HEART DISEASES

APPROVED

CONGENITAL HEART DISEASE

INFLAMMATORY AND VALVULAR HEART DISEASE

ISCHEMIC HEART DISEASE and SUDDEN CARDIAC DEATH

CARDIOMYOPATHY: HYPERTENSIVE, HYPERTROPHIC, AND DILATED

ISCHEMIC HEART DISEASE

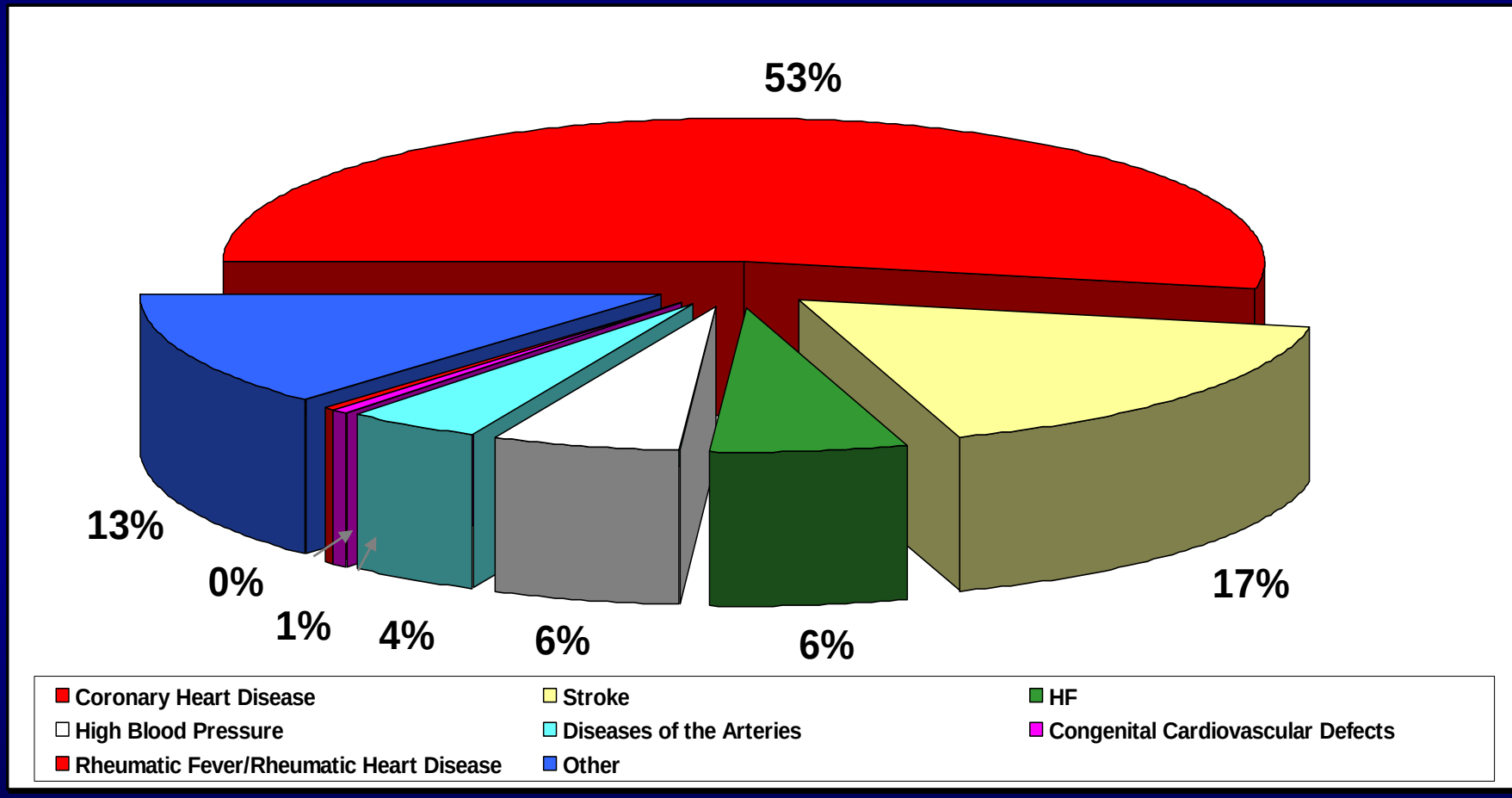
ISCHEMIC HEART DISEASE (IHD)
CORONARY HEART DISEASE (CHD)
CORONARY ARTERY DISEASE (CAD)
ATHEROSCLEROTIC HEART DISEASE (ASHD)

All ways of saying there is compromise of blood flow and oxygen to the myocardium.

Synonymous terms referring to syndromes resulting in and from myocardial ischemia

Percentage Breakdown of Deaths From Cardiovascular Diseases
United States:2003*

American Heart Association®
Learn and Live℠



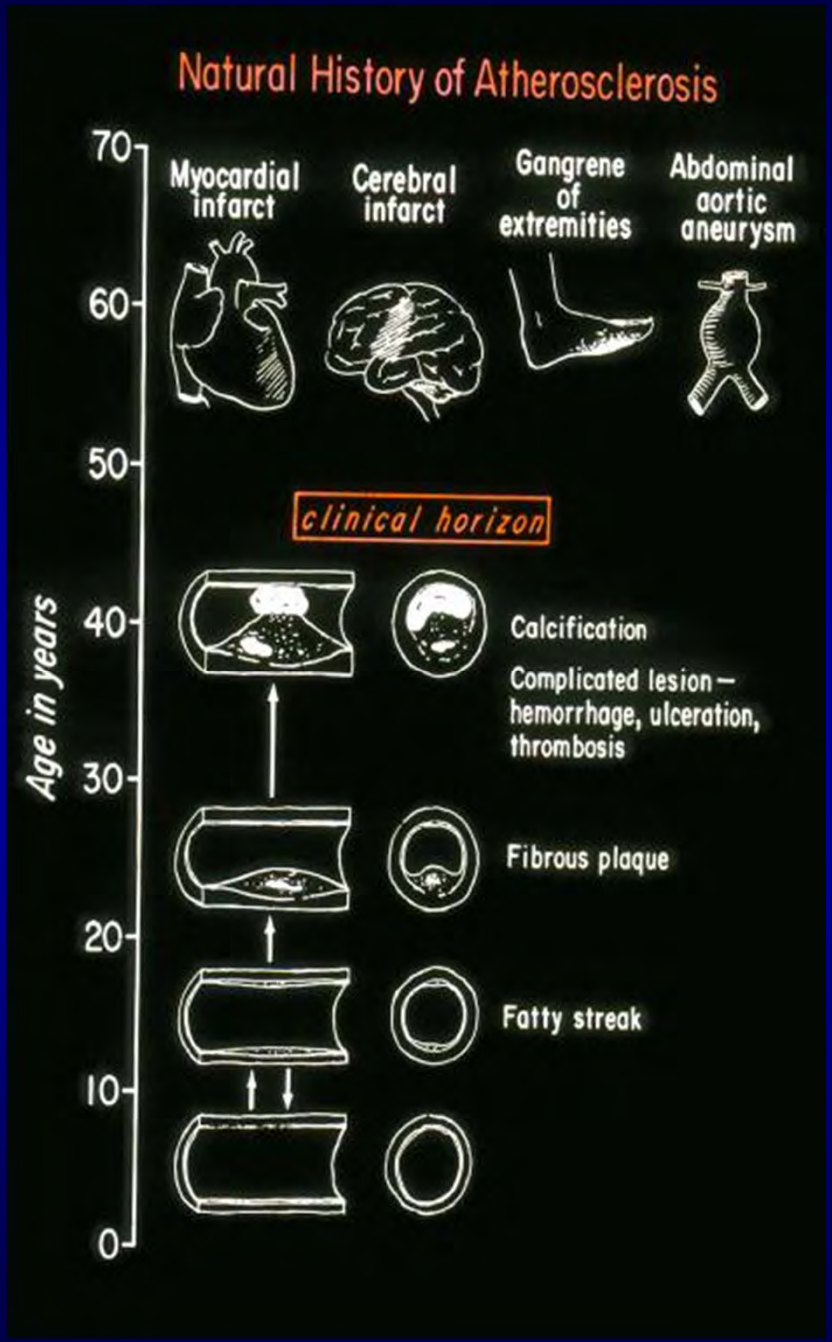
*Source: CDC/NCHS and NHLBI. *Preliminary*

ISCHEMIC HEART DISEASE

Although atherosclerosis of the coronary arteries is the most common mechanism responsible for myocardial ischemia, other less common mechanisms can also cause ischemia. These include:

- **Coronary emboli**
- **Coronary spasm (incl. toxic)**
- **Complications of connective tissue disorders**

Can be spontaneous or toxic induced (i.e. cocaine)



Know the risk factors of patients.

Atherosclerosis Risk Factors:

Genetics

Cigarette smoking

Hypertension

Diabetes mellitus

Dyslipidemias

Inflammation

MAJOR SYNDROMES

ANGINA PECTORIS

STABLE ANGINA

On exertion patient will have chest pain but at night or with nitrates it will go away. Usually due to a critical stenosis, which becomes apparent when the heart needs greater blood flow.

May occur during sleep and does not respond to angina.

UNSTABLE ANGINA

MYOCARDIAL INFARCT

SUDDEN CARDIAC DEATH

ISCHEMIC CARDIOMYOPATHY

When the heart doesn't get good blood and oxygen, the heart doesn't function properly. You will see both functional change and change in heart structure which can affect the mitral valve. If myocardium is ischemic, you can also get mitral regurgitation.

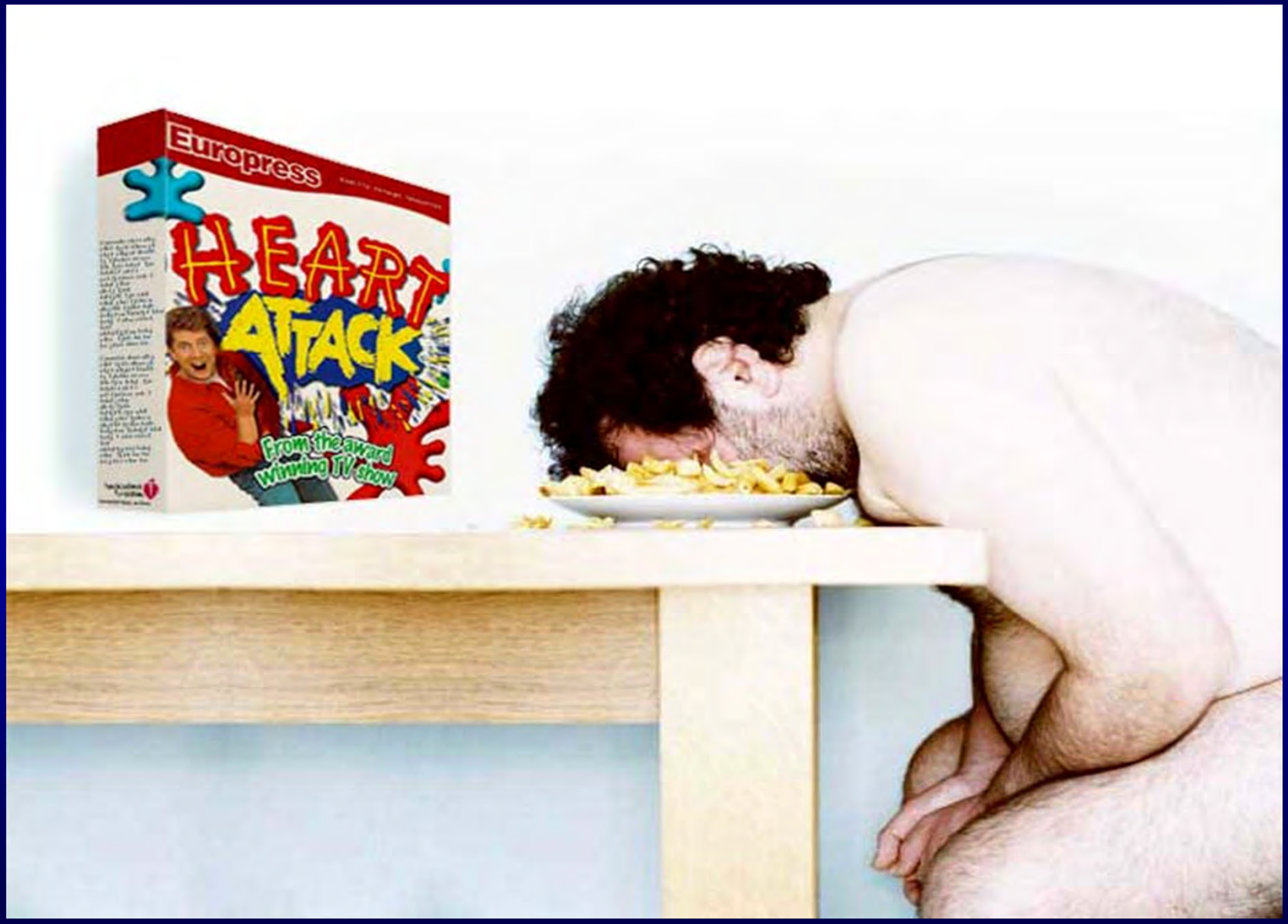
PREVALENCE OF ISCHEMIC HEART DISEASE

13.5 million Americans (7% of adult population) have symptomatic IHD evidenced by:

- **Angina Pectoris (50%)**
- **Previous MI (>50%) … or both**

>500,000 deaths/year (one-third of all U.S. deaths) one-third are premature, i.e. before age 75

Sudden Cardiac Death



Definition:

- **Natural Unexpected Death Secondary to Cardiac Causes With Rapid Loss of Consciousness**

Patient has some cardiac issue that leads to sudden cessation of cardiac function. Arrhythmia, MI, aneurysm

- **Risk factors and Existing Disease may be previously documented**

Interestingly, you can survive sudden cardiac death. If you are resuscitated or defibrillated, you have survived a sudden cardiac death event. However, most patients will die within 24 hours.

Atherosclerosis: CAD

- 50% of deaths from CAD are SCD
- 50 – 60% of SCD is the first Clinical manifestation of CAD
- 10% of patients with CAD first presentation is SCD

SCD: Incidence

- 300,000- 350,000 annually in the U.S.
- 0.1-0.2% per year for > 35 years old
- **Age peaks:**
  - Birth to 6 months (SIDS, congenital)
  - 45 -75 years old
    - Teens - 30 yo: incidence is only .001%
- **Gender:**
  - Male: Female **3-7:1 prior to menopause**

Sudden Infant Death Syndrome

Etiology: Age Dependent

- > 30 years
  - **Atherosclerosis (ischemia) ~ 2/3 of SCD**
  - Cardiomyopathies
    - LVH, HOCM, ARVD, DCM
  - Myocarditis / Endocarditis /Infectious
  - Infiltrative / Storage Disorders
    - Fabry's, Hemochromatosis, Sarcoid, Amyloid, Desminopathy
  - Vascular Disease / Valvular Disease
    - Aneurysms, Dissections, Cong. Coronary Anomalies
  - Conduction System/Channelopathies
- **CHF – may be feature of many prior to "sudden death"**

Hypertrophic cardiomyopathy

Arhythmogenic ventricular dysplasia

dilated cardiomyopathy

Can be structural or genetic

SUDDEN CARDIAC DEATH

ELECTROPHYSIOLOGY: Ventricular Fibrillation, Asystole, PEA

If there is asystole, generally you are not going to resuscitate that patient.

ANATOMIC FINDINGS:

Mostly discovered during autopsy

- Acute Coronary Plaque Rupture or Thrombosis (minority of cases)
- Acute or Organizing (clinically silent?) MI (minority of cases)

Patient won't know that they have had an MI.

- No acute lesion but >60% stenosis of a coronary artery, often LAD (1º VF)

ISCHEMIC HEART DISEASE

The underlying cause of ischemic heart disease is usually atherosclerosis of the coronary arteries

The most common cause of acute coronary syndromes (unstable angina or acute myocardial infarction) is a sudden increase in luminal narrowing due to thrombosis and/or plaque rupture.

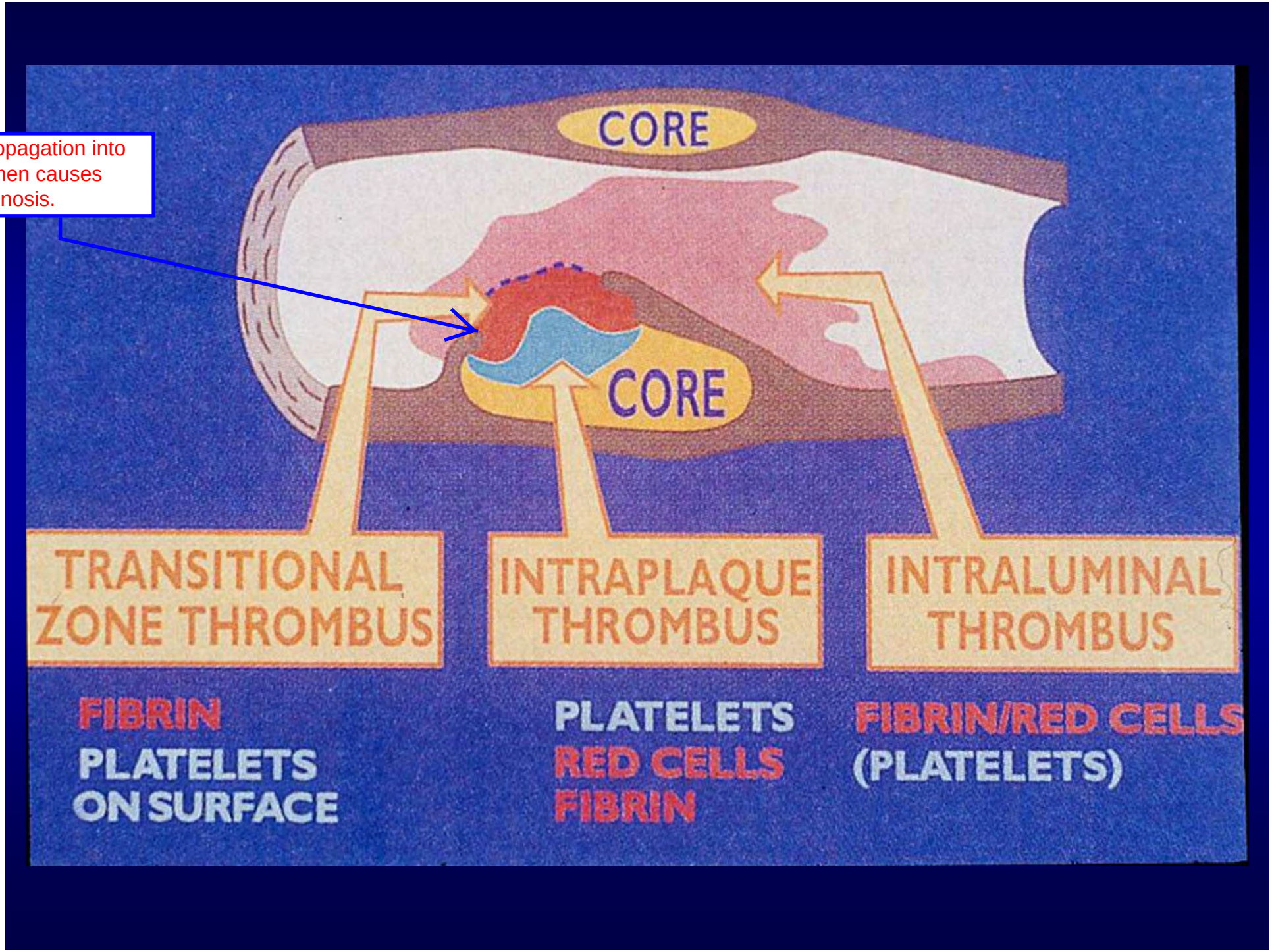
Plaque Rupture and Thrombosis

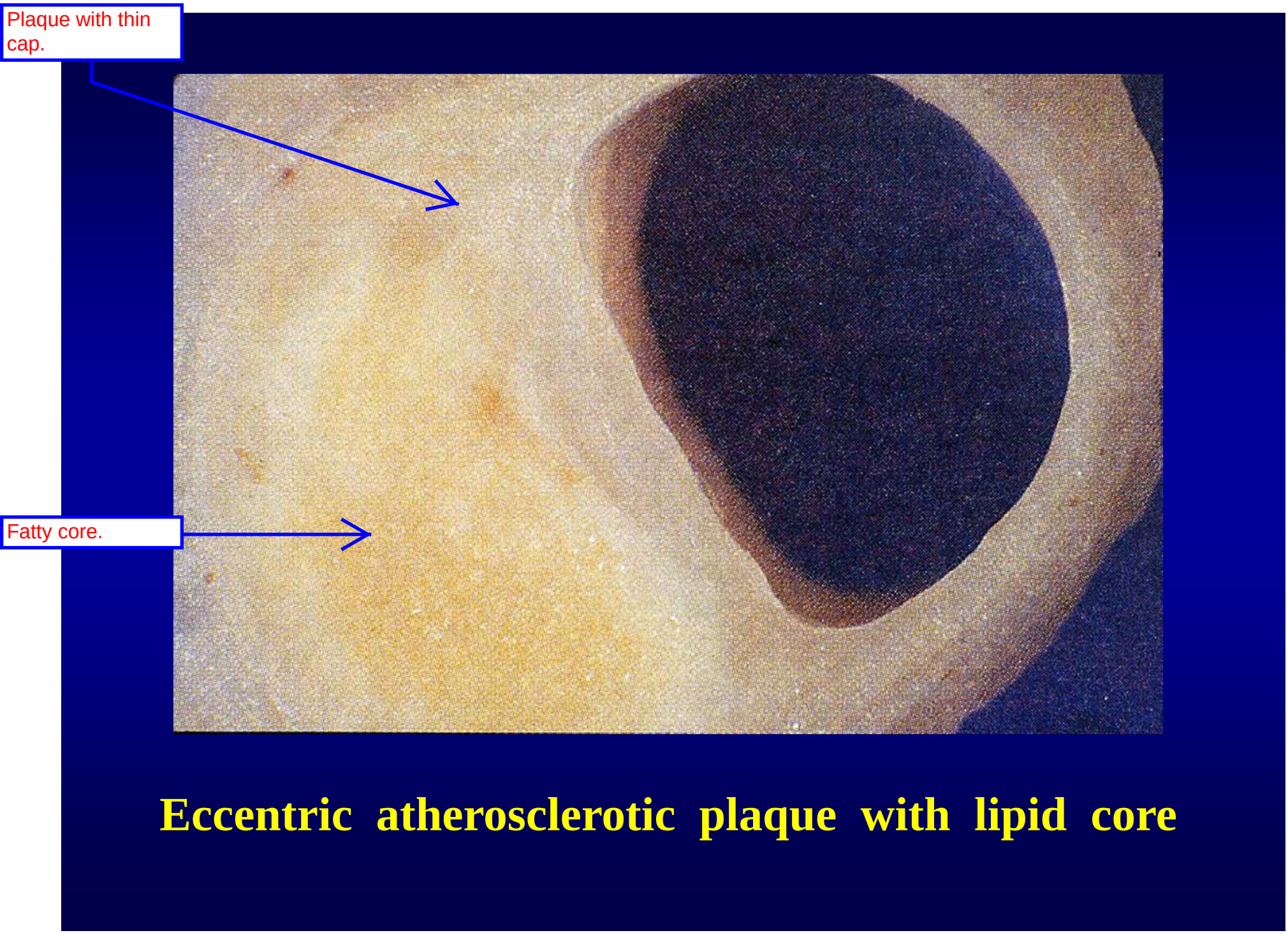
Acute Arterial Occlusion

Vulnerability to Plaque Rupture

- Large Atheromatous Core
- Calcification with Erosion
- Thin Fibrous Cap/Increased Cap Tension
- Inflammation, Foam Cells in Fibrous Cap
- Matrix Metalloproteases
- Cap Fatigue

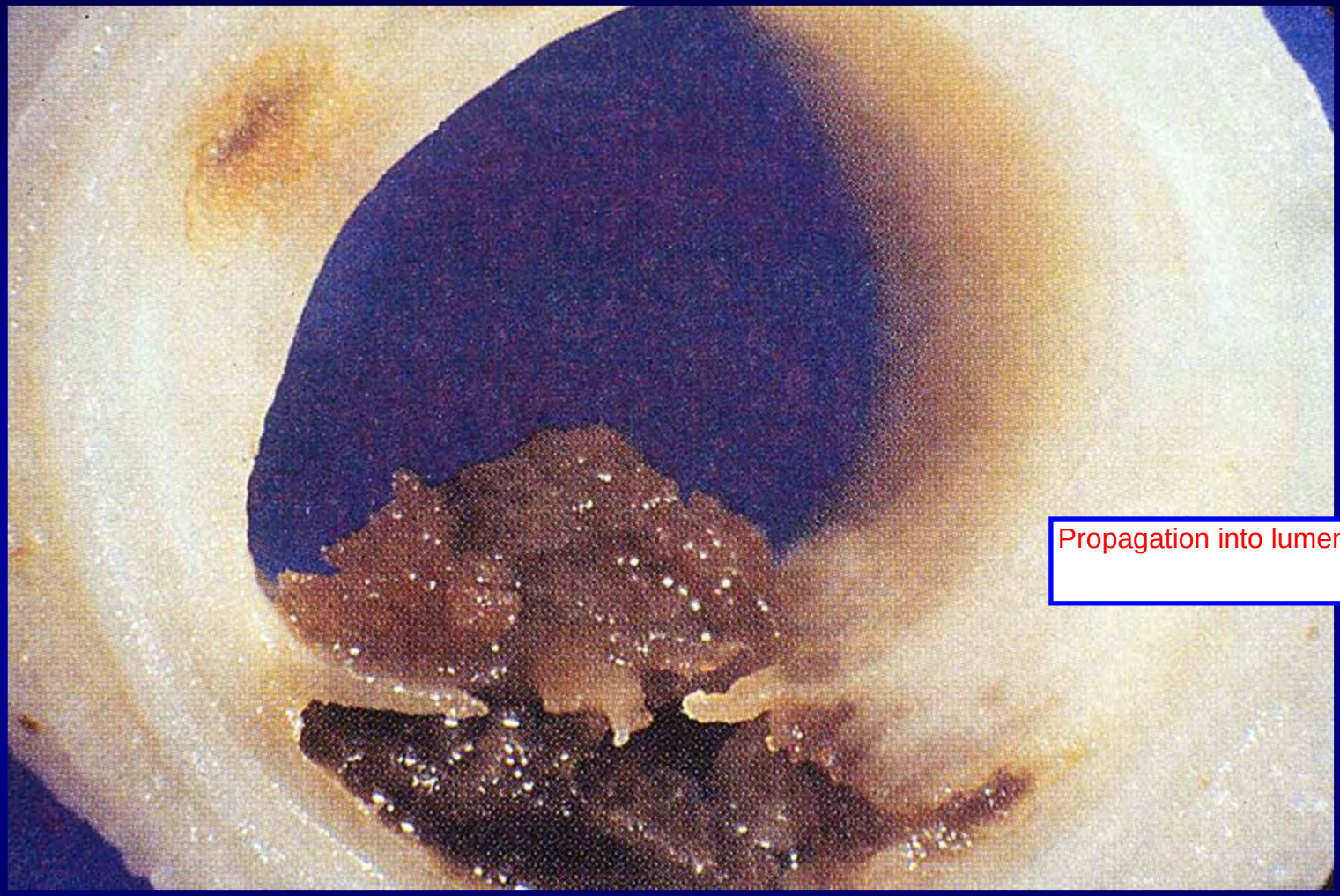
If a patient has vulnerable plaques, its not usually the severity but rather the fact that they have one or more of the conditions on this list, which leads to higher risk of rupture. Can occur at 20-40% stenosis.


Propagation into lumen causes stenosis.
CORE
CORE
TRANSITIONAL ZONE THROMBUS
INTRAPLAQUE THROMBUS
INTRALUMINAL THROMBUS
FIBRIN
PLATELETS
ON SURFACE
PLATELETS
RED CELLS
FIBRIN
FIBRIN/RED CELLS
(PLATELETS)



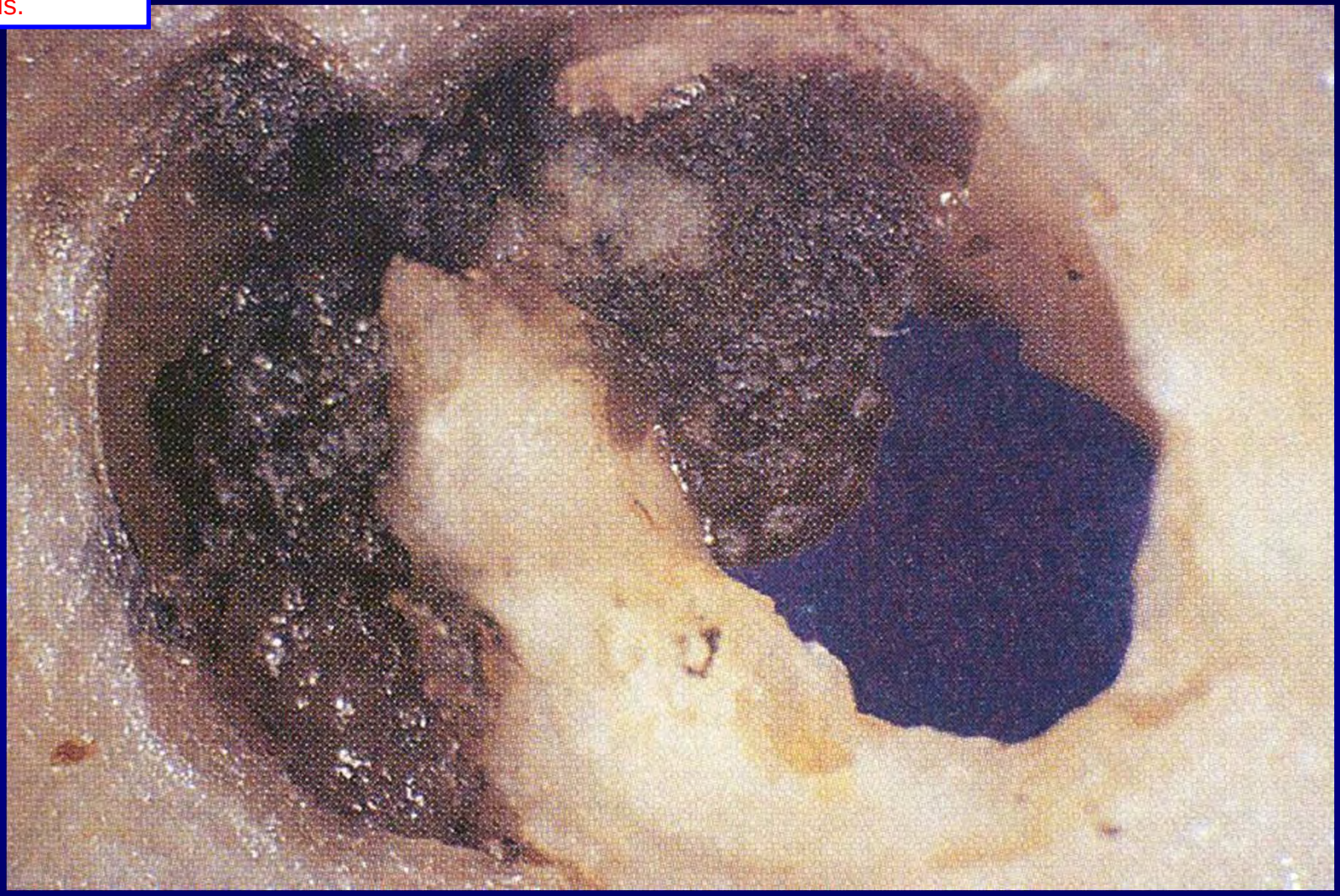
Eccentric atherosclerotic plaque with lipid core

Ruptured atherosclerotic plaque with hemorrhage into plaque



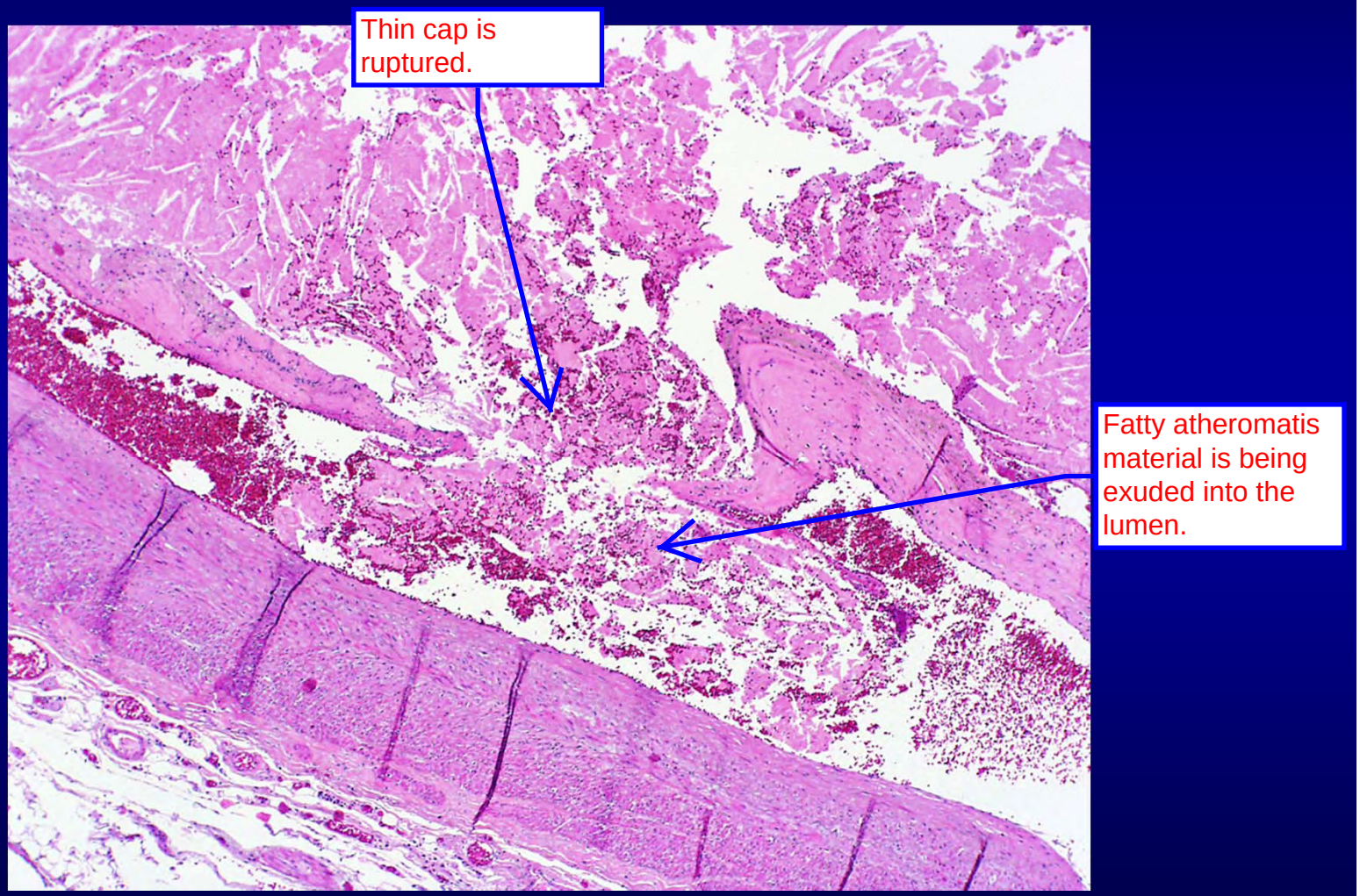
Ruptured atherosclerotic plaque with hemorrhage and thrombus on the surface

Plaque continues to propagate and causes acute stenosis.

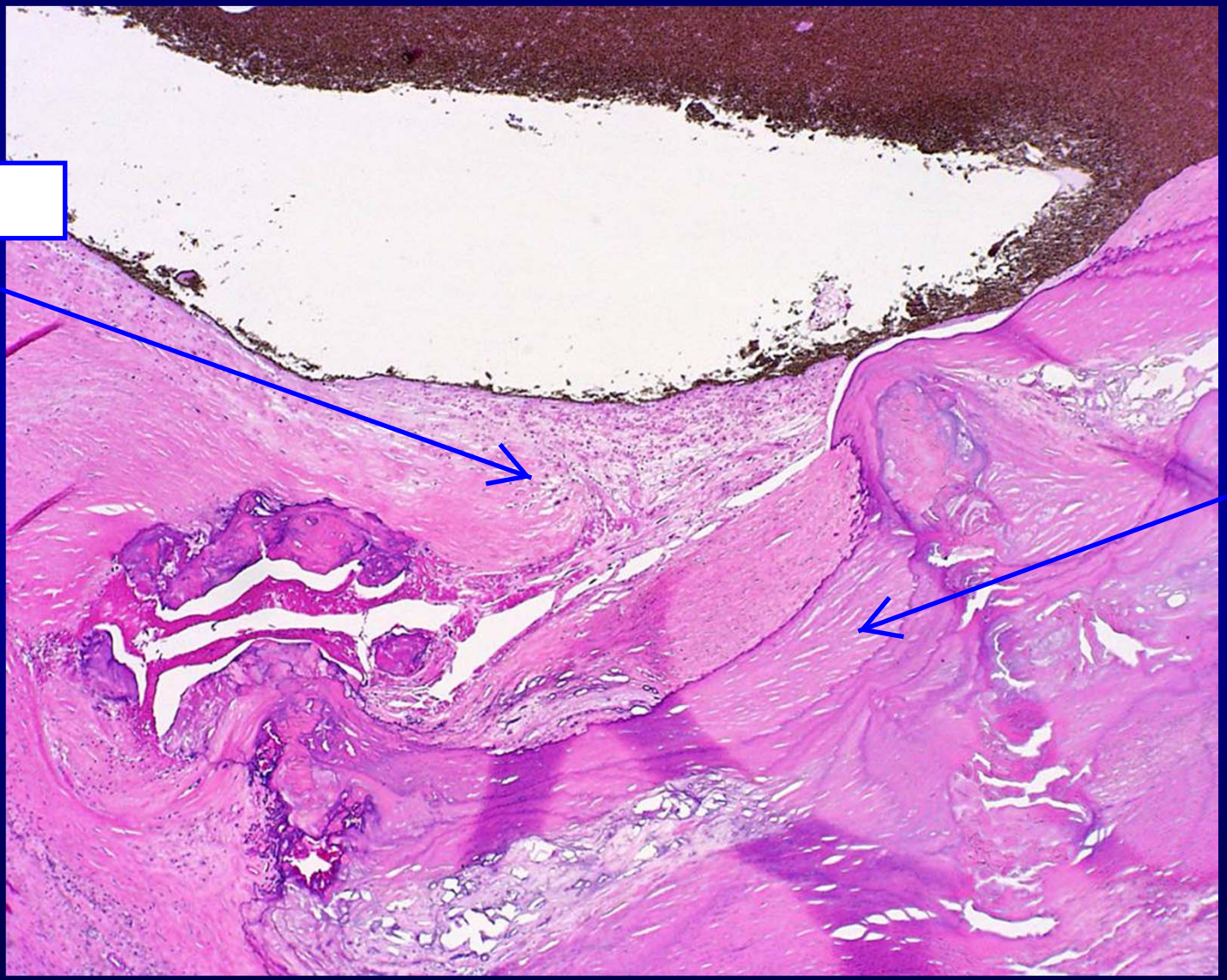


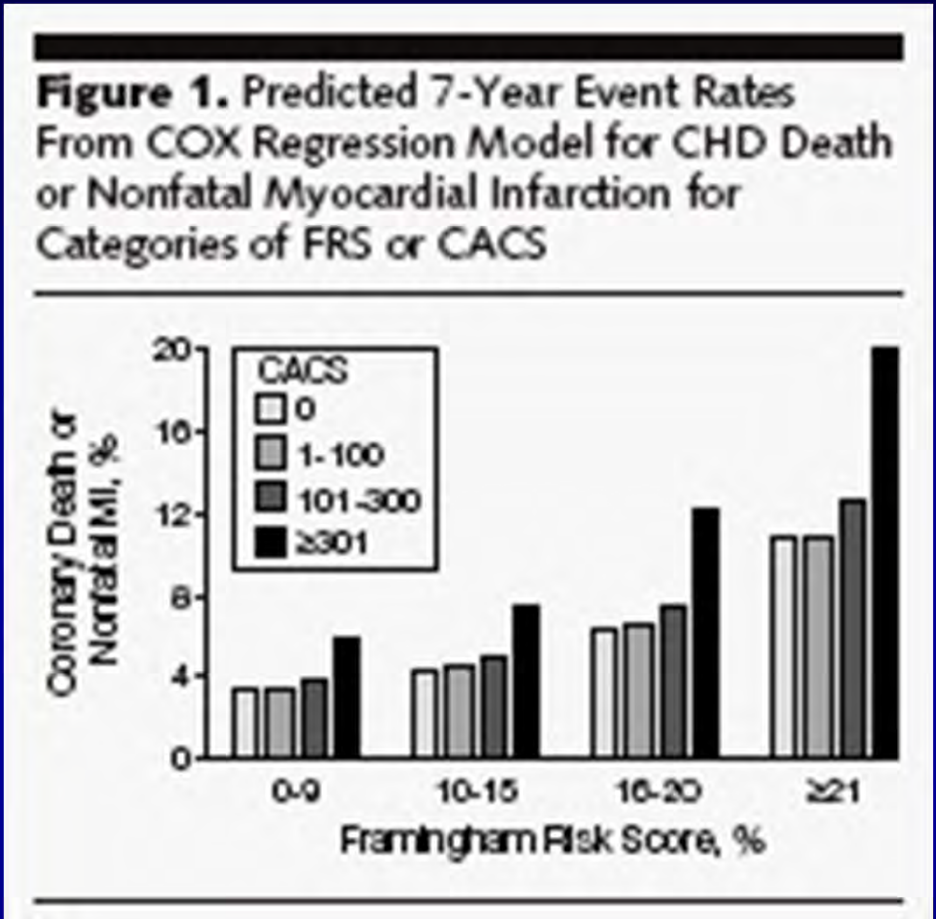
Ruptured atherosclerotic plaque with hemorrhage and thrombus on the surface

Plaque Rupture and Thrombosis



Plaque Calcification





Coronary Artery Calcium Score Combined with Framingham Score for Risk Prediction in Asymptomatic Individuals. JAMA 2004; 291:210-215

Framingham Score is based on the following risk factors: age, gender, diabetes, smoking history, blood pressure, total cholesterol, and LDL cholesterol

Coronary Artery Calcium Score (CACS) is based on CT scan evaluation of coronary calcification

If you have many of these risk factors, you will have a much higher chance of cardiac death. Calcification increases the risk even more.

If you don't regularly exercise and then randomly exert yourself you have a much higher risk than a person that works out.

Triggers of SCD

Exertion: 6- 30%

- **CAD/ plaque rupture; Neurogenic conditioning**
- **< weekly exercise: 75x risk, > 5/week: 11 x risk**
- **Overall: 1 SCD per 1,510,000 severe exertions**

Sleep: 12%

- Increased occurrence for nonstructural disease

Stress

Sexual Activity:

- Low even with CAD

So don't worry too much.

Ischemia: How does it Kill?

- **Arrhythmia (VF/VT) – 2 Phases:**
  - **Substrate and Trigger**
  - **1A: 2 – 10 minutes post occlusion**
    - **Altered extracellular K^+ affects refractory periods**
    - **Injury Currents – normal cells reexcite prematurely**
  - **1B: 18 – 30 minutes post occlusion (greater role)**
    - **Epicardial cells demonstrate depression of excitability before mid and subendocardial cells**
    - **Electrical signals produced by unequal stretching of cells at border of ischemic zone**

Set up for ventricular fibrillation

2 important time periods for someone having an MI.

Cells are firing off too early

Creates gradient of excitability

Injured myocardium stretches differently from the healthy myocardium. That injury actually causes electrical signal, which is the trigger.

Ischemia: How does it Kill?

Later deaths

- **Infarcts – Prior scar creates reentry paths**
  - **Autonomic Denervation**
    - **Baroreflex Sensitivity: Vagal protection loss**
    - **Nerve " Sprouting": sympathetic reinnervation post MI demonstrated with marker studies.**

Lose the ability of the vagus nerve to tell the heart to chill out.

Overgrowth of sympathetic nerves that stimulate the heart.

- **Ventricular Dysfunction - ↓ LVF, Regurg**

When you have death of a bunch of myocardial cells.

MANAGEMENT OF ACS RELATED SUDDEN CARDIAC DEATH

Prevention of IHD (Risk factor control)

Identification of High Risk Patients

- **Prophylactic drug therapy (ß blockers)**
- **Implantable automatic defibrillator**

Rapid Resuscitation (each minute of VF decreases survival rate by 7-10%)

Best thing to do is defibrillate a patient to save their life.

ISCHEMIC HEART DISEASE

Pathology of Myocardial Infarcts

Heart will undergo coagulative necrosis first, then there is inflammation then there is cleanup by macrophages and scar formation.

Patient Prognosis is Inversely Related to Infarct Size

Larger Infarcts:

- **Higher frequency of arrhythmias**
- **Higher frequency of hemodynamic complications**
- **Higher short-term mortality**

Cardiogenic Shock is usually associated with infarcts occupying > 30% (mean = 40%) of the Left Ventricle

Gross Pathology: Determinants of Infarct Size

Size of the Vascular Territory involved (Area at Risk)

Larger infarct if the occlusion is proximal rather than distal because it supplies a larger territory.

Duration of Ischemia: Wavefront Phenomenon

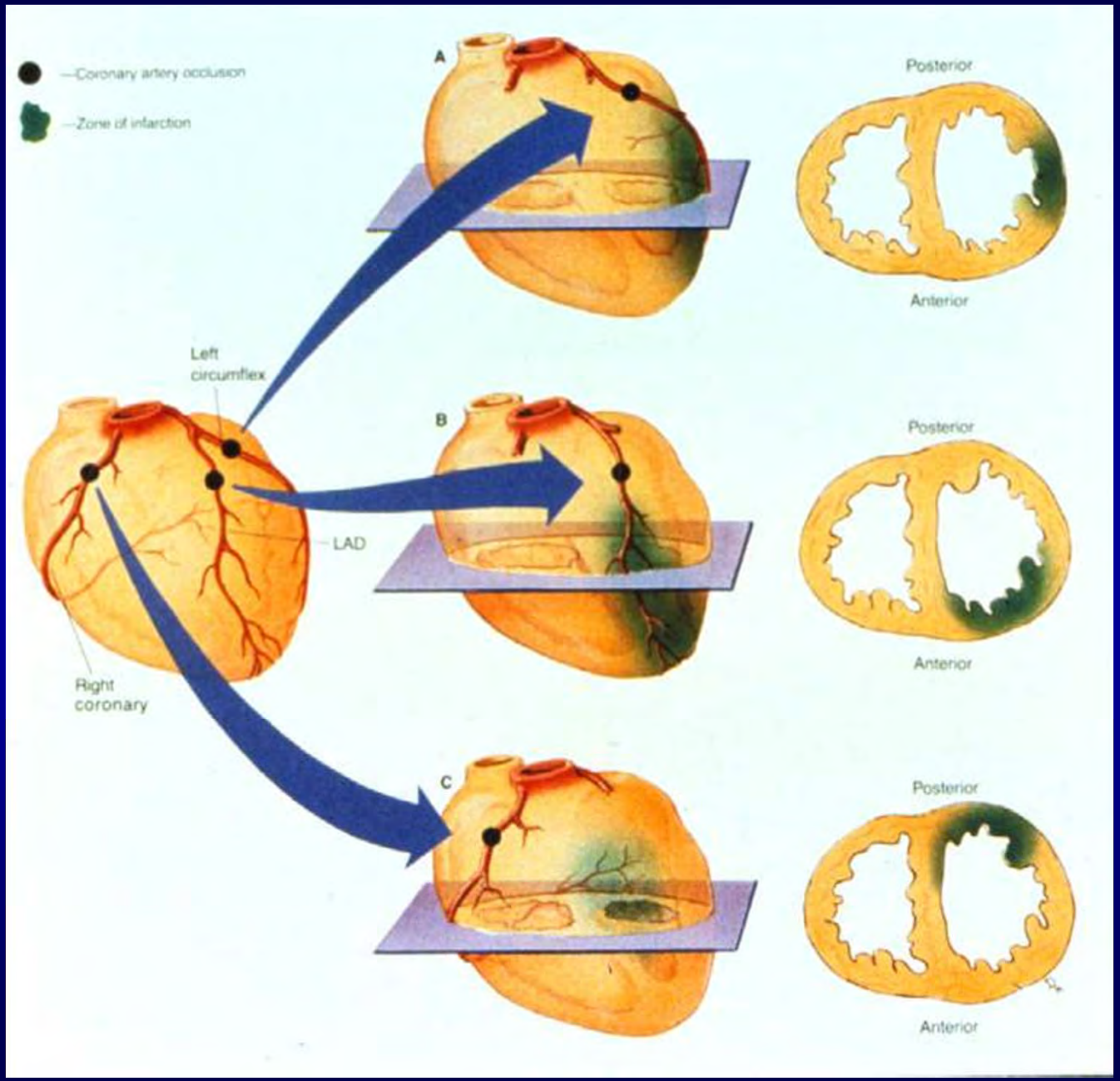
Magnitude of Collateral Blood Flow to the Area at Risk

Can slow down the progression of an MI

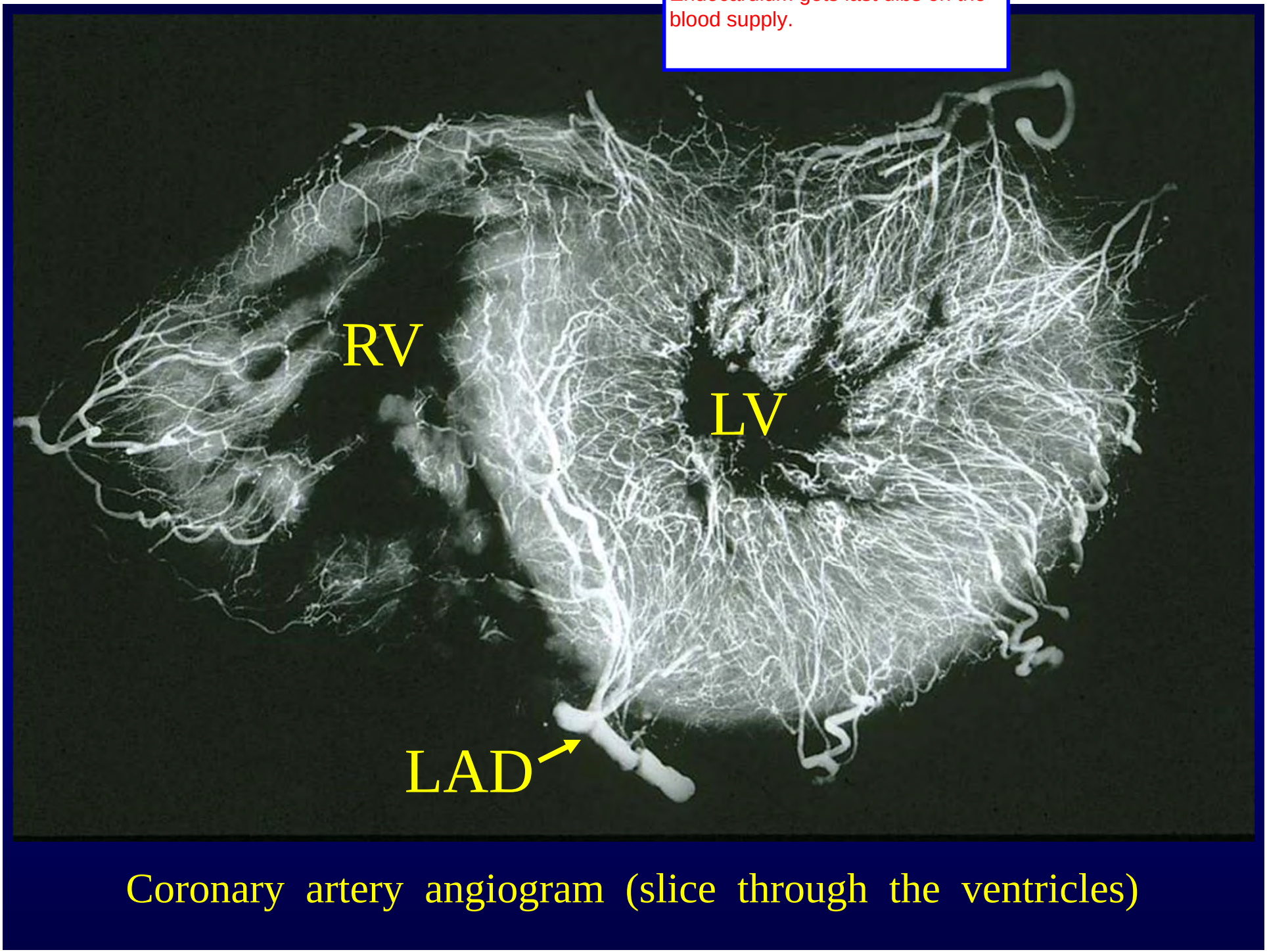
Metabolic Rate of Myocardium during Ischemia

- **Hemodynamic Determinants - Heart rate, Systolic LV pressure, Contractile state**
- **Myocardial Temperature**

How hard was the heart working before losing blood flow? In a person that was sleeping it will take longer for the infarct to develop, than if the person was exercising.

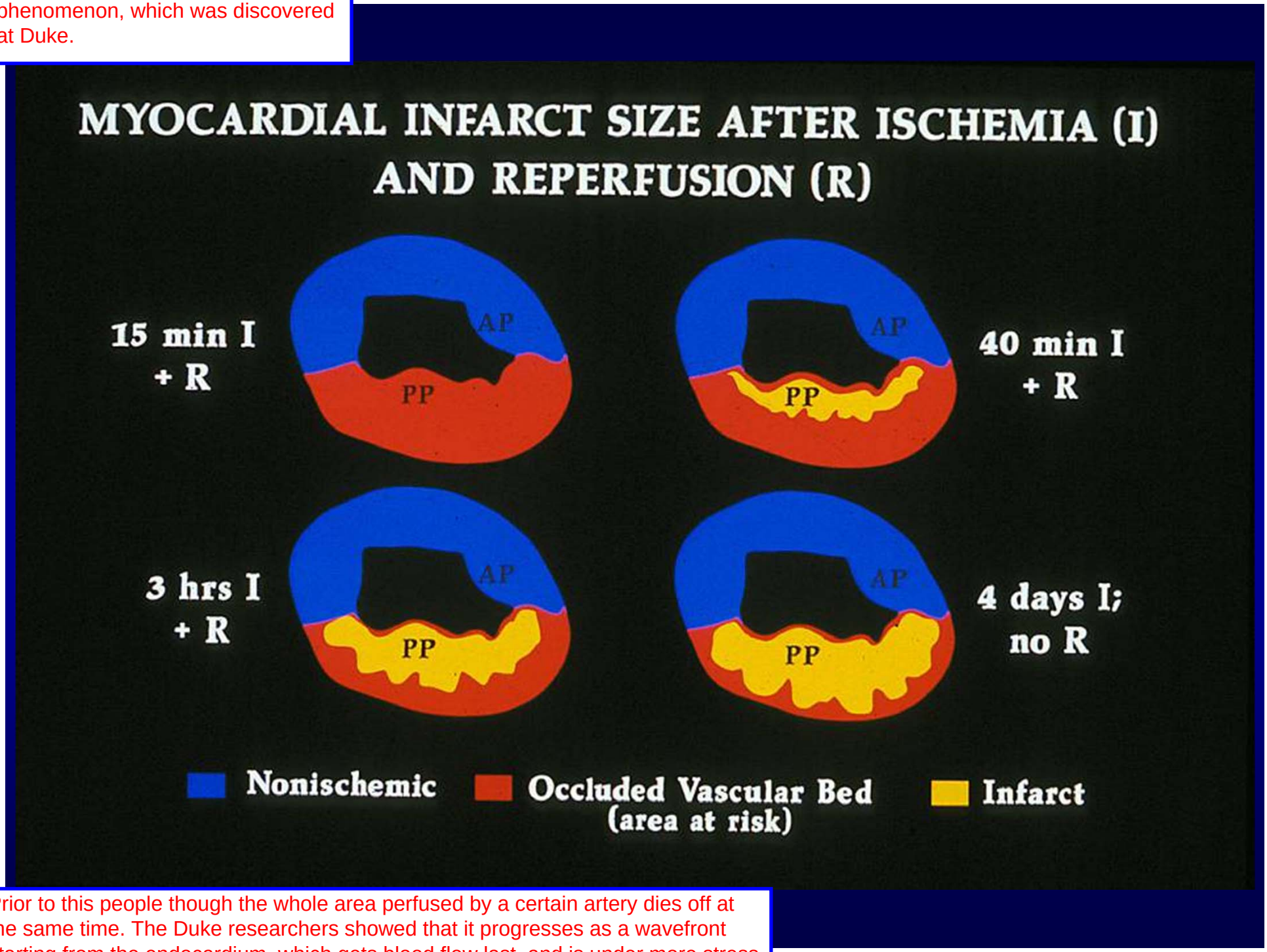

—Coronary artery occlusion
—Zone of infarction
A
Posterior
Anterior
Left
circumflex
B
Posterior
LAD
Anterior
Right
coronary
C
Posterior
Anterior

Endocardium gets last dibs on the blood supply.

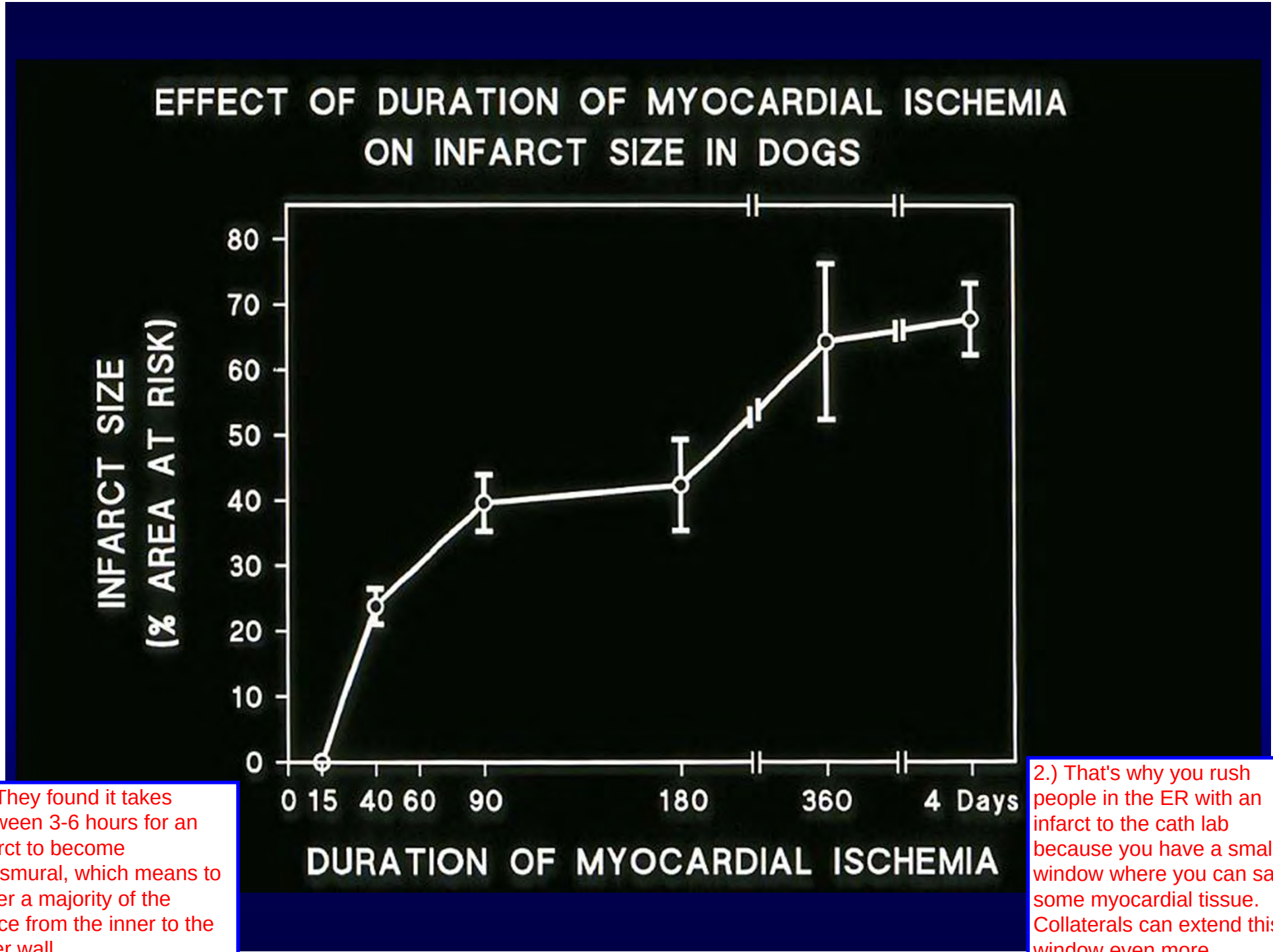


Coronary artery angiogram (slice through the ventricles)

From the paper discussing wavefront phenomenon, which was discovered at Duke.



Prior to this people though the whole area perfused by a certain artery dies off at the same time. The Duke researchers showed that it progresses as a wavefront starting from the endocardium, which gets blood flow last, and is under more stress so requires more oxygen. Then the infarct progresses to the epicardium.



1.) They found it takes between 3-6 hours for an infarct to become transmural, which means to cover a majority of the space from the inner to the outer wall.

2.) That's why you rush people in the ER with an infarct to the cath lab because you have a small window where you can save some myocardial tissue. Collaterals can extend this window even more.

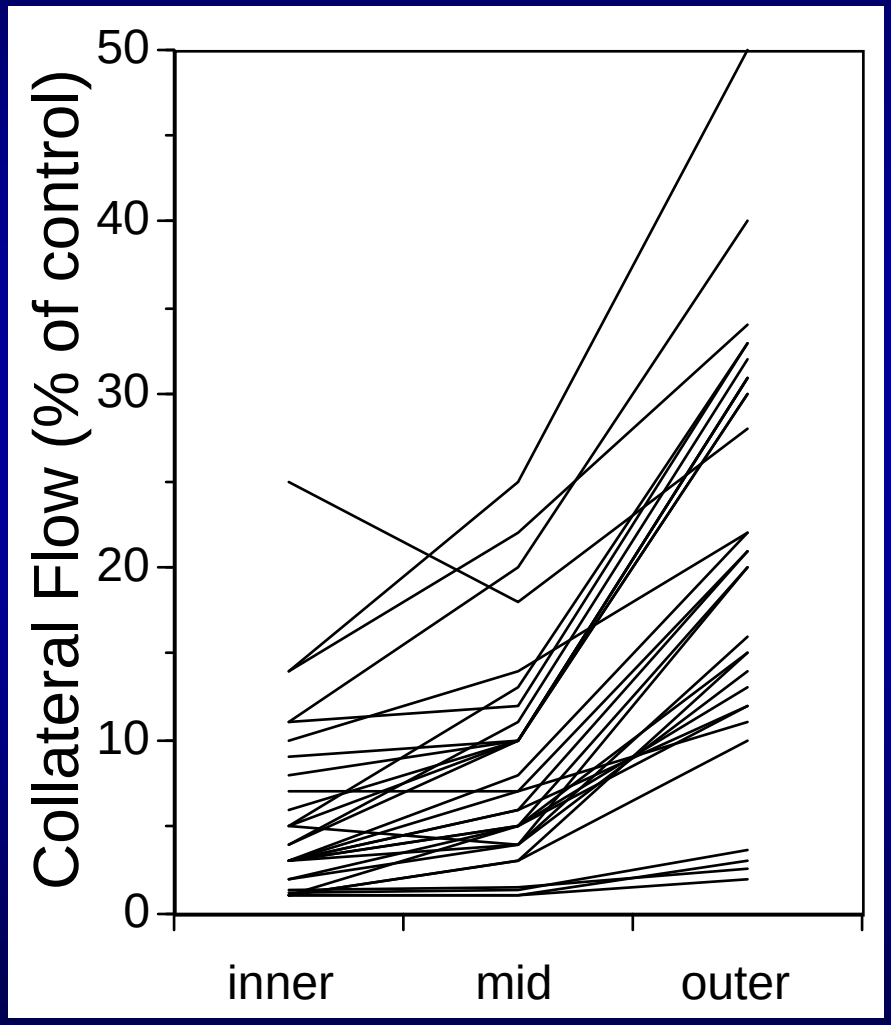
Relationship between Collateral Flow and Infarct Size

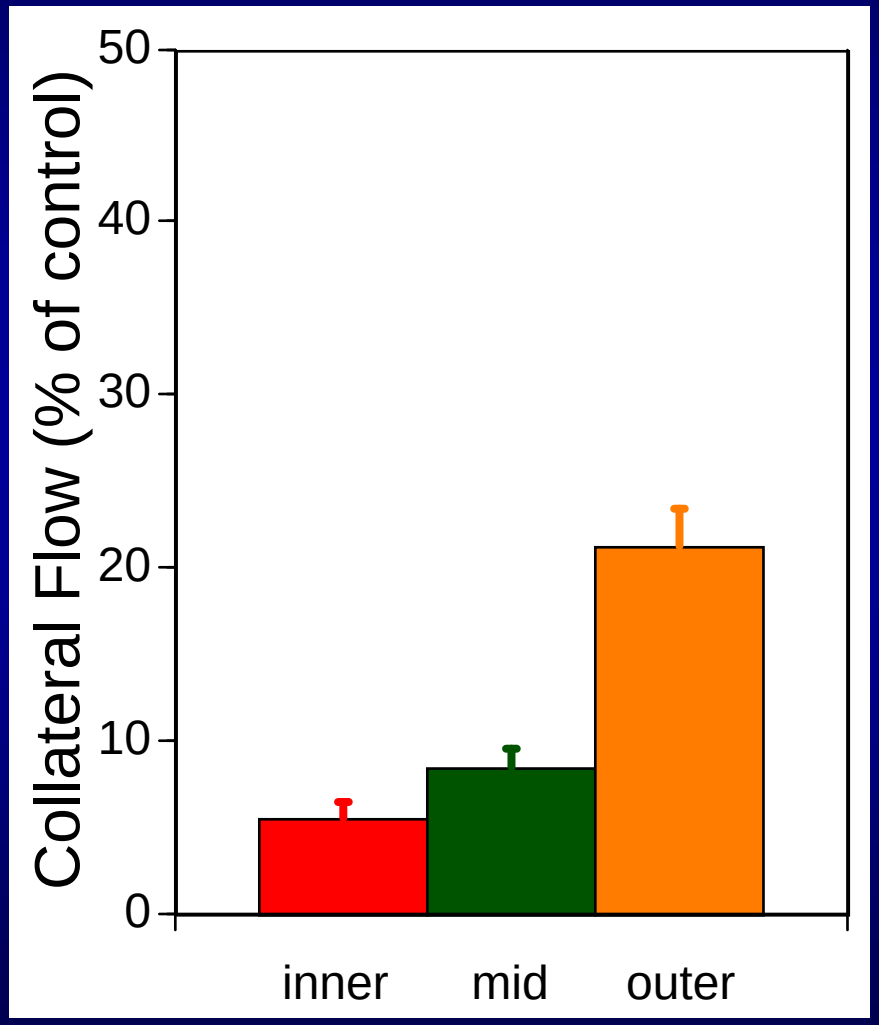
Collateral flow is highest in the outer layer of the myocardium; if collateral flow is high enough, the infarct will not be transmural regardless of duration.

Gradual stenosis of a coronary artery promotes the development of collateral circulation.

Some patients with virtually complete occlusion of a major coronary artery do not have an infarct.

Collateral Flow in Different Layers (inner third, middle third, outer third) of the Myocardium following Coronary Occlusion





Dating Myocardial Infarcts

- **Importance**
  - **Potential for intervention/myocardium salvage**
  - **Forensic: Cause of death vs. Contributing Factor**
  - **Medico-legal: Assess Negligence**

- **Assessment**
  - **History: Risk Factors, HPI, Physical Exam, Labs**
  - **Gross: Autopsy > Surgical Specimens**
  - **Histology: Routine and Special Stains**

MI: Gross Appearance

If blood flow is restored, it can heal quicker and you will have different features than if blood flow was not restored.

- **REPERFUSION? – Key question**
  - Pallor vs. Hemorrhage
  - Timing of Reperfusion/Ischemia
  - Border vs. Central Healing

-When no reperfusion, there is low blood flow, and low risk of hemorrhage.
-When you do have reperfusion, blood vessels are often injured and will leak. So restoration of blood flow leads to hemorrhagic infarcts.
-May also see contraction band necrosis where reperfusion causes calcium flux and the contractile fibers in necrotic myocytes over-contract and you get these dense bands.

Healing occurs from outside in.

- Acute findings
  - **May be absent**
  - Pallor or hemorrhage
    - **Inflammation → Myophagocytosis**

May not see anything within the first 4-6 hours because it takes time for necrosis and inflammation to set in.

- Subacute
  - Granulation tissue
  - Mummified myocytes

scarring

- Advanced healing – Mature fibrous scar
  - Fatty change – mesenchymal differentiation

some people get really fatty infarcts

Just pay attention to the yellow words and times.

Morphologic Stages of Myocardial Infarction: Inflammatory Response and Repair

-This is what generally happens in non-reperfused infarcts.

0 - 6 hours	**No Change (Gross or Microscopic)**
6 - 24 hours	+/- "Wavy-fiber Change" Early features of **Coagulative Necrosis** (Cytoplasmic eosinophilia; Nuclear pyknosis followed by karyolysis)
1 - 4 days	Coagulative Necrosis with **Acute Inflammatory Response** (mostly neutrophils) - maximum influx at 2 - 3 days; neutrophils intact at first, disintegrating by 3 - 5 days
5 - 7 days	**Macrophage Activity** (phagocytic removal of dead myocytes, pigmented macrophages increasing)
7 - 10 days	Developing peripheral rim of **Granulation Tissue**
1 - 6 weeks	Progressive **Organization** of infarct
1 - 3 months	Progressive **Collagen Deposition, Mature replacement scar**

***Consider Variable Reperfusion, Interventions and Infarct Size**

Dating Myocardial Infarcts

Who cares?

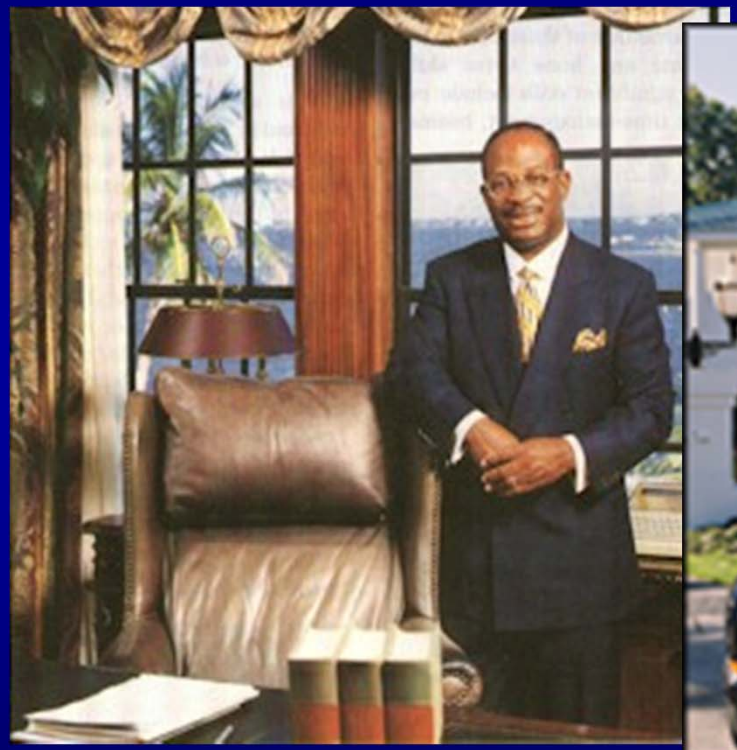
Case

- 47 yo male with a history of hypertension, tobacco abuse presents with reported new onset chest pain.
- He is worked up for cardiac as well as pulmonary and GI disease
- An ECG and Cardiac enzymes are eventually performed and are noted to be positive 12 hours after admission
- The patient is taken for cardiac catheterization where a thrombus in the LAD is treated with angioplasty and stenting. Did the right thing, but somewhat delayed.
- The patient has continued low ventricular funtion and succumbs that night to severe cardiogenic shock

Now Who Cares?

FAISON & GILLESPIE

Who *REALLY* Cares?




N901WG
Wings of Justice
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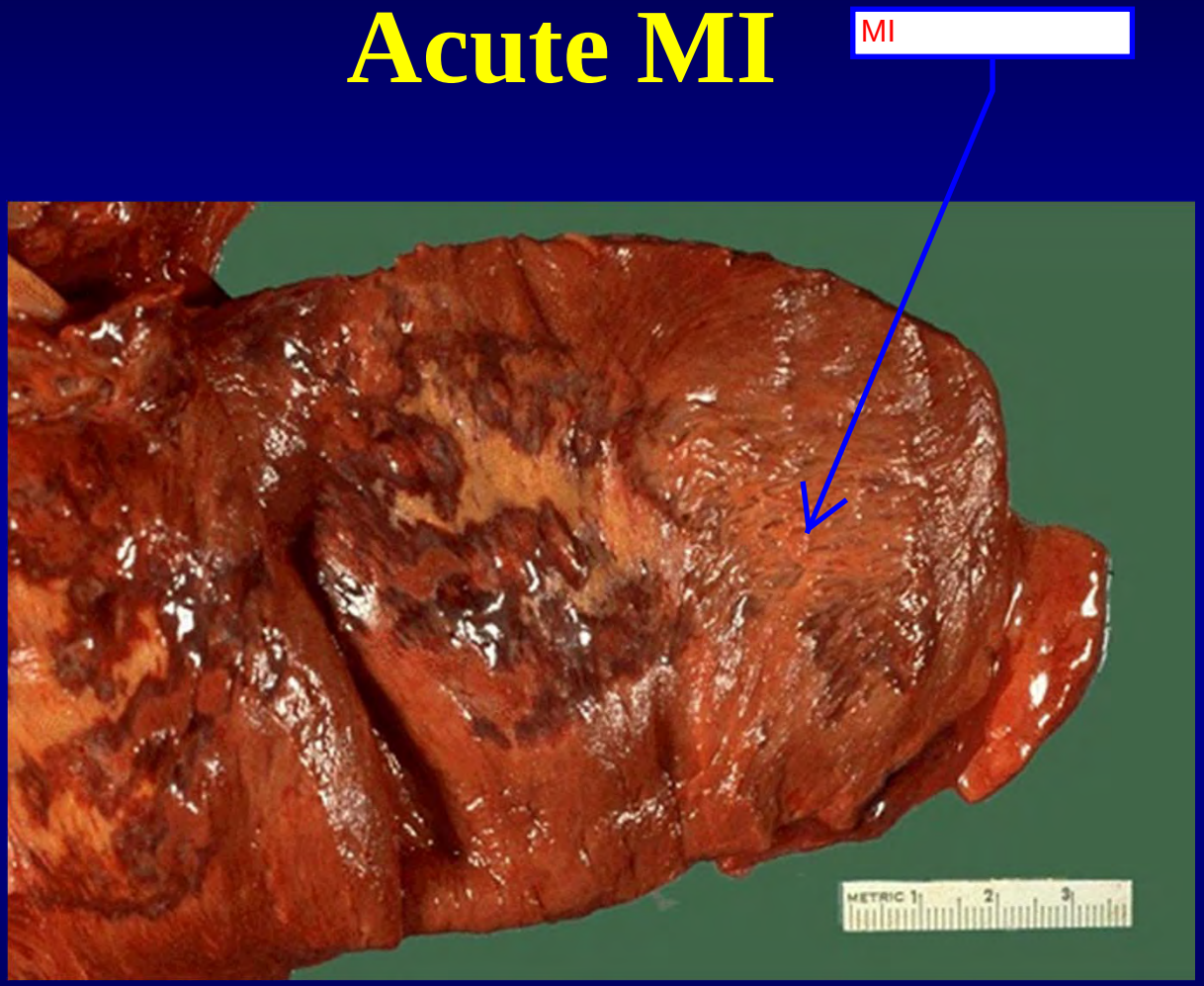
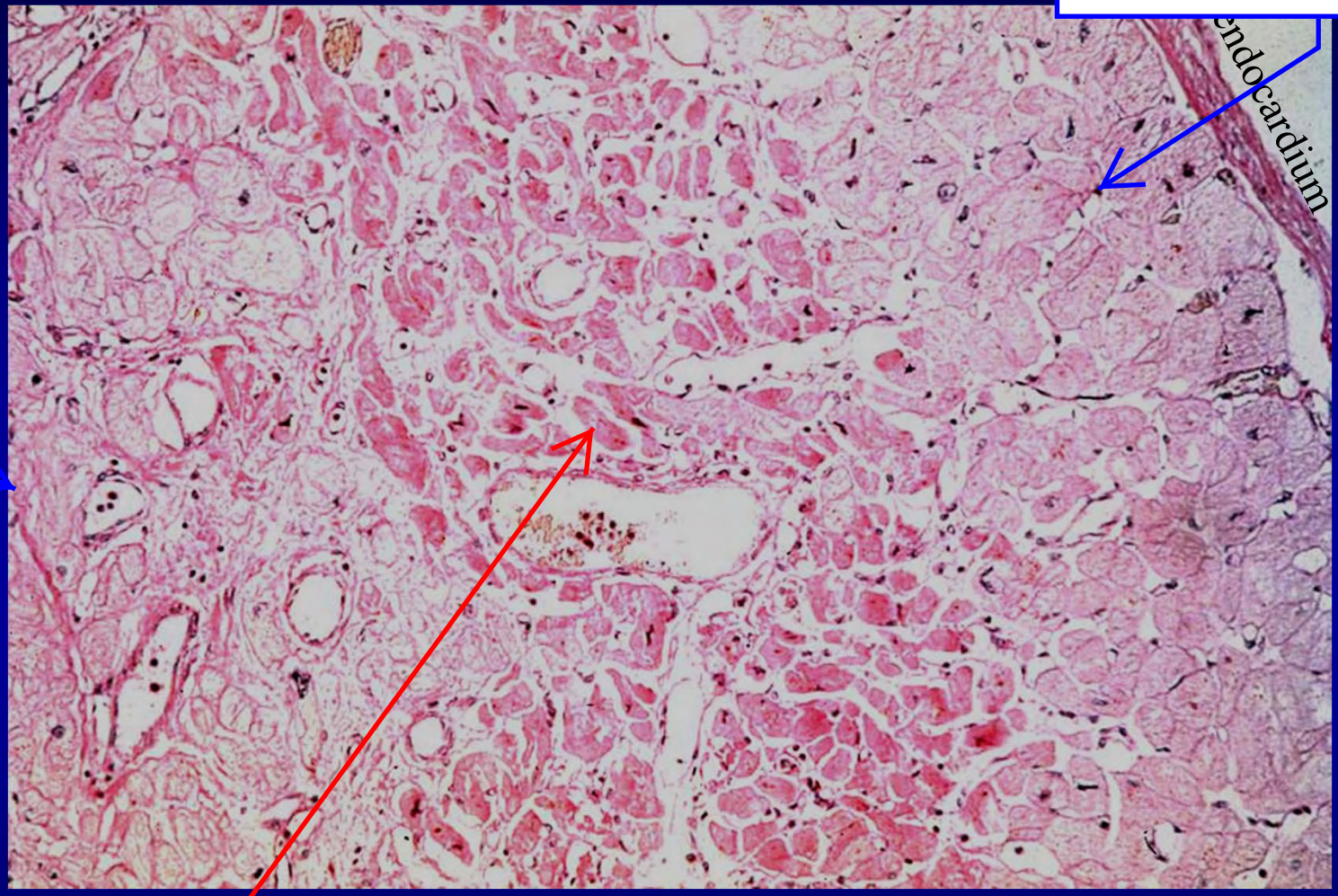
Pathology Scenario A

Acute MI



Pallor with hyperemic border

Viable myocardium under endocardium surface because oxygen can directly diffuse into these cells from the ventricular chamber.



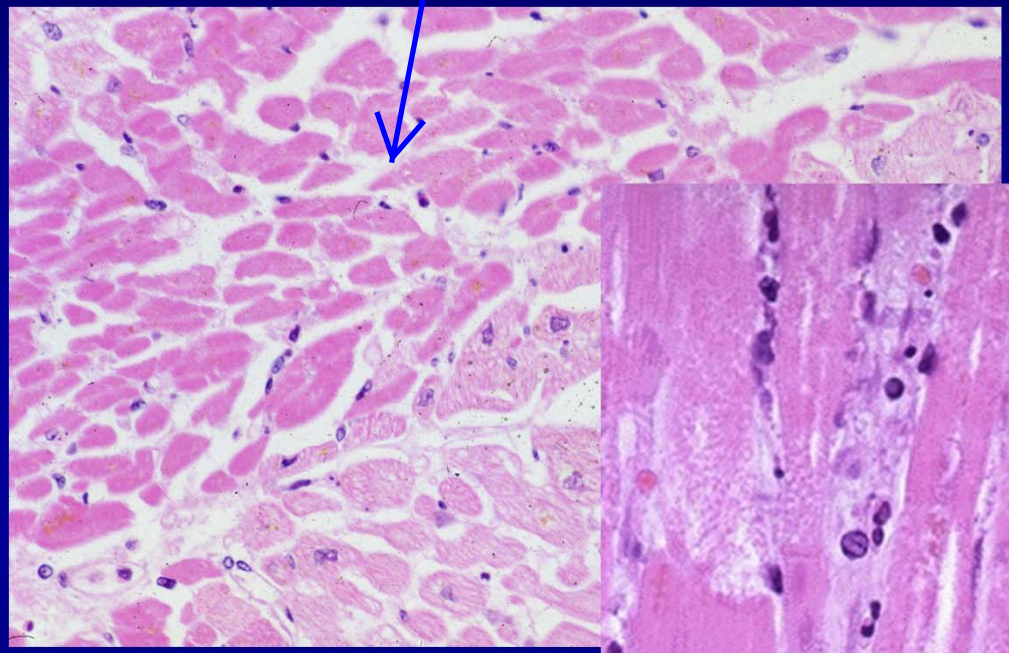
More viable cells

H&E stained section of subendocardium with hypereosinophilic necrotic myocytes, separated from the endocardium by a layer of intact myocytes.

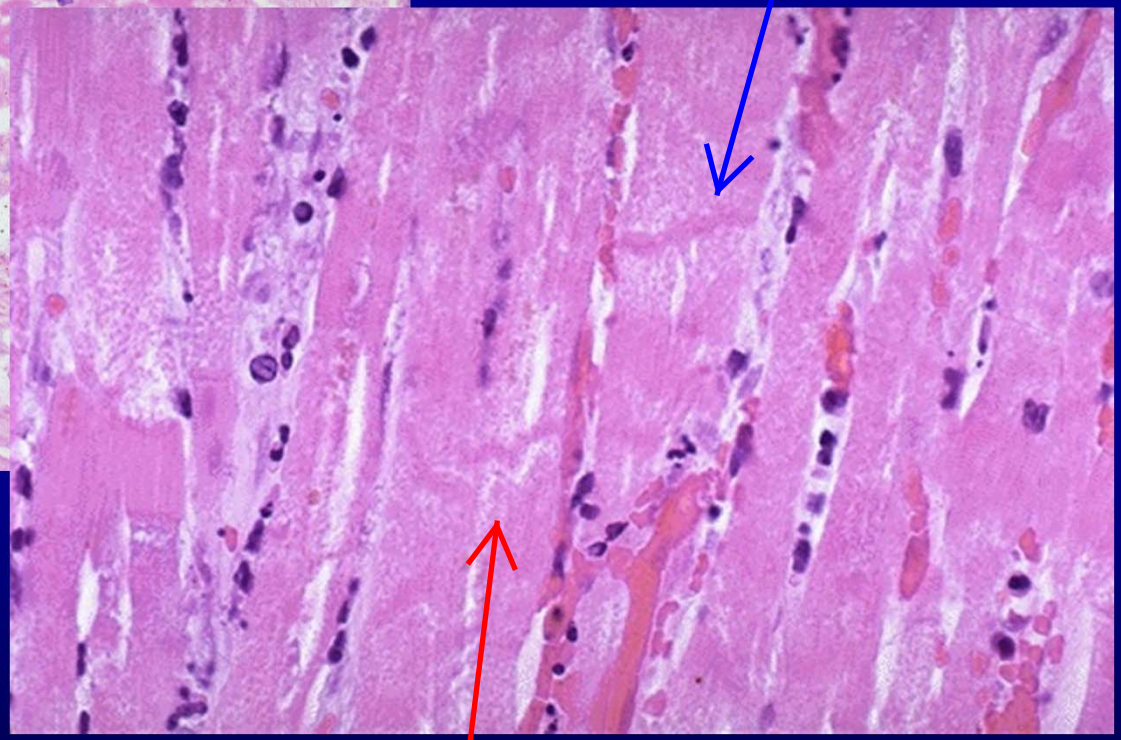
Acute MI

More pink, loss of nuclei,

Contraction band, can have them in infarcts that arent completely reperfused.



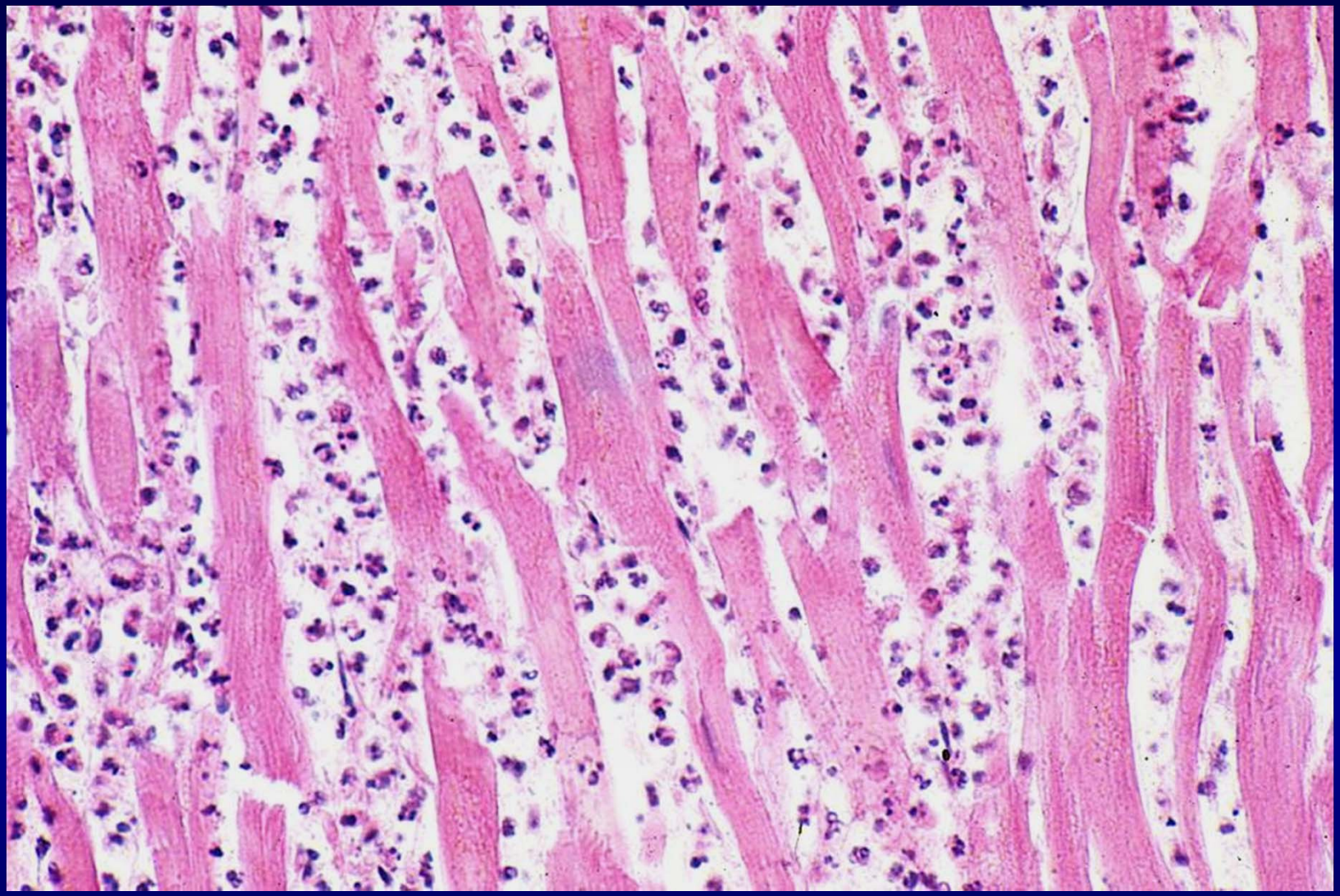
Hypereosinophilia



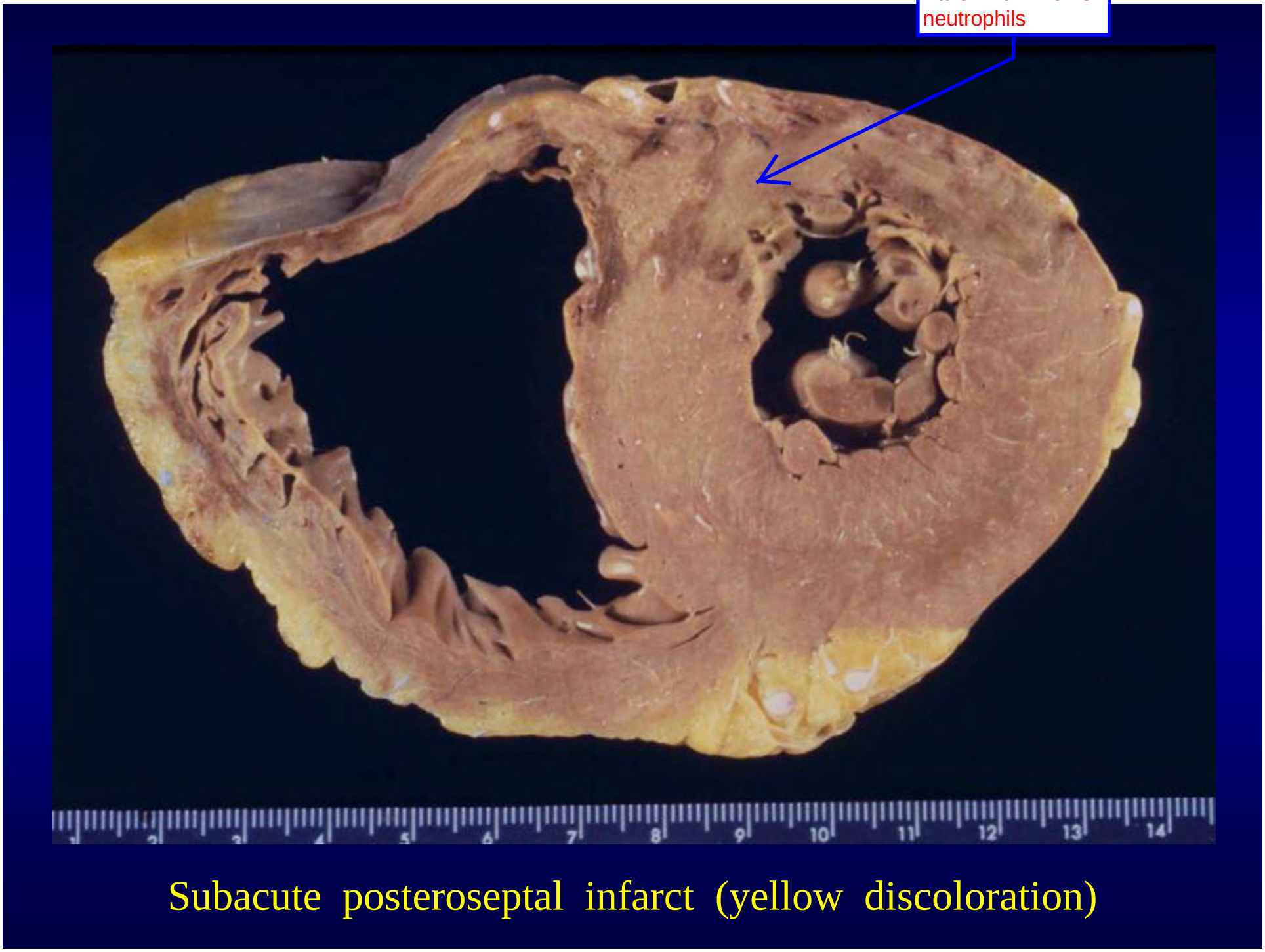
Contraction bands

RESULT:

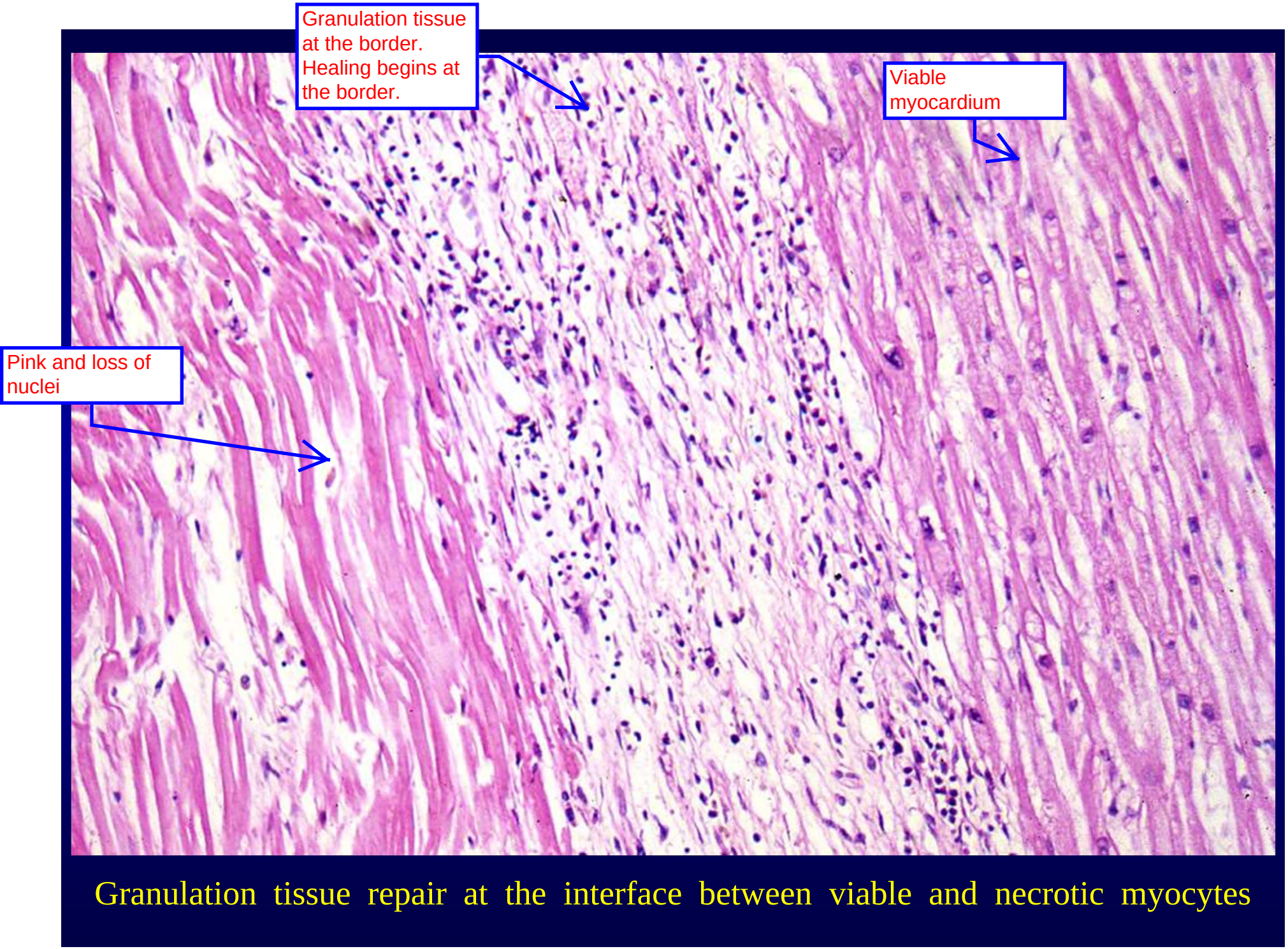
Pathology Scenario B



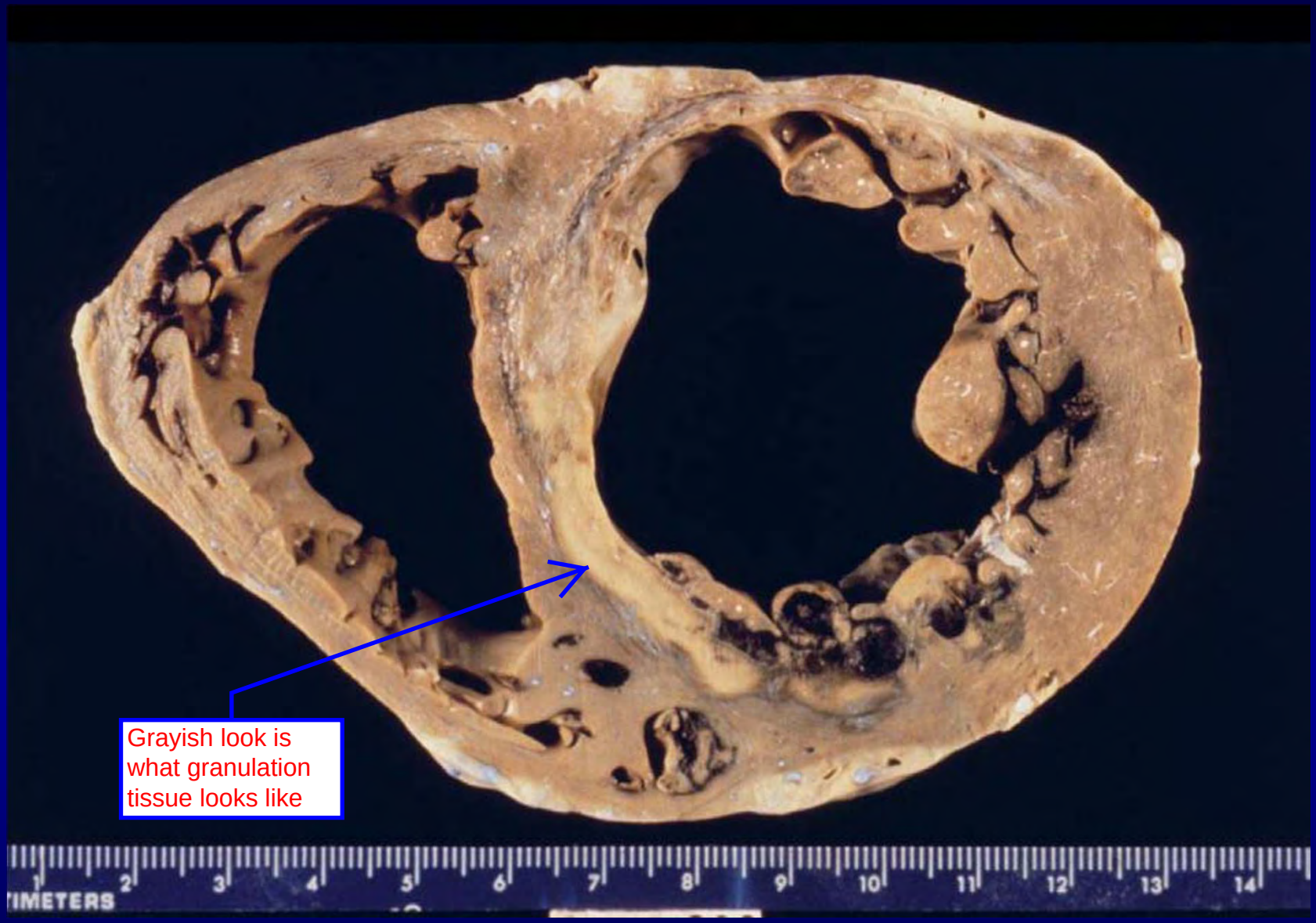
3-4 day old myocardial infarct with early karyolysis and numerous neutrophils



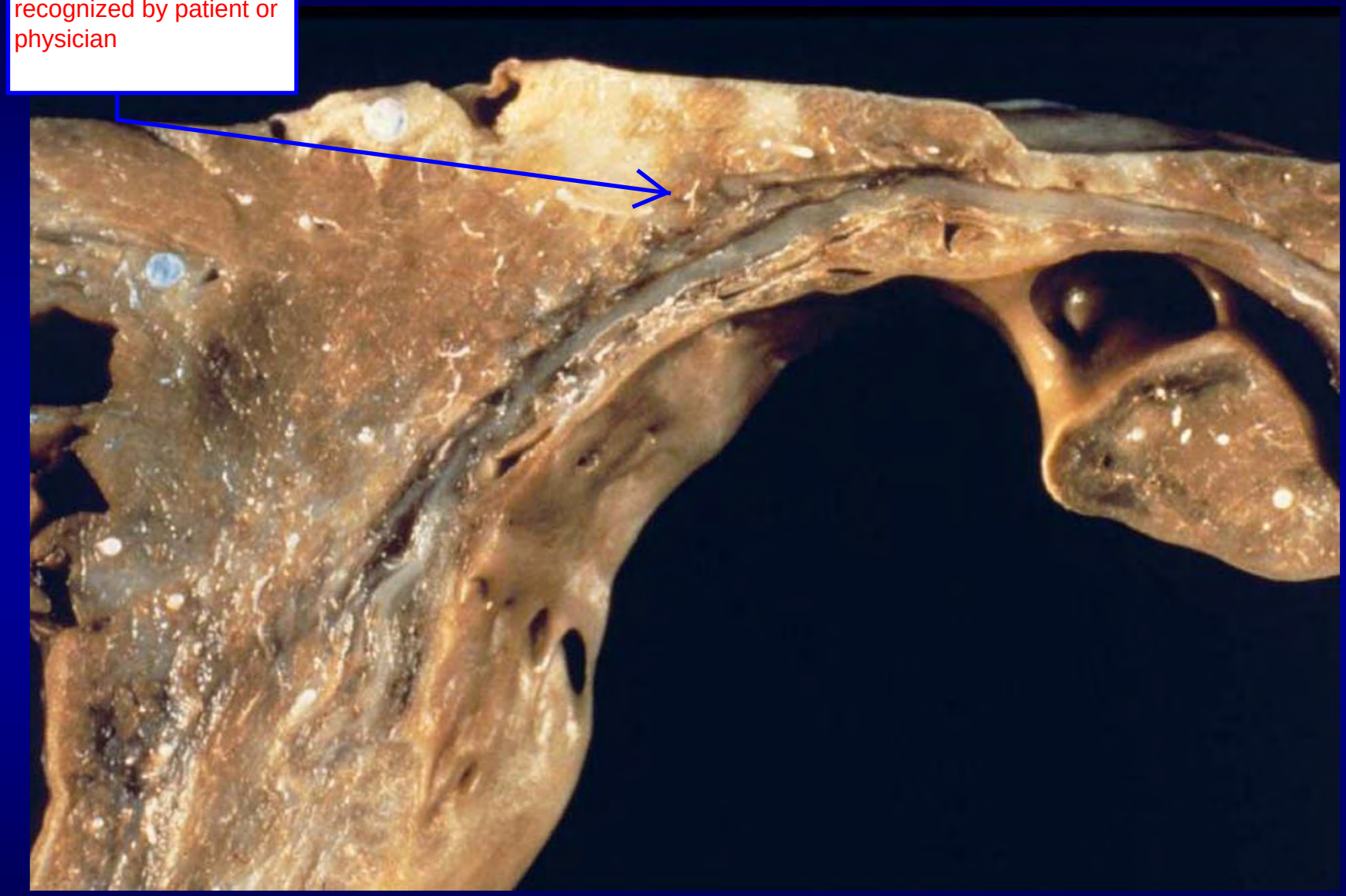
Subacute posteroseptal infarct (yellow discoloration)



Granulation tissue repair at the interface between viable and necrotic myocytes



Organizing anteroseptal MI; healed posteroseptal MI with aneurysmal thinning



Healed posteroseptal MI with aneurysmal thinning

RESULT:

Pathologic findings indicate infarct was maximal size at time of presentation to ER

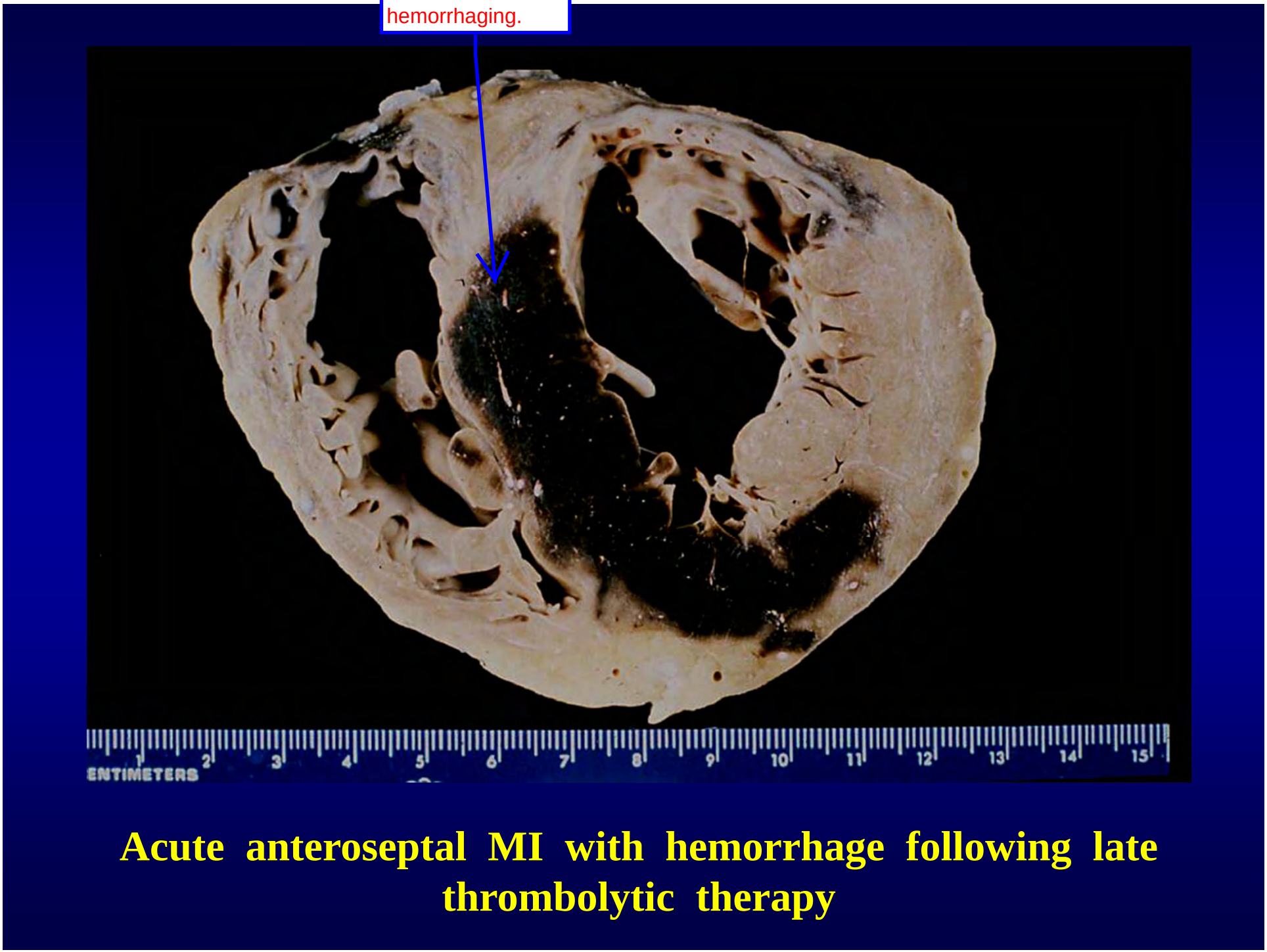
Possibly also shows prior large healed infarcts

“ The Miscarriage of Justice”

REPERFUSION

1. Accelerates disintegration of irreversibly injured myocytes (causes contraction band necrosis)
2. May accentuate hemorrhage into areas of microvascular injury (causes hemorrhagic infarct)
3. May or may not cause lethal reperfusion injury
4. Limits myocardial infarct size if early enough
5. Supports slow metabolic and contractile recovery of viable myocytes (stunning)

Cells that are not fully injured become irreversibly injured by reperfusion bc of stimulation of Nitric oxide and physical obstruction.



Acute anteroseptal MI with hemorrhage following late thrombolytic therapy

Interventions to Limit Myocardial Infarct Size

Restoration of Myocardial Perfusion

- Thrombolytic Therapy
- Emergency Coronary Angioplasty

Adjunctive Therapy

- To delay lethal myocyte injury until reperfusion has been achieved
- To prevent lethal reperfusion injury

Didn't spend much time on.

Myocardial Infarction - Mortality & Morbidity

Acute In-hospital Mortality - 7%

One Year Mortality - 35%

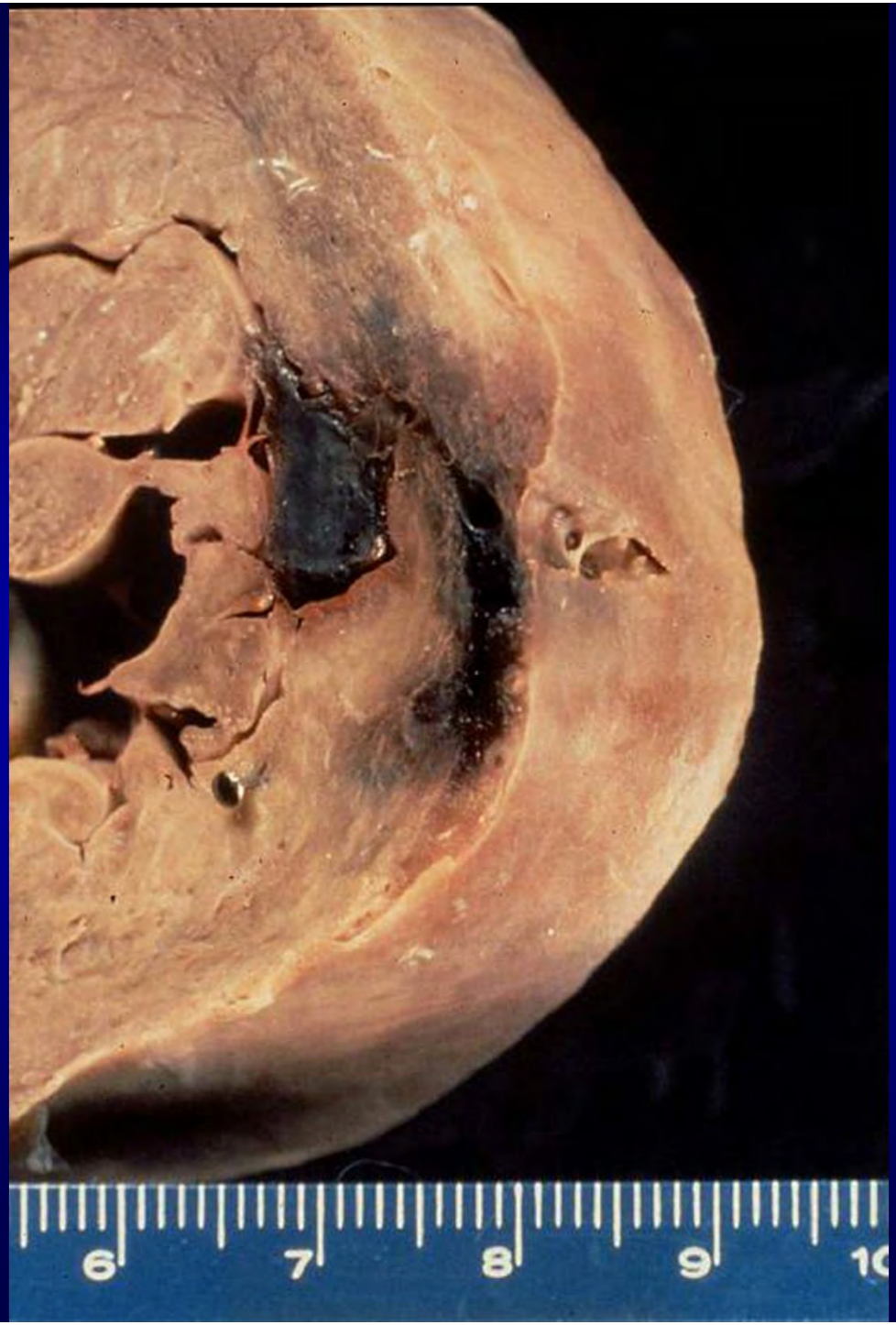
Arrhythmias - 40 - 50 % of deaths

Pump Failure - 40 - 45 % of deaths

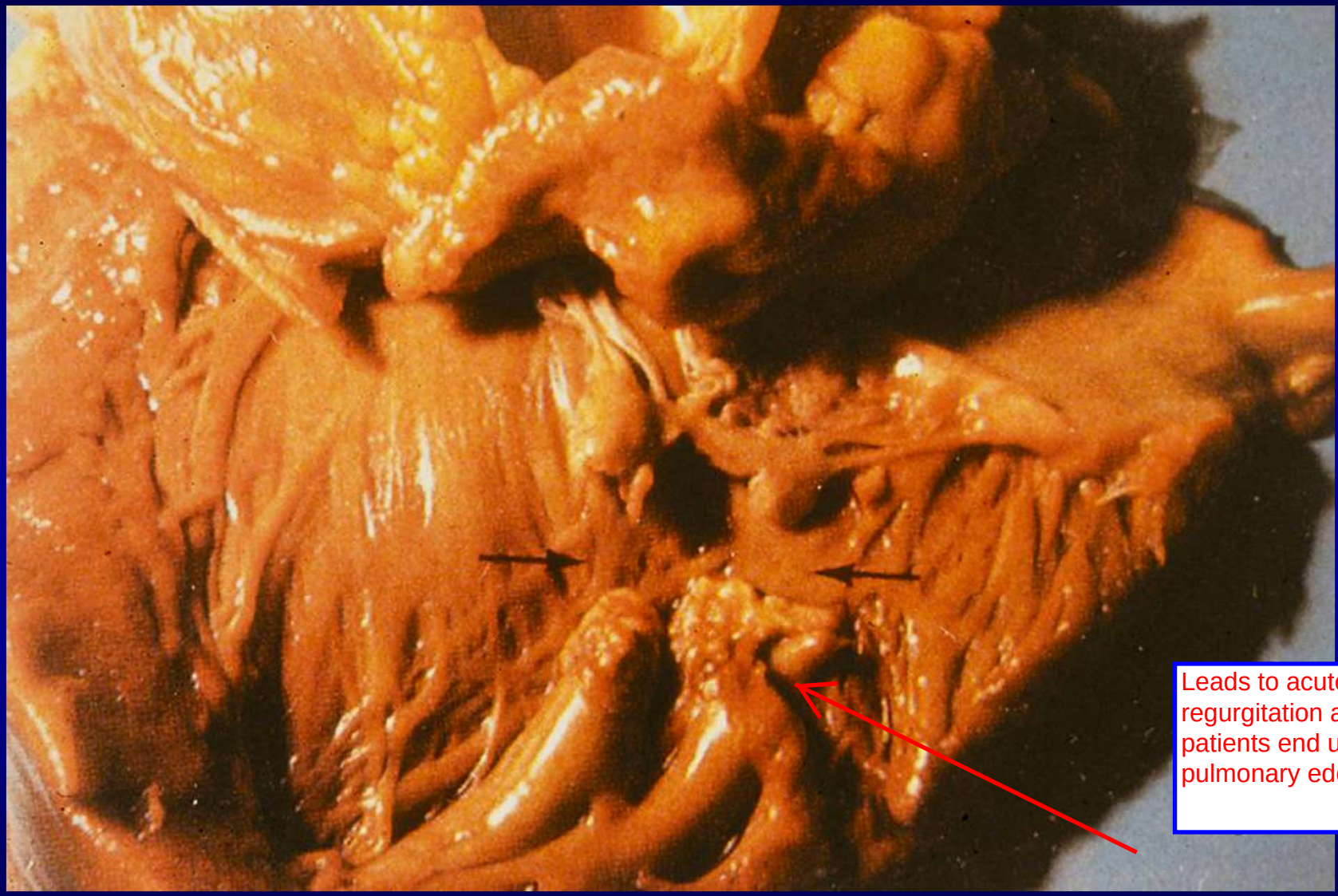
- **Cardiogenic Shock**
- **Congestive Heart Failure - 20 % of patients surviving MI develop CHF**

Other Complications

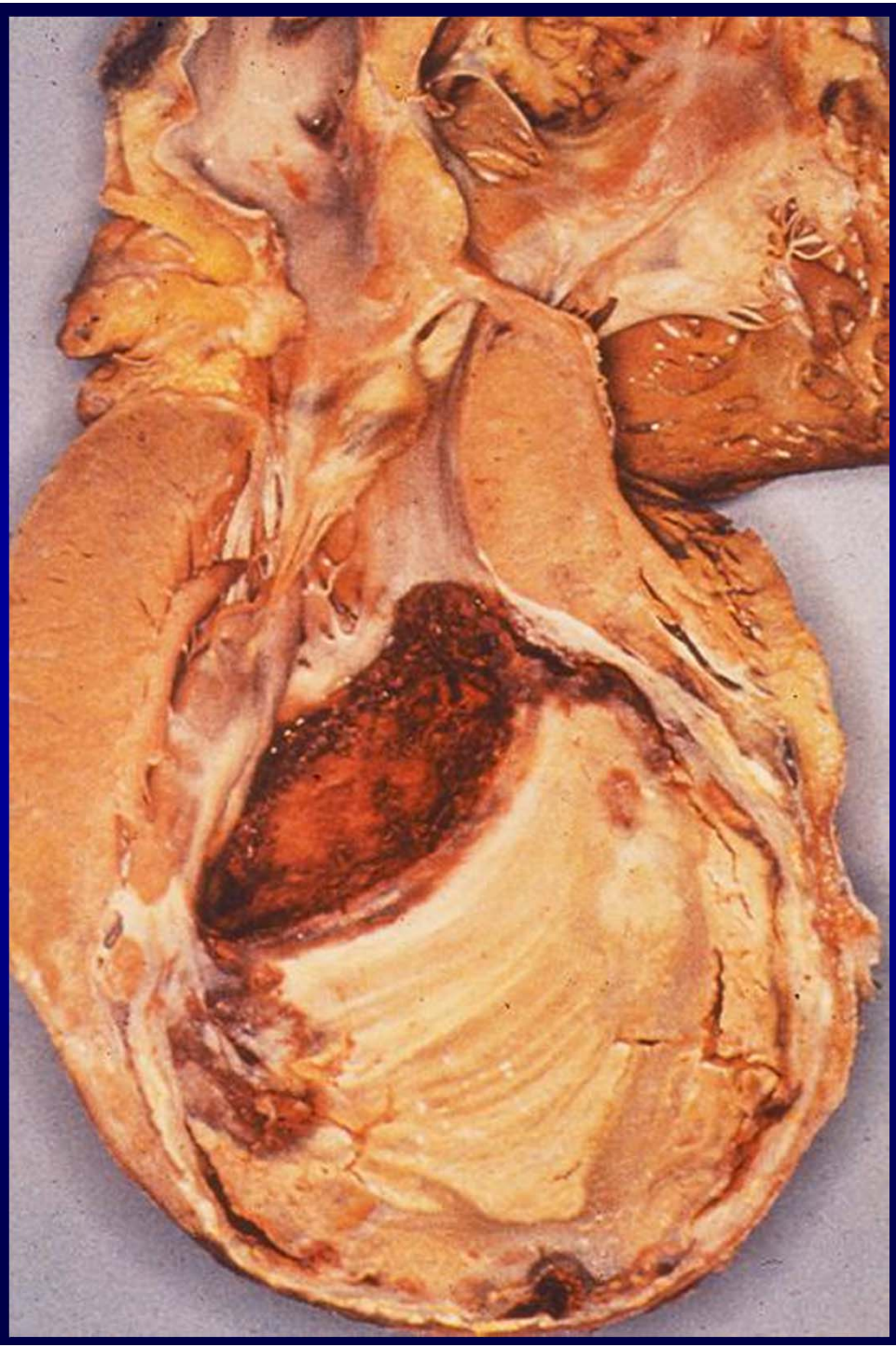
- **Rupture - LV free wall, interventricular septum, or papillary muscle**
- **Mitral insufficiency**
- **Ventricular Aneurysm**
- **Mural Thrombosis**



Acute infarct of the lateral wall of the left ventricle with rupture of the wall



Ruptured papillary muscle following acute MI



Healed transmural apical infarct of the left ventricle with aneurysm and laminated mural thrombus in the apex

Cardiomyopathies

dysfunction of the heart muscle itself.

- **LVEF most powerful risk stratifier**
  - **≤ 30% improved survival with ICD placement**
- **Ischemic:**
  - **Scarring**
    - **Arrhythmia**
    - **Aneurysm**
    - **CHF**

Hypertrophic Cardiomyopathy

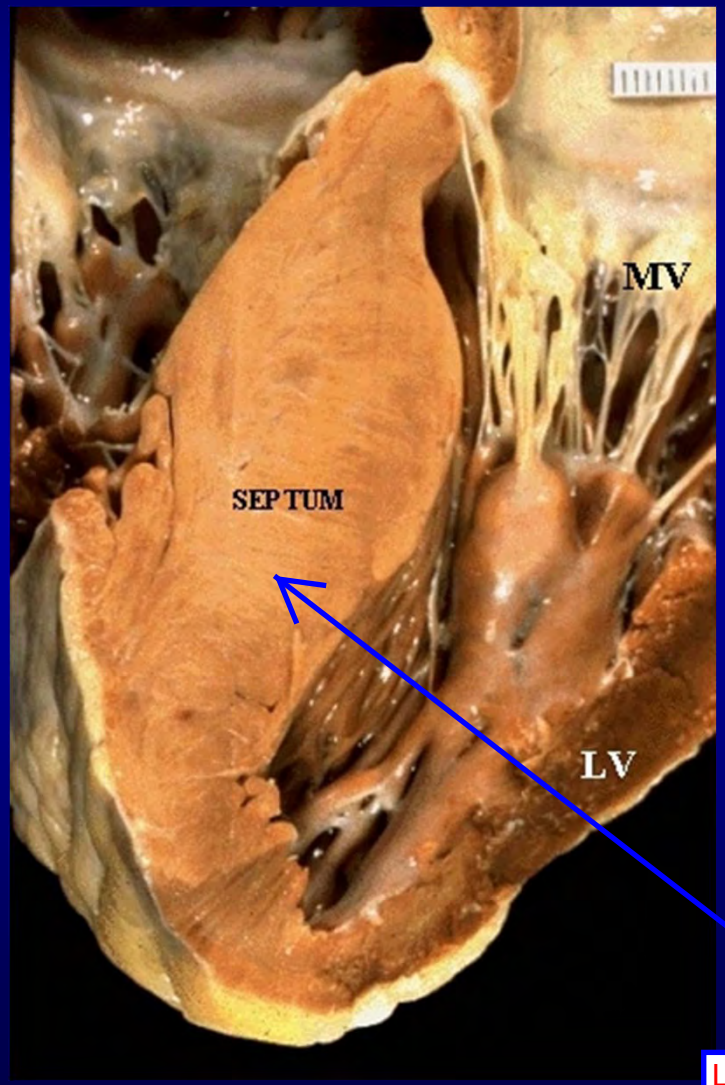
- Classic Form – Asymmetric vs Concentric
- Incidence 0.2%
- Genetics: Cardiac sarcomere proteins:
  - β myosin heavy chain
  - Myosin binding protein C
  - Cardiac troponin T and I (↑ SCD)
  - ά-tropomyosin
- Frequently autosomal dominant with 55% penetrance by age 30
- Phenotypes may be markedly different

Involves septum more than the ventricle.

-These are the athletes that die suddenly.
-Shows up at a pretty young age.

Different in terms of extent of fibrosis and enlargement

Hypertrophic Cardiomyopathy: Gross



Large lump of muscle blocks outflow into the aorta.

Asymmetric

Thickness > 3.0 cm high risk

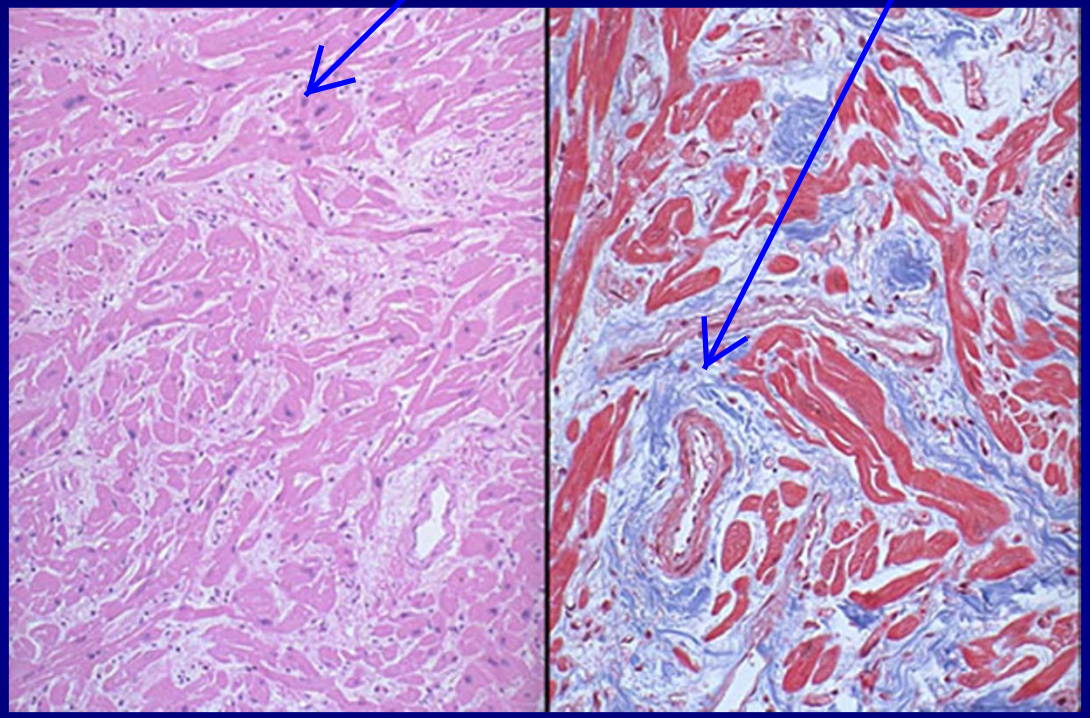
***But Majority of SCD at lesser thicknesses**

Degree of LVOT obstruction

Treatment is to go in and shave the muscle down.

Hypertrophic Cardiomyopathy

- **Histology:**
  - **Myocyte hypertrophy**
  - **Disarray**
  - **Fibrosis**
  - **Small vessel disease**



Degree of hypertrophy and fibrosis is variable

"Burnt out" phase – fibrosis with wall thinning

Ends up looking dilated

Screening?

- **Practical only when limited by Family History**

Don't really do any screening besides family history.

- **Risk SCD in HS athletes 0.46/100,000**
- **USAF basic training 1.2/100,000**

- **Italian study suggests benefits to ECG screening of athletes – Only subset with identifiable hypertrophy prior to risk SCD**

Other Hypertrophic CM's

- **HYPERTENSIVE**
  - **Concentric, requires ↑ preload**
  - **Increased susc. to ischemia/hypoxia**
- **Storage Disorders – enzyme deficiencies:**
  - **Fabry's disease (ά-galactosidase)**
  - **Pompe's disease (ά-1,4-glucosidase)**
  - **Other Glycogen Storage Disorders**
    - **LAMP2 (Danon's disease)**
    - **PRKAG2**
    - **Both associated with VF/VT with hypertrophy and diminished extracardiac lesions**

All can lead to hypertrophy and sudden cardiac death.

Often time heart is the only organ affected.

Dilated Cardiomyopathy

- Less well-delineated causes
- Less unexpected sudden death though can occur with arrhythmias

- Myocarditis “inflammatory cardiomyopathy”
  - Enterovirus, Adenovirus, Influenza, HIV
  - Protozoan – Toxoplasma, Trypanosoma (Chagas)

- Toxic: Alcohol, Iron

Cardiomyopathy: ARVD

- **Arrhythmogenic Right Ventricular Dysplasia**
  - **Fibrofatty replacement with thinning**
    - **"Triangle of Dysplasia": Inflow, outflow, apex**
  - **Frequent VT in young adults**
  - **If survive may progresses to RV failure**
  - **Ultimately involves LV failure**

Major and Minor Criteria include Gross, EP, Hx

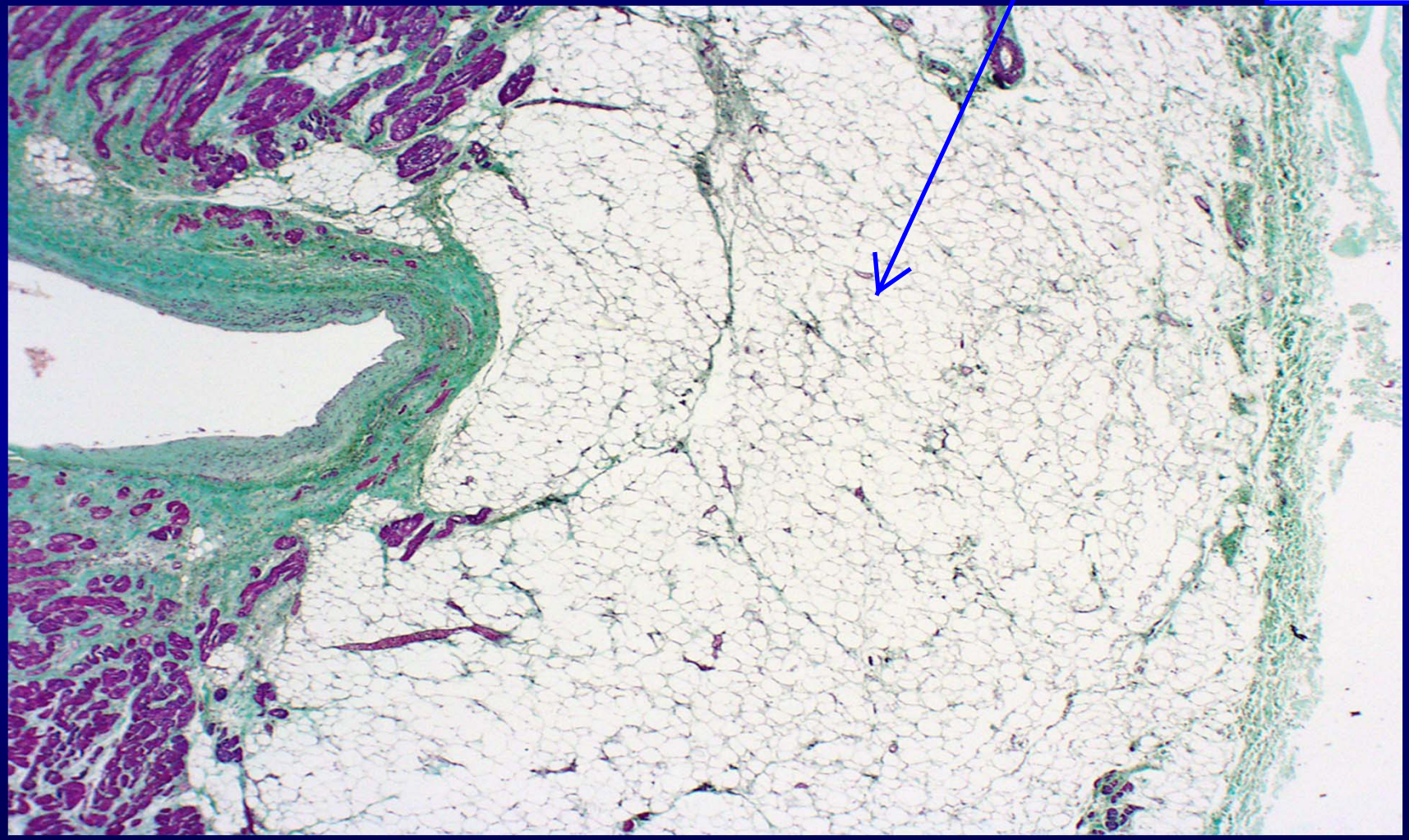
-Wall of right ventricle is replaced by fibrofatty tissue.

From gross picture:
-Starts at apex of RV and can spread to LV as well.

ARVD

Transmural replacement with fatty tissue.

No treatment other than giving patient a defribillator to keep them alive. Some will go to transplant.



Genetic Arrhythmias: No anatomic Cause
Ion channels

- **Long QT Syndrome: Torsades, SCD in youth**
  - **7 mutations identified. Some with associated syndromes**
- **Brugada Syndrome: ↑ST in right leads, RBBB**
  - **SCD in 20-30's often during rest/sleep**
  - **Cardiac sodium channel genes, *SCN5A* (LQT3), KCNQ1 gene in forms associated with AF**
- **Catecholaminergic VT: Dom and recessive**
  - **CA^{++} channel protein Ryanodine and CA^{++} regulatory proteins.**
  - **Stress related trigger**

For people who suffer SAD and don't have a cause, they take a blood sample and check for these disorders.

2nd leading cause of death in athletes.

Commotio cordis

- **Sudden death following precordial impact**
- **Impact location – directly over heart**
- **Impact timing - T wave upstroke in window between 15-30 milliseconds prior to apex**
  - **Potassium channels may play a role**
- **2nd leading cause of SCD in athletes behind HCM**

Questions?