of atherogenic particles"** that can enter the arterial wall and initiate/maintain atherosclerosis.
- One lipoprotein particle usually carries **one apoB molecule**, therefore apoB is a good marker of **particle number**:
  - **LDL** (apoB-100),
  - **VLDL/IDL and their remnants** (apoB-100),
  - **Lp(a)** (apoB-100 + apo(a)),
  - **chylomicrons carry apoB-48** (intestinal variant; in fasting blood there are usually few of them).

Why is apoB important in the pathophysiology of atherosclerosis?

- Atherosclerosis is initiated mainly by **retention of apoB-containing lipoproteins in the intima** (they bind to **proteoglycans**), followed by modification and an **inflammatory response** of the vessel wall. **More apoB means more particles** that have a chance to be trapped.
- **ApoB vs. LDL-cholesterol (LDL-C) – the difference**
  - **LDL-C:** how much cholesterol is "loaded" within LDL.
  - **ApoB:** how many atherogenic particles circulate in the blood; in some conditions (e.g., **insulin resistance, hypertriglyceridemia**) apoB can be **relatively high even with normal LDL-C**, because there are many small "cholesterol-poor" particles.

Atherosclerosis (ATS) and Dentistry

- **Patients in the dental clinic:** high prevalence of risk factors (smoking, **DM**, **HT**, dyslipidemia)
- **Chronic oral inflammation** = a systemic pro-inflammatory signal
- **Dental practice** = an opportunity for screening and counseling/recommendations
- understand why inflammation and risk factors accelerate **endothelial dysfunction** and **plaque progression**. For the link between periodontitis and CVD, biologically plausible mechanisms exist, although causality is complex.

- **Periodontitis and other chronic oral inflammatory conditions** represent a long-term systemic pro-inflammatory stimulus.
- There is **robust evidence of an association** between **severe periodontitis** and a higher risk of **cardiovascular disease**.
- **Oral inflammation** is part of the body’s overall **systemic inflammatory burden**.

Atherosclerosis

- Atherosclerosis begins with endothelial dysfunction and hemodynamically predisposed sites where apoB-lipoproteins penetrate the intima and are retained on proteoglycans.
- Retention leads to modifications of LDL and activation of the endothelium, which recruits monocytes.
- Monocytes differentiate into macrophages, internalize lipids, and form foam cells that produce cytokines and maintain inflammation.
- Failure of efferocytosis results in a necrotic core and smooth muscle cells form a fibrous cap.
- Plaque stability depends primarily on the quality of the cap and the intensity of inflammation. If the cap ruptures, rupture occurs, exposing the thrombogenic core and thrombosis; alternatively, erosion may occur, where endothelial loss and thrombosis at the plaque surface are the primary problems. Acute ischemic events correspond to these mechanisms.

The arterial wall and "places where plaque forms"

- **Arterial wall and "where the plaque forms"**
- **Intima** – the site of **lipoprotein retention**
- **Turbulent flow / low shear stress** (at **bifurcations**) → **endothelial activation**
- "**Predilection**" sites: **coronary arteries, carotids, aorta, femoral arteries**
- **Hemodynamics** explains why the same **LDL level** leads to plaque formation mainly in **specific vascular segments**.

Endothelium as an organ

- Vasodilation (NO), antithrombotic and anti-inflammatory properties
- Endothelial dysfunction: ↓NO, ↑permeability, ↑adhesion molecules
- Endothelial dysfunction is a “gateway” for atherogenesis: more LDL in the intima and easier adhesion of leukocytes.

“Response-to-retention”: lesion initiation

- **ApoB lipoproteins** (LDL and remnants) **enter the intima**.
- **Retention on proteoglycans → prolonged residence → LDL modifications**.
- **Triggering of the inflammatory response**.
- Key point: it is not only “**high LDL in the blood**,” but its **retention** and the subsequent **biological response of the vessel wall**.

LDL modifications and why they matter

- Oxidation/enzymatic modifications → “neoantigens”
- Activation of endothelial cells and macrophages
- Formation of a pro-inflammatory microenvironment
- Rationale: modified LDL acts as a danger signal and reshapes the immune response.

Leukocyte recruitment

- **VCAM-1/ICAM-1, selectins** → rolling and adhesion
- **Chemotaxis** (e.g., MCP-1/CCL2)
- **Monocytes** → macrophages
- This is the **"tipping point"**: a shift from purely metabolic risk to **chronic inflammation in the intima**

Foam cells

- **Macrophages internalize modified LDL** (via **scavenger receptors**).
- **Foam cells are the basis of the "fatty streak."**
- **Cytokines, ROS, proteases → progression** (of the lesion/plaque).
- The **fatty streak** can remain **subclinical for a long time**, but it **creates conditions for an advanced plaque**.

Role of VSMCs (vascular smooth muscle cells)

- **Migration into the intima, proliferation**
- **Synthesis of extracellular matrix (collagen) → fibrous cap**
- **Phenotypic switch** (contractile → synthetic/pro-inflammatory)
- **Modern view:** VSMCs are **active immunometabolic players**, not just “structural/building” cells.

VSMCs as a source of foam cells

- Foam cells do not arise only from macrophages.
- A substantial proportion of foam cells may originate from VSMCs.
- **Implications:** cap stability and plaque composition.
- **Evidence shift:** a cell type we consider “stabilizing” can, under certain conditions, contribute to lipid accumulation and plaque dysfunction.

Necrotic core: why it forms

- Apoptosis/necroptosis of cells within the plaque
- Failure of efferocytosis (clearance of apoptotic cells)
- Lipid core + tissue factor → thrombogenicity
- The necrotic core is the hallmark of a vulnerable plaque: high thrombogenic potential when exposed to blood.

Fibrous cap: stability vs. risk

- Collagen (produced by VSMCs) vs. degradation (matrix metalloproteinases)
- Thinner cap + large necrotic core = “vulnerability”
- Inflammation (macrophages) → weakening of the cap
- Stability is more about the “biology of the cap” than the “degree of stenosis.”

Calcification: micro vs. macro

- **Micro-calcifications** in the fibrous cap can **increase local mechanical stress**.
- **Macro-calcification** may be a sign of a **“more mature” lesion**.
- **Clinically: CT calcium score** as a marker of **overall plaque burden**.
- **Calcification** is part of **remodeling and inflammation**.

Neovascularization and intraplaque hemorrhage

- **Vasa vasorum → fragile new microvessels**
- **Bleeding into the plaque → core expansion, more inflammation**
- **Progression and destabilization**
- This mechanism explains **rapid "jumps" in plaque progression**

Innate immunity and the inflammasome

- Cholesterol crystals and Damage-Associated Molecular Patterns
- Activation of the NLRP3 inflammasome (NOD-like receptor family, pyrin domain containing 3) → IL-1β / IL-18
- Link between metabolism and inflammation
- Important for understanding "inflammation as a target"
- Adaptive immunity
- T lymphocytes (Th1) – pro-inflammatory profile
- B lymphocytes and antibodies (heterogeneous effects)
- Autoantigens: modified lipoproteins
- Key point: the plaque is immunologically active tissue.

“Stable” vs. “unstable” plaque

- **Stable:** thicker cap, more fibrosis, smaller core
- **Unstable:** thin cap, large necrotic core, intense inflammation
- **Clinical:** stable angina vs. acute coronary syndrome
- **Clinical events** often do not arise from the **largest stenosis**, but from a **biologically vulnerable plaque**.

Plaque rupture: mechanism

- **Cap rupture** → blood comes into contact with the **necrotic core**
- **Thrombosis (within minutes)** → occlusion/embolization
- Typically **strong inflammatory signal**
- Rupture is the classic mechanism of **myocardial infarction (MI)** and part of **coronary artery disease (CAD)**; the link to **“instability/rupture”** is key.

Plaque erosion: mechanism (distinct phenotype)

- **No cap rupture**
- **Loss of the endothelial layer** → thrombus forms on an **"eroded" surface**
- Often **matrix/VSMC-rich**, with a **smaller lipid core**
- Erosion is the **second major mechanism** of **acute coronary syndromes (ACS)** and has **different biology** than rupture.

Why a thrombus forms

- **Platelet activation** (adhesion, aggregation)
- **Coagulation cascade** (tissue factor)
- **Stabilization by fibrin**
- Linking the **“plaque”** to an **“acute event”**

Risk factors as biological pathways

- **LDL/apoB:** substrate for retention
- **Hypertension (HT):** mechanical stress on the endothelium
- **Diabetes mellitus (DM):** glycation, oxidative stress, dyslipidemia, inflammation
- **Smoking:** endothelial dysfunction, procoagulant state
- **Risk factors = mechanisms** that increase **retention** and **inflammation**

Biomarkers (what a dentist should know)

- **LDL-C** as a practical indicator of atherogenic **apoB-containing particles**
- **ApoB** (conceptually: the “number of particles”)
- **Lp(a)** as a genetic risk factor
- **Without prescribing medications:** just understanding why the target is **LDL/apoB**

Periodontitis and atherosclerosis: biological plausibility

- **Chronic inflammation** → cytokines, CRP, endothelial activation
- **Bacterial products/periodontal pathogens** → systemic effects
- **Shared risk factors** (smoking, diabetes mellitus) = confounding
- Need to distinguish: (a) **association**, (b) **mechanisms**, (c) **causality**. The links are being studied intensively, but interpretation must remain cautious.

Mechanisms linking the two

- **Systemic inflammatory response** (IL-6/CRP)
- **Endothelial dysfunction**
- **Procoagulant shift**
- **Possible presence of bacteria/DNA in plaques** (mechanistic line of evidence)
- A dentist should know that **chronic oral inflammation** acts as a systemic “stress” for the **endothelium and the immune system**.

Chronic apical periodontitis (CAP) and atherosclerosis

- **CAP = a chronic inflammatory lesion** with possible systemic spillover
- **Some data suggest an association** between CAP and atherosclerosis
- **Cautious interpretation** (population selection, comorbidities)
- **Local chronic inflammation may correlate** with systemic inflammation and atherosclerosis, but **a causal relationship cannot be inferred automatically** from that.

Transient bacteremia during dental procedures in the context of atherosclerosis

- **Short-term bacteremia can occur** with invasive procedures as well as with routine cleaning
- **More important than “plaque infection”** is the overall **chronic inflammatory tone**
- **Practical emphasis:** stabilization of oral health and **risk-factor control**

Clinical relevance for dental practice

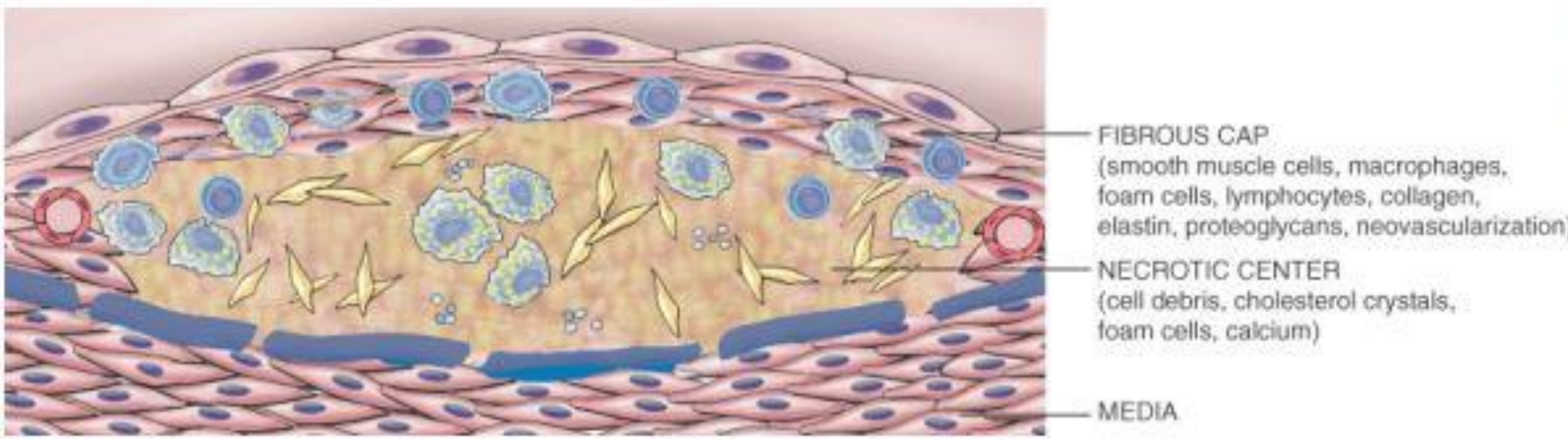
- What a patient with advanced atherosclerosis “looks like” in the medical history
- History of MI/heart attack, angina, PAD; prior stents, CABG
- Diabetes, CKD, smoking, hypertension
- Medications: statin, antiplatelet therapy, antihypertensives
- Goal: identify a high-risk patient and ask the right questions

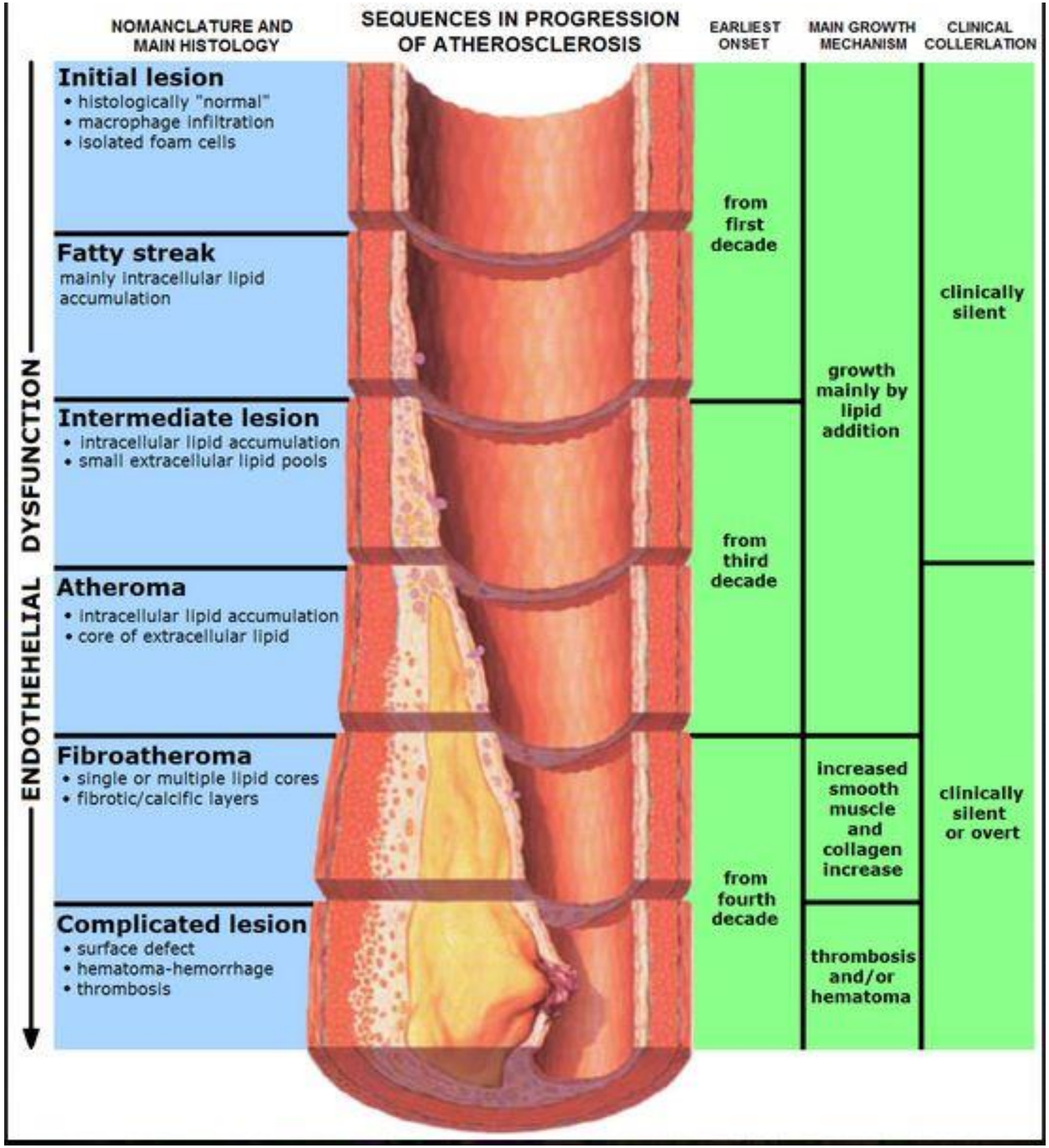
Basic screening in a dental office (minimum standard)

- **Blood pressure, pulse** (if the practice does this)
- **Brief targeted medical history** (MI/heart attack/CMP, diabetes, smoking)
- **Refer to a primary care physician** if there is obvious risk
- **Emphasize scope of competence and documentation**

Summary

- Atherosclerosis begins in the **intima** with retention of **apoB-containing lipoproteins**.
- **Endothelial dysfunction** is the "gatekeeper" of atherogenesis.
- The plaque is an **immunologically active tissue**.
- **VSMCs** are essential both for the fibrous cap and for plaque composition.
- **Vulnerability** = thin cap + large necrotic core + inflammation.
- **ACS** arises mainly from thrombosis after **rupture or erosion**.
- Risk factors accelerate the same biological pathways (endothelium, retention, inflammation).
- Chronic oral inflammation may promote a systemic inflammatory profile; **causality must be interpreted cautiously**.
- For the dentist, the key is to recognize risk and refer appropriately.
- Prevention (risk factors + oral health) is a **shared domain** of medicine and dentistry.

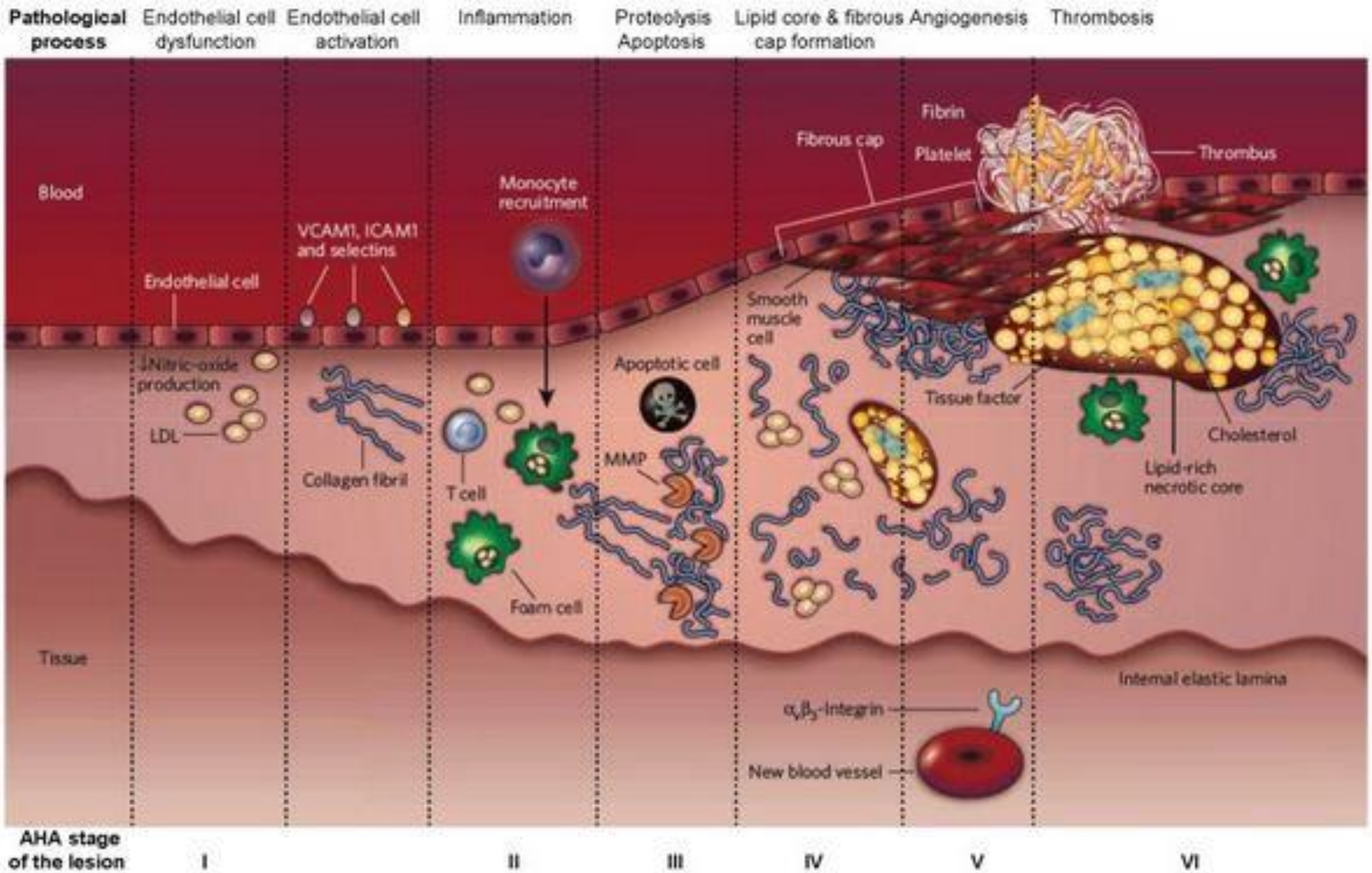

FIBROUS CAP
(smooth muscle cells, macrophages, foam cells, lymphocytes, collagen, elastin, proteoglycans, neovascularization)
NECROTIC CENTER
(cell debris, cholesterol crystals, foam cells, calcium)
MEDIA



NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
Intermediate lesion
• intracellular lipid accumulation
• small extracellular lipid pools
Atheroma
• intracellular lipid accumulation
• core of extracellular lipid
Fibroatheroma
• single or multiple lipid cores
• fibrotic/calcific layers
Complicated lesion
• surface defect
• hematoma-hemorrhage
• thrombosis
from first decade
from third decade
from fourth decade
growth mainly by lipid addition
increased smooth muscle and collagen increase
thrombosis and/or hematoma
clinically silent
clinically silent or overt

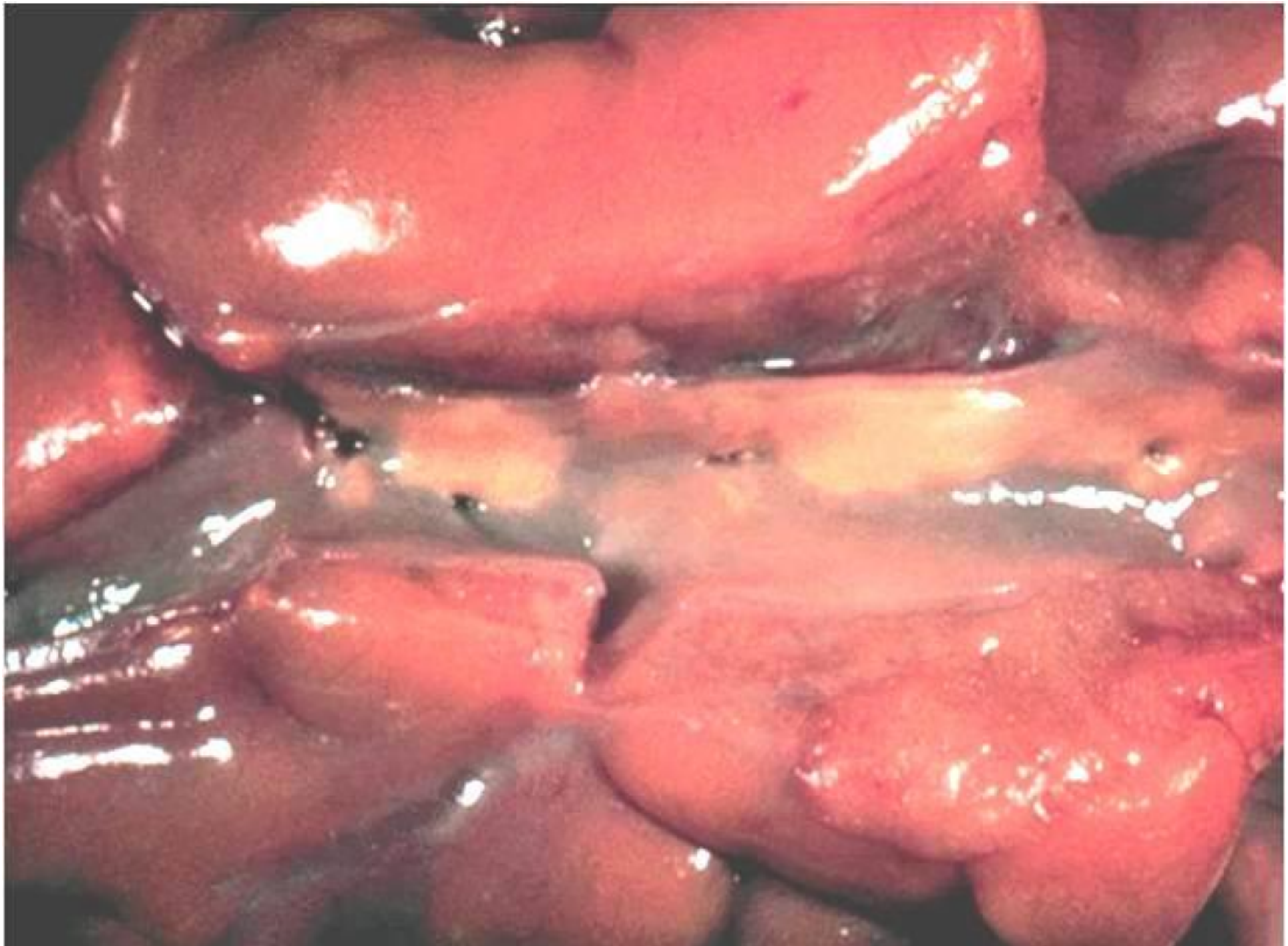
atherosclerosis

Nomenclature and main histology	Sequences in progression	Main growth mechanism	Earliest onset	Clinical correlation
Type I (initial) lesion Isolated macrophage foam cells	I	Growth mainly by lipid accumulation	From first decade	Clinically silent
Type II (fatty streak) lesion Mainly intracellular lipid accumulation	II			
Type III (intermediate) lesion Type II changes and small extracellular lipid pools	III		From third decade	
Type IV (atheroma) lesion Type II changes and core of extracellular lipid	IV			Clinically silent or overt
Type V (fibroatheroma) lesion Lipid core and fibrotic layer, or multiple lipid cores and fibrotic layers, or mainly calcific, or mainly fibrotic	V	Accelerated smooth muscle and collagen increase	From fourth decade	
Type VI (complicated) lesion Surface defect, hematoma-hemorrhage, thrombus	VI	Thrombosis, hematoma		

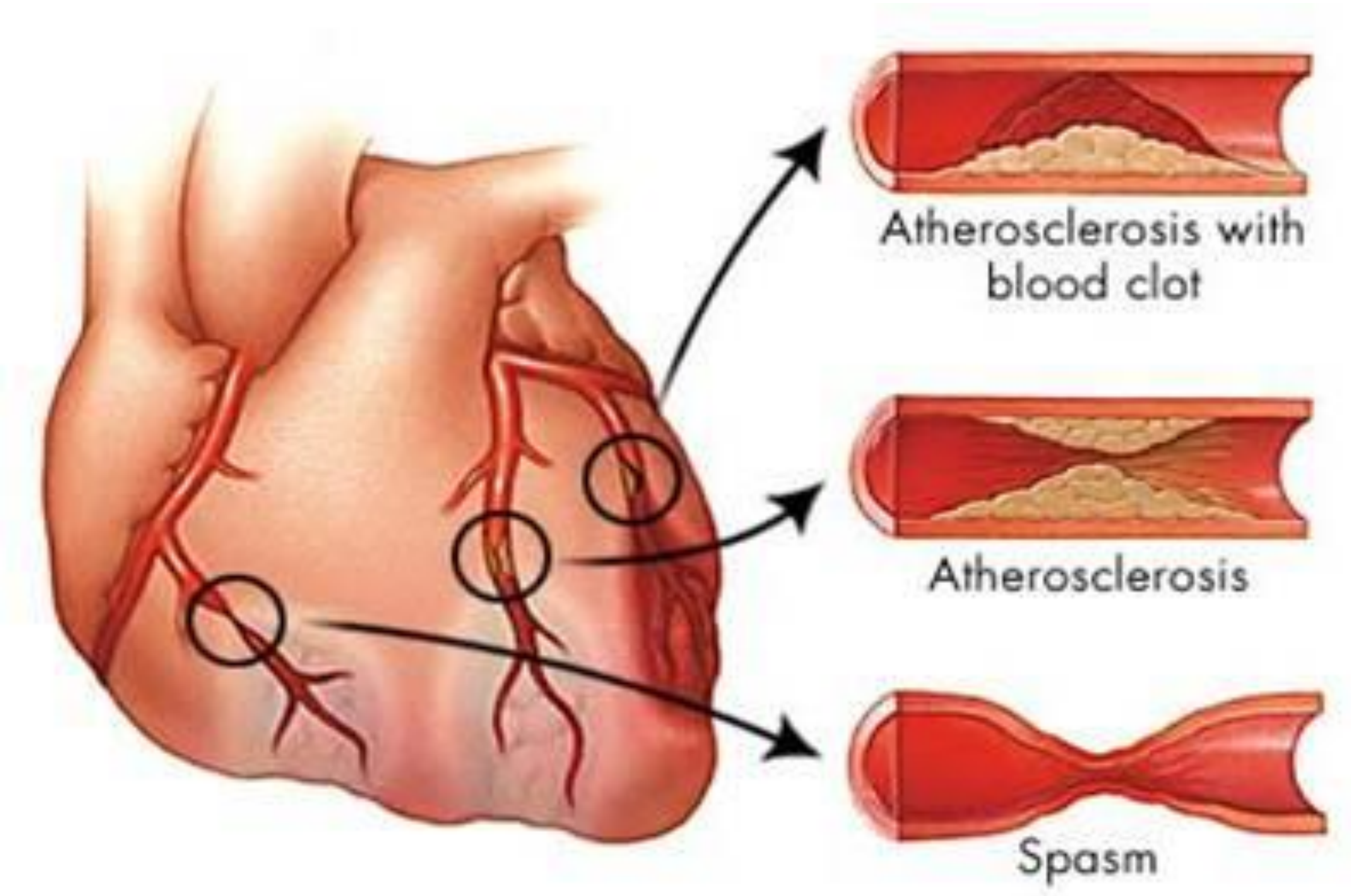


Pathological process
Endothelial cell dysfunction
Endothelial cell activation
Inflammation
Proteolysis Apoptosis
Lipid core & fibrous cap formation
Angiogenesis
Thrombosis
Blood
Endothelial cell
↓Nitric-oxide production
LDL
VCAM1, ICAM1 and selectins
Collagen fibril
Monocyte recruitment
T cell
Foam cell
Apoptotic cell
MMP
Smooth muscle cell
Fibrous cap
Fibrin
Platelet
Thrombus
Tissue factor
Cholesterol
Lipid-rich necrotic core
Tissue
Internal elastic lamina
$\alpha_v\beta_3$-Integrin
New blood vessel
AHA stage of the lesion
I
II
III
IV
V
VI

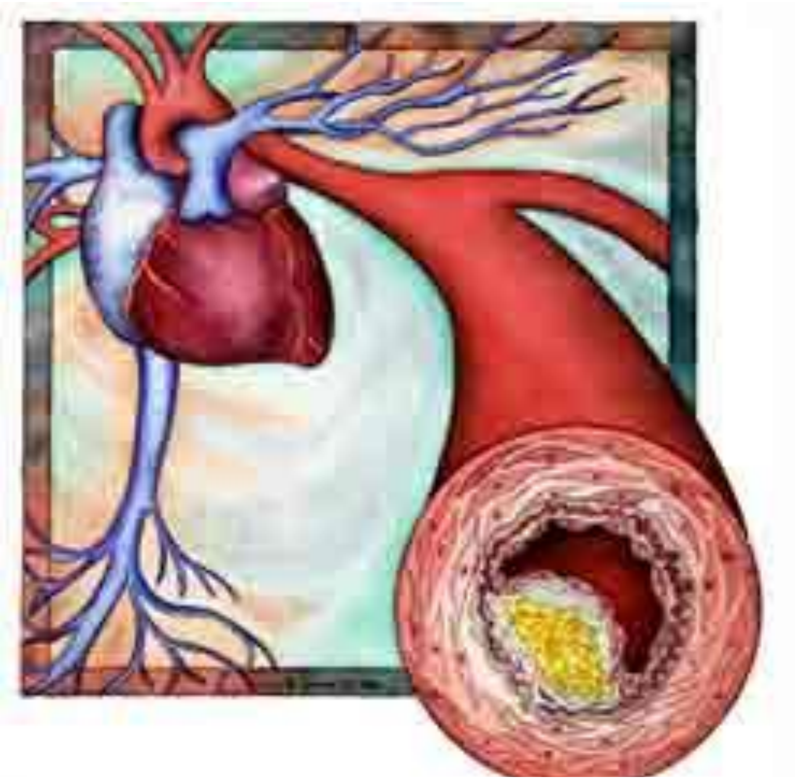
Atherosclerosis - atheromas



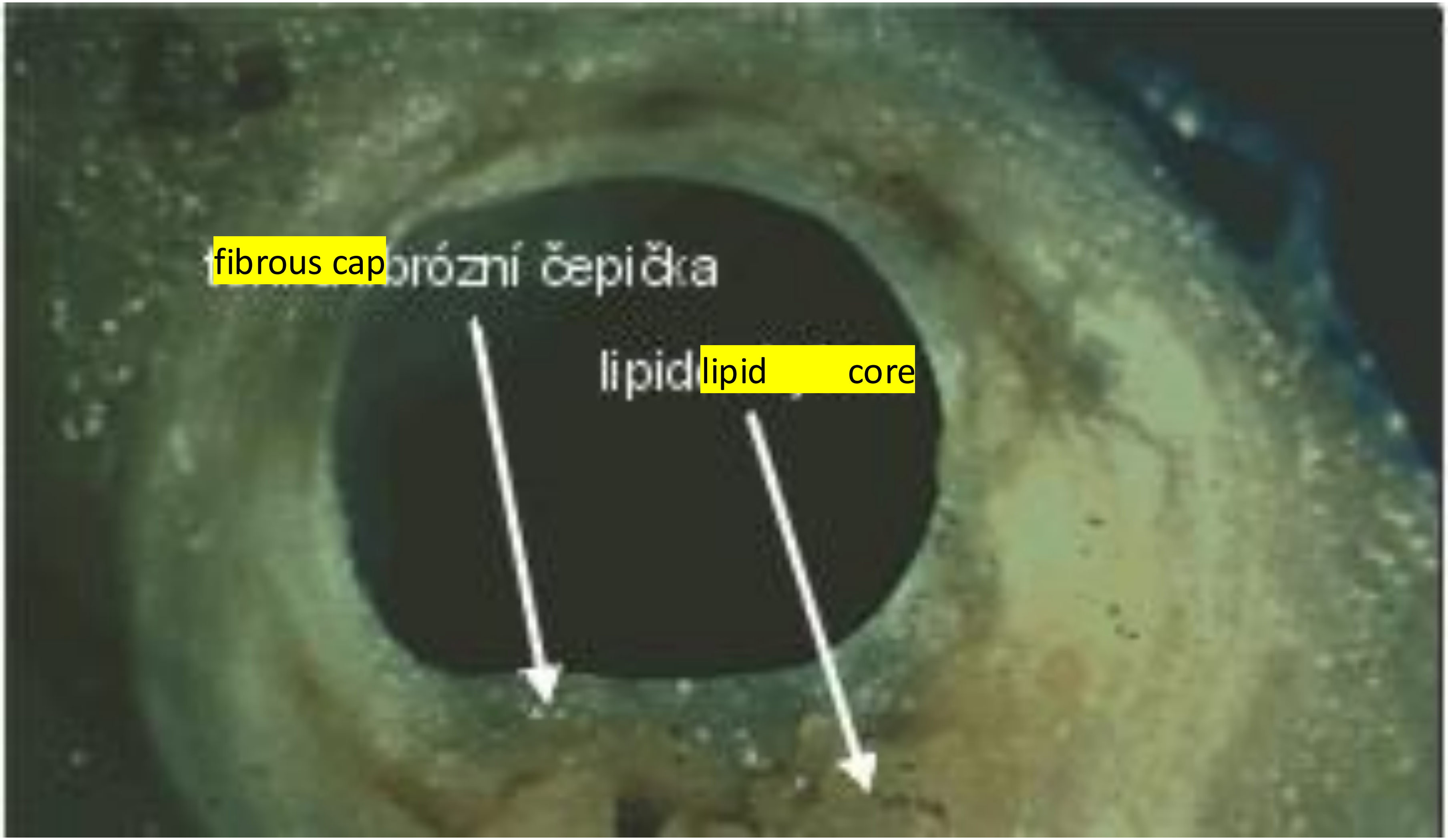
Atherosclerosis



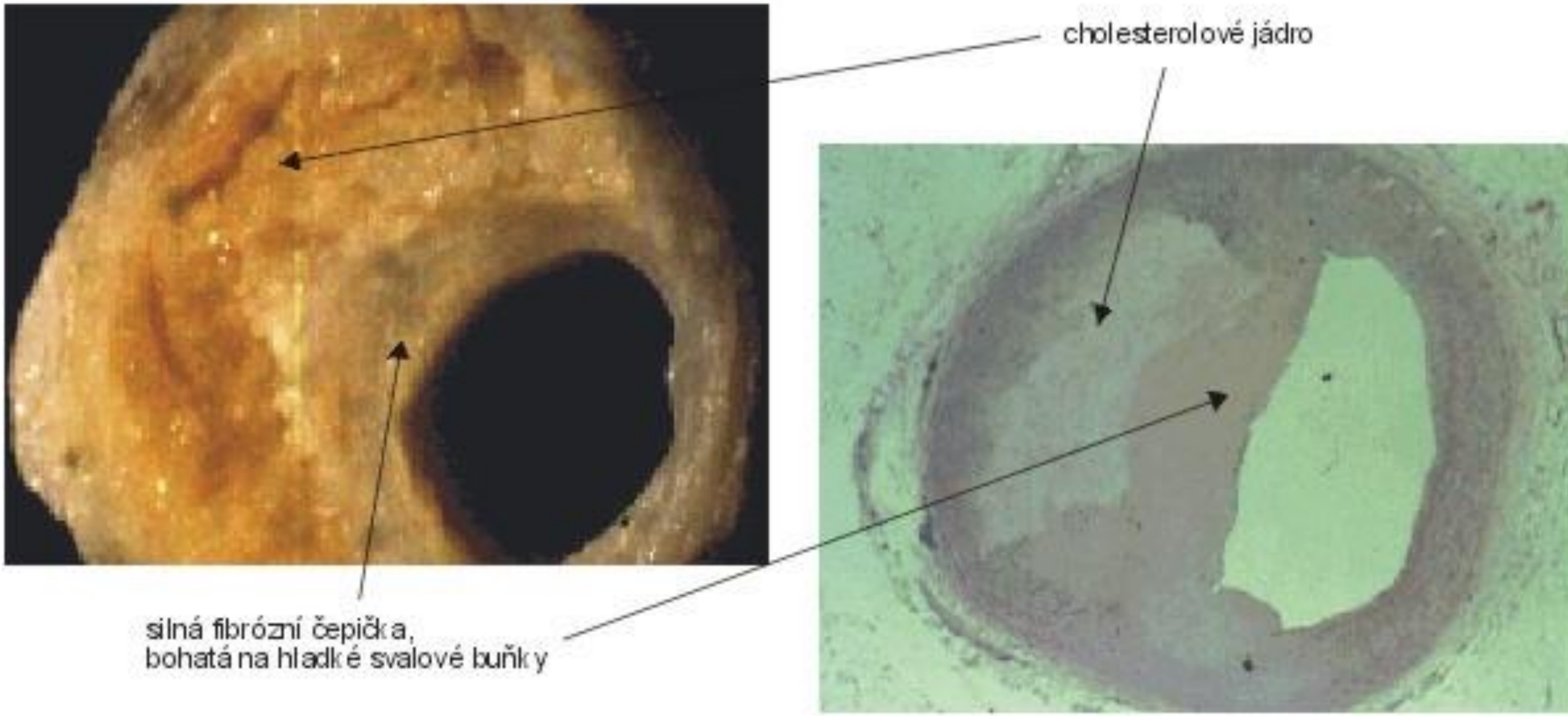
Atherosclerosis



Atherosclerosis a vulnerable plaque



Ateroskleróza – stabilný plát



Ateroskleróza – ruptúra plátu