Pulmonary hypertension

Martin Vokurka

Ohm's Law

$$P = Q \times R$$

pressure

flow

resistance

Ohm's Law

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↑ pressure

↑ flow

resistance

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↑ pressure

flow

↑ resistance

Ohm's Law

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↑ resistance

Q↑ R↑

Flow increase

- anatomical (vessel anomaly, shunts)
- functional - vasodilatation

HYPERKINETIC CIRCULATION

Resistance increase

- anatomical (reduction of vessel bed)
-functional – vasoconstriction
-increased pressure from pulmonary veins (LA, LV)

Classification of PH

Table 1. Diagnostic Classification of Pulmonary Hypertension.*

Pulmonary arterial hypertension

Idiopathic
Familial
Associated with
- Collagen vascular disease
- Congenital left-to-right shunt
- Portal hypertension
- Infection with human immunodeficiency virus
- Drugs and toxins
- Other conditions†

Associated with substantial venous or capillary involvement
- Pulmonary veno-occlusive disease
- Pulmonary capillary hemangiomatosis

Persistent pulmonary hypertension of the newborn

Pulmonary hypertension with left heart disease

Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease

Pulmonary hypertension associated with lung disease or hypoxemia or both

Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities

Pulmonary hypertension due to chronic thrombotic or embolic disease or both

Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

Miscellaneous

Sarcoidosis, pulmonary Langerhans'-cell histiocytosis, lymphangiomatosis, and compression of pulmonary vessels (adenopathy, tumor, and fibrosing mediastinitis)

* This classification was adapted from Simonneau et al.[3]
† These conditions include thyroid disorders, type 1 glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, and splenectomy.

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3. precapillary
    - restrictive – loss of pulmonary tissue
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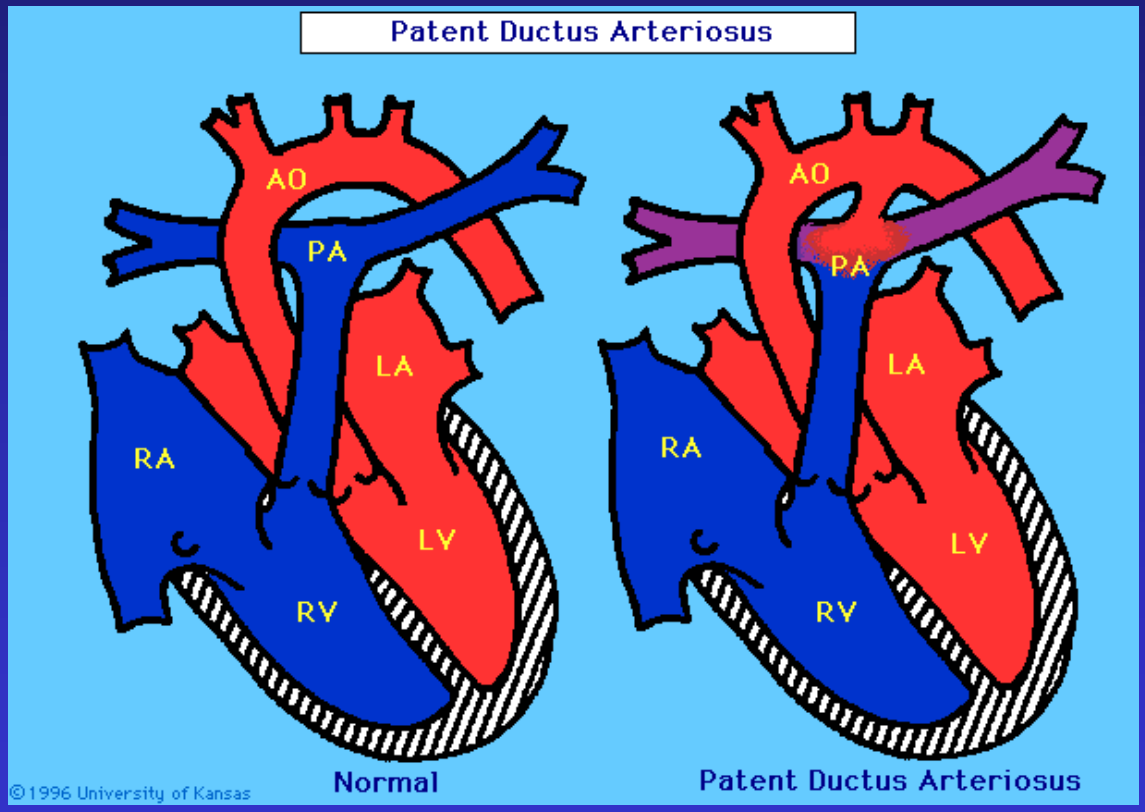
Left-right shunts

Excessive blood flow through the lung vessels.



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Hypoxic pulmonary hypertension

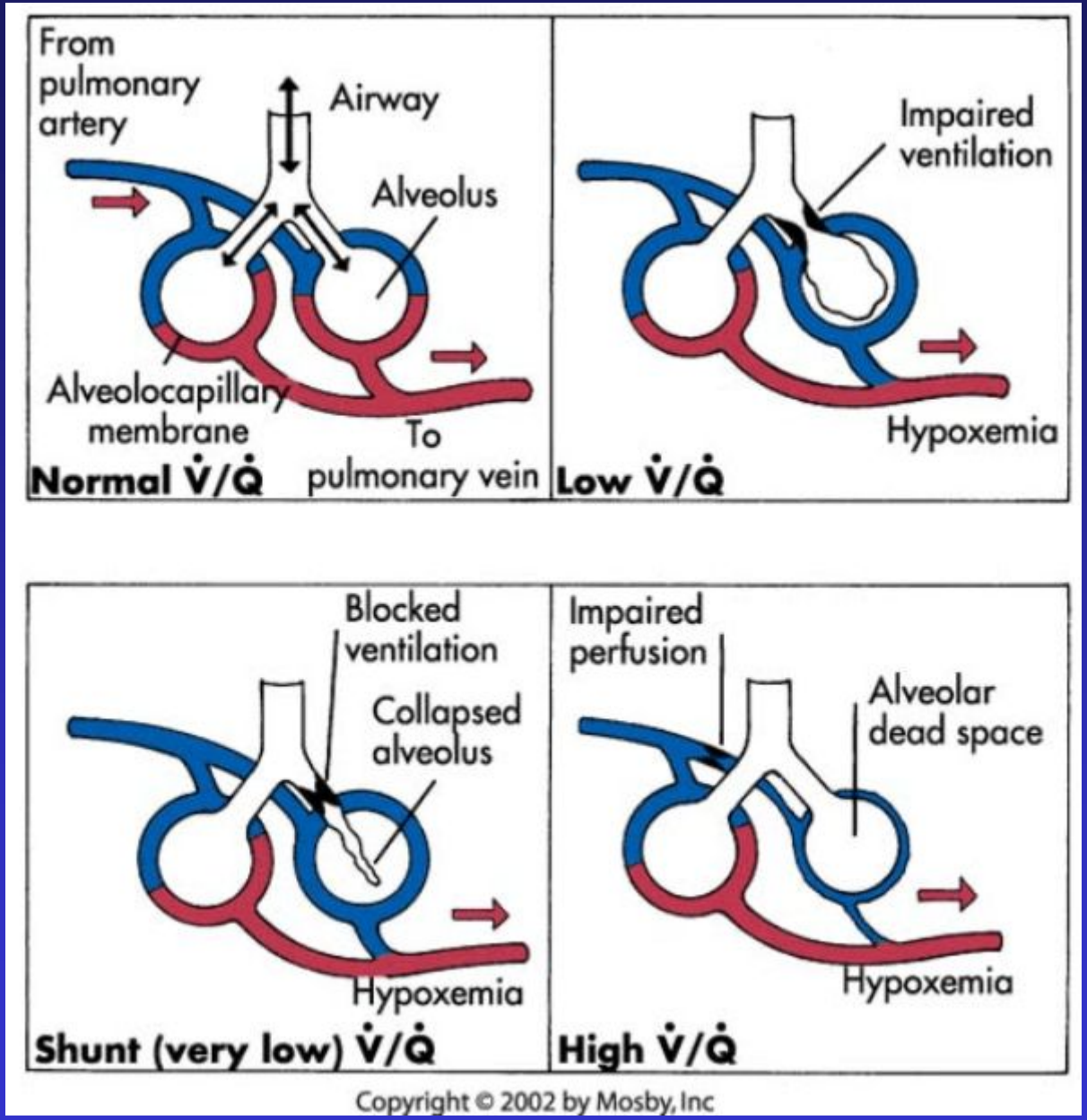
-many lung diseases, mainly chronic obstructive disease, alveolar hypoventilation, severe obesity, lung fibrosis

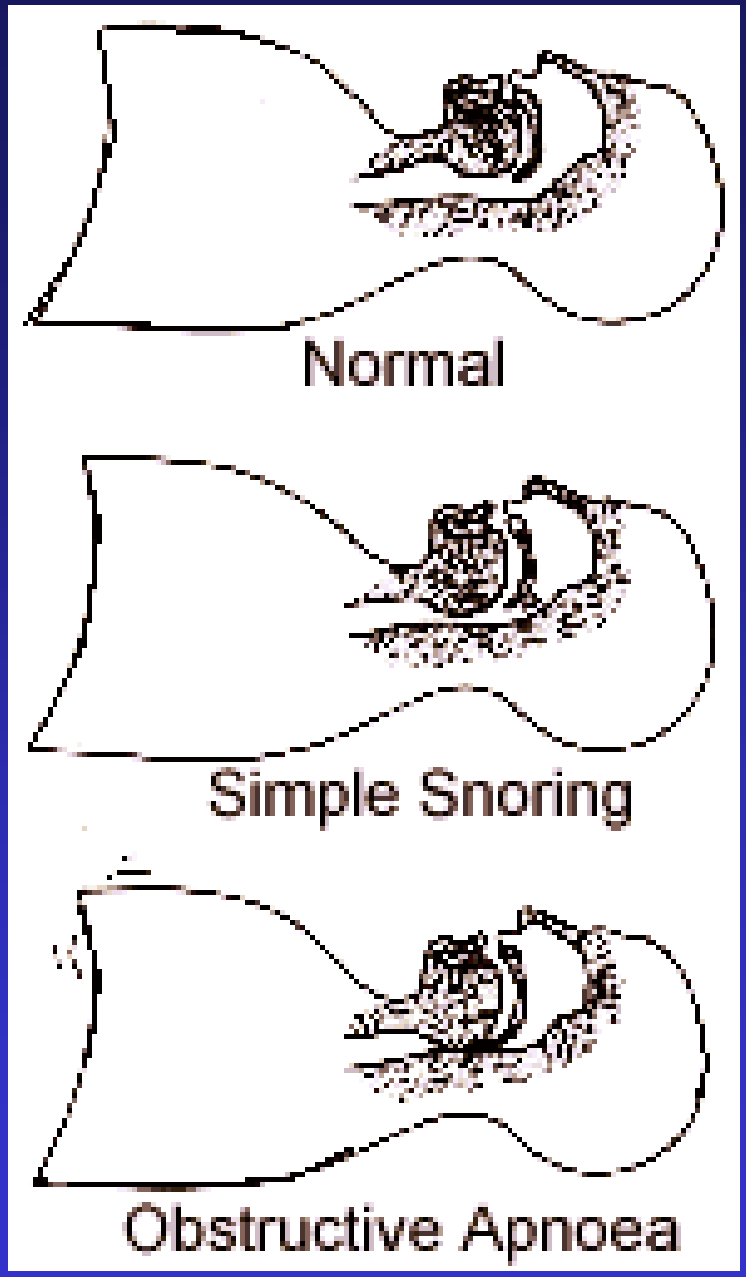
-high altitude

-syndrome of sleep apnoe

mainly obstructive (relaxation of muscles…)
apnoe over 10 sec, often even several dozens
dozens or hundreds of such episodes during the night

decreased ventilation and oxygen saturation




Normal
Simple Snoring
Obstructive Apnoea

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Thromboembolic pulmonary hypertension

- arteries are occluded by thrombus and emboli
- may be asymptomatic in the beginning (if not massive)
- vasoconstriction
- non perfused areas can be normally ventilated
- continous increase of obstructed areas

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Pulmonary arterial hypertension

- a mean pulmonary artery pressure in excess of 25 mm Hg at rest (30 in exercise)
- normal pulmonary wedge pressure (15) and normal end-diastolic pressure in LV

More causes, similar vessel reactivity

exact pathogenesis is unknown

- **fibromuscular intimal hypertrophy (remodelation)**
- **loss of small arteries**
- **prothrombotic activity**
- **vasoconstriction**

Imbalance between mediators of
-vasoconstriction a vasodilation
-growth inhibitors and growth factors
-antithromb. a prothromb. factors

Very rare idiopathic PAH

mutations in signal pathways

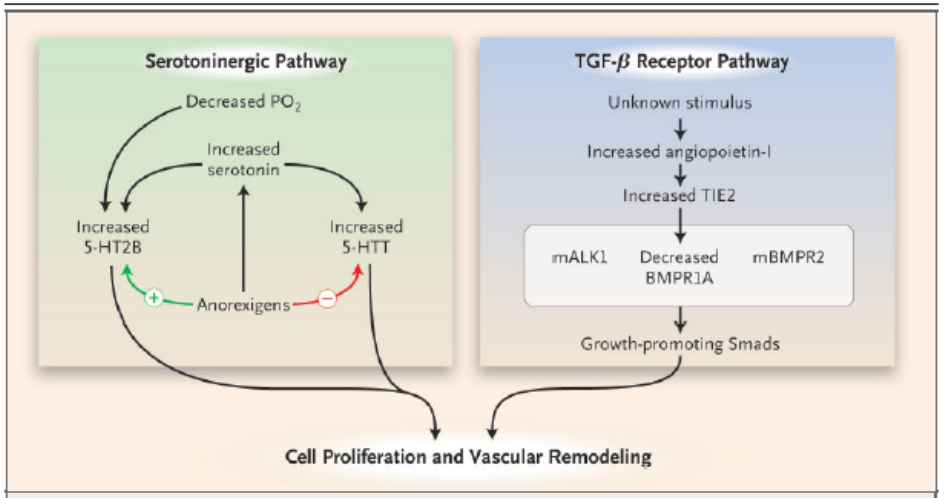


Figure 2. **Mechanistic Pathways Promoting Pulmonary Arterial Hypertension.**

In the serotoninergic pathway, hypoxia increases the expression of the serotonin receptor 5-HT2B. Increased expression of the serotonin transporter 5-HTT is accompanied by an enhanced sensitivity to serotonin as a stimulus of the proliferation of vascular smooth-muscle cells and vascular remodeling. Anorexigens, especially *nor*-dexfenfluramine, boost (+) the serotonin-dependent increase in 5-HT2B responses and suppress (–) the serotonin-dependent increase in 5-HTT responses. In the transforming growth factor β (TGF-β) receptor pathway, an unknown stimulus increases the expression of angiopoietin-1 as well as that of its receptor TIE2, which, in turn, leads to a decrease in the expression of bone morphogenetic protein receptor type 1A (BMPR1A). This member of the TGF-receptor family is required for optimal signaling with its partner receptor BMPR type 2 (BMPR2). Mutant forms of BMPR2 (mBMPR2) and activin-receptor–like kinase (mALK1) are associated with familial forms of idiopathic pulmonary arterial hypertension, and both mutations result in enhanced (unrestrained) signaling through the growth-promoting Smads, which ultimately stimulate vascular smooth-muscle cell proliferation and vascular remodeling. PO_2 denotes the partial pressure of oxygen.

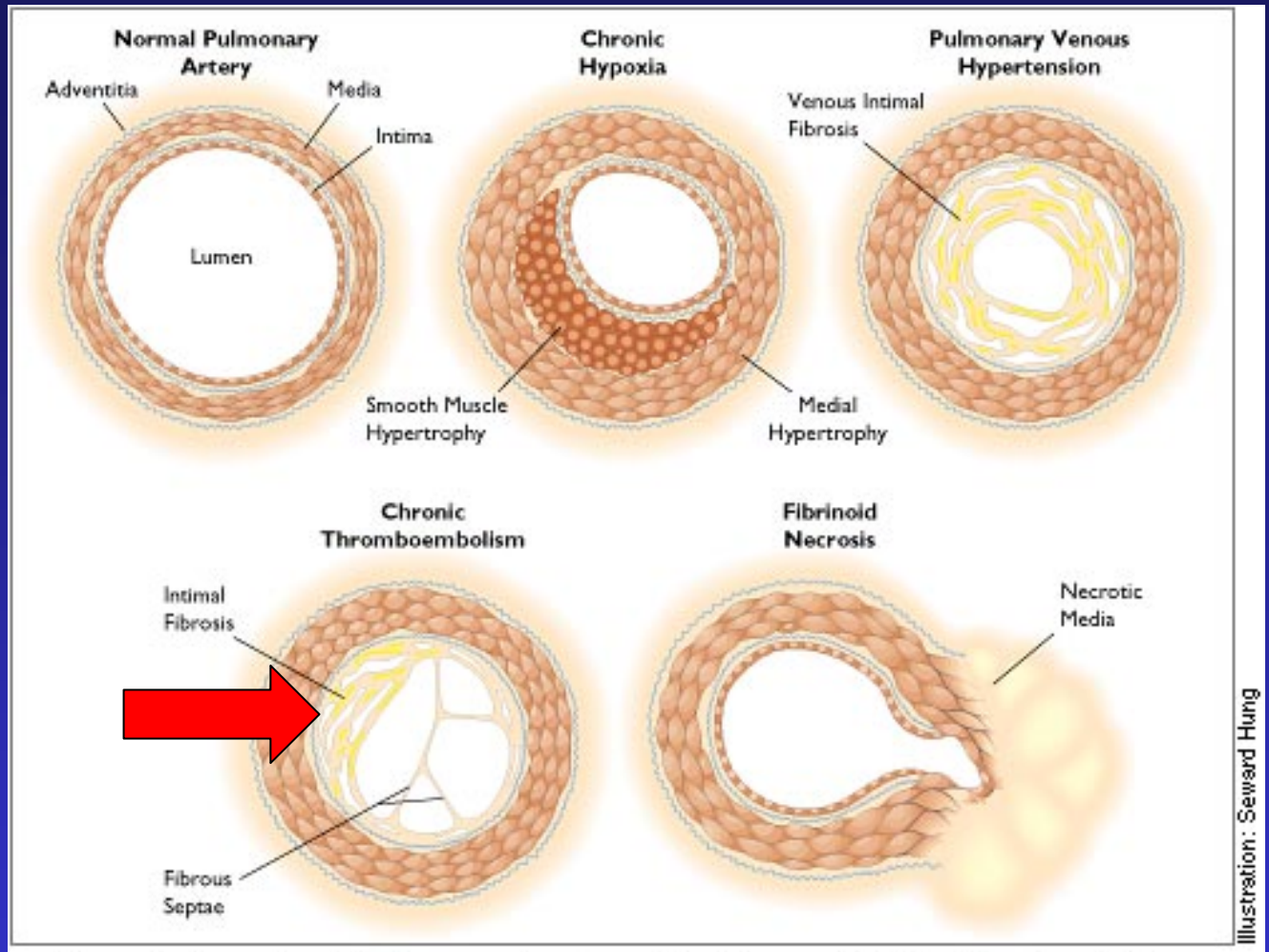


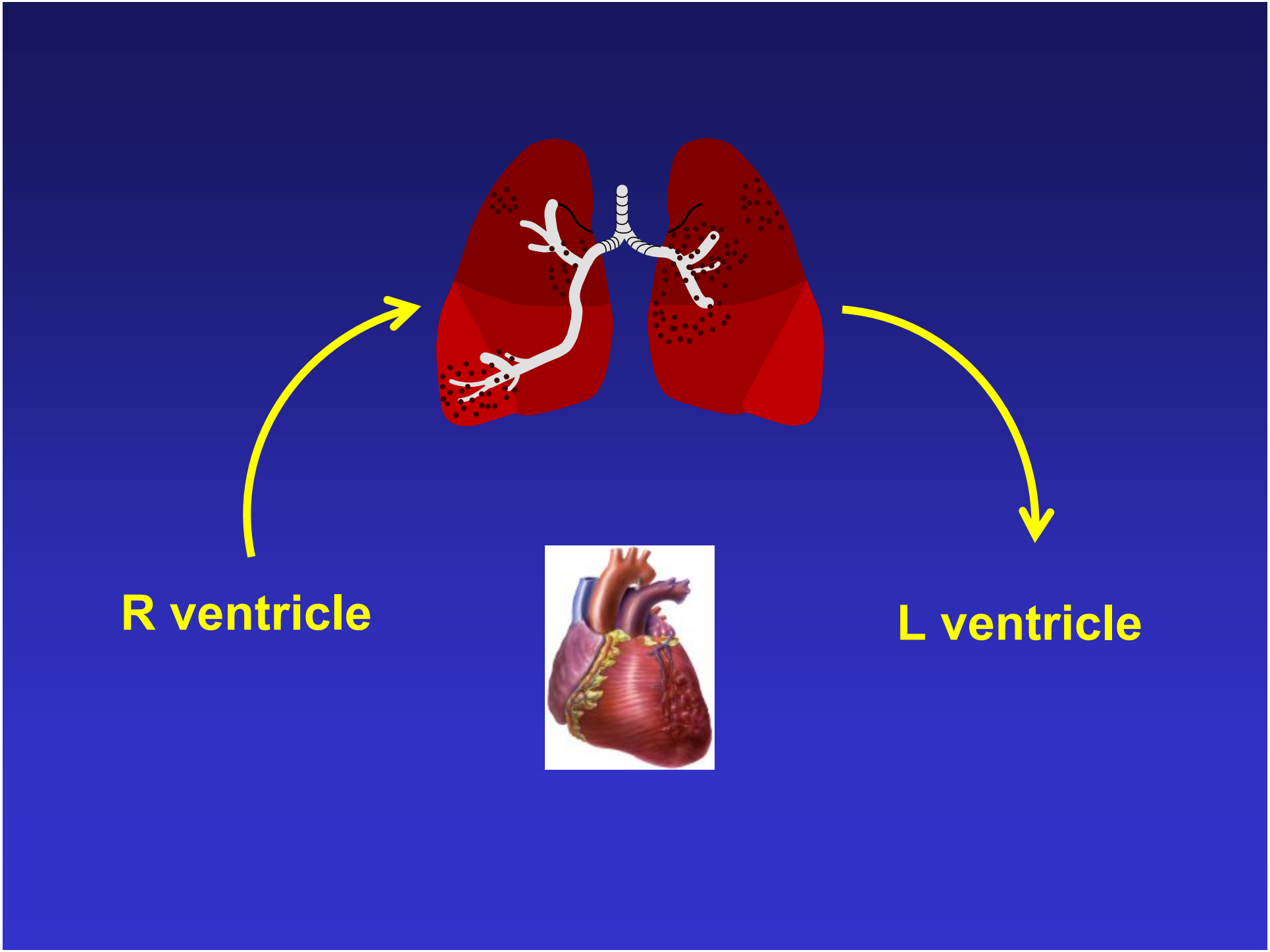
Figure 2. In contrast to the normal pulmonary artery, lung biopsy in patients with pulmonary hypertension may show a variety of lesions: the longitudinal smooth muscle hypertrophy of chronic hypoxia, the symmetric venous intimal fibrosis of venous hypertension, the eccentric intimal fibrosis and fibrous septae of chronic thromboembolism, the necrotic media of fibrinoid necrosis, or the plexiform lesion of primary plexogenic arteriopathy (not shown) (Adapted from Rounds and Hill, 1984)

Symptoms and sequelae of PH

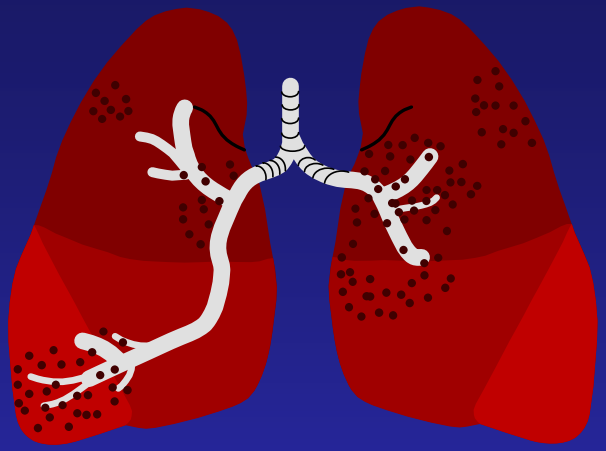
progressive dyspnea

symptoms of right heart failure

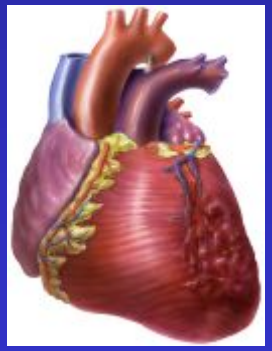
symptoms of decreased cardiac output


R ventricle
L ventricle

increased resistance

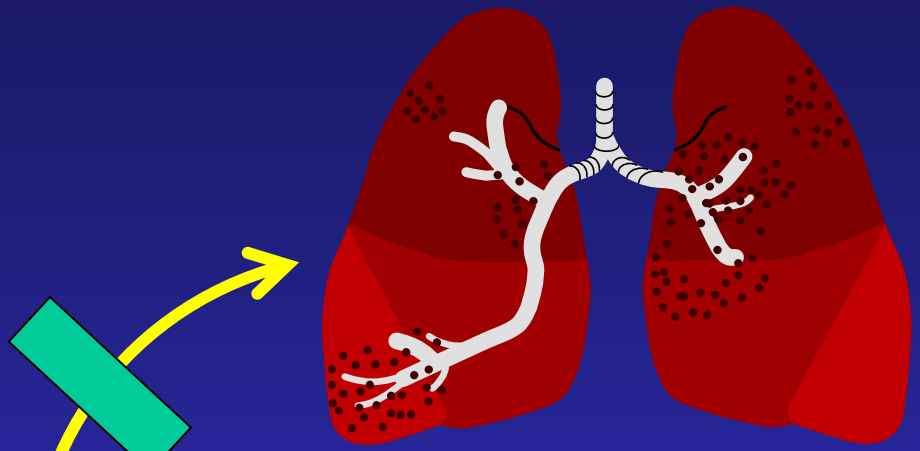


R ventricle



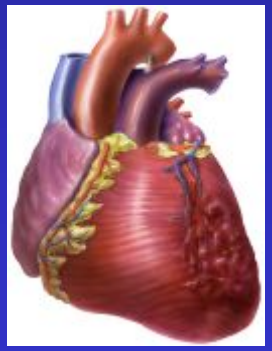
L ventricle

Right heart failure



insufficient filling

R ventricle



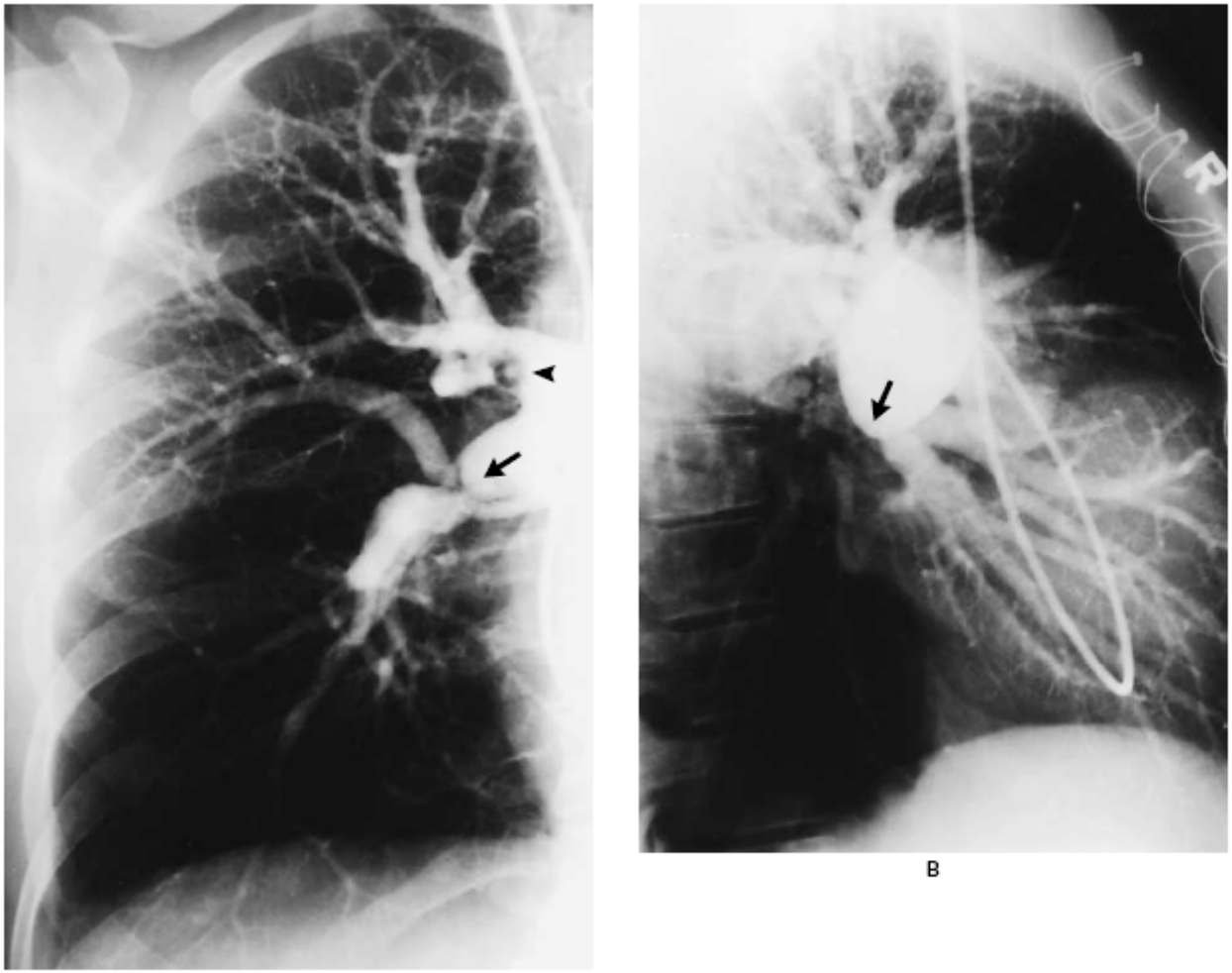
L ventricle

Decrease of cardiac output

Diagnosis

changes of the lungs + heart + lung vessels

-physical examination changes (auscultation), symptoms of right heart failure
-RTG - angiography
-echokardiography
-ECG
-right heart catheterization
-ventilation-perfusion scan
-lung functions
-blood gases (oxygen, carbon dioxide)



A B

Figure 3. Right Pulmonary Angiogram Showing Features of Chronic Thromboembolic Disease.
The anterior–posterior view (Panel A) shows abrupt narrowing in a rounded fashion ("pouch defect") of the right interlobar artery (arrow), followed by opacification of vessels to the right lower lung field. An intraluminal thrombus (arrowhead) is present in the proximal upper-lobe artery. The lateral view in the same patient (Panel B) shows the extent of thromboembolic obstruction. The vessels in the right middle lobe are dilated, with complete obstruction of flow to the right lower lobe (arrow).

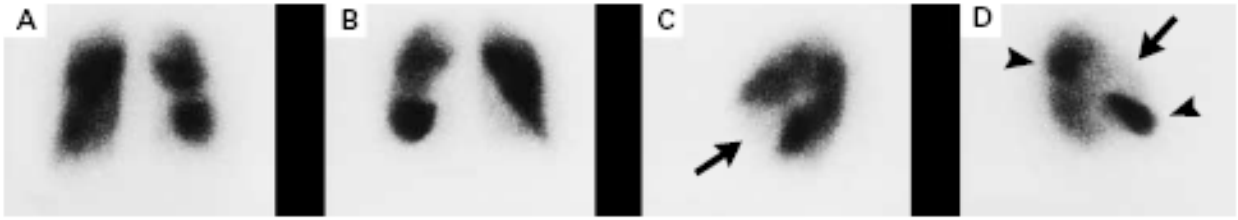
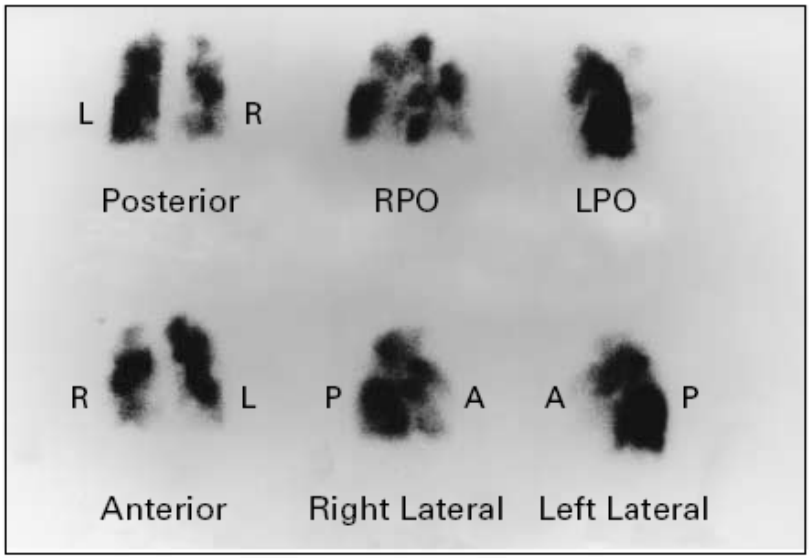


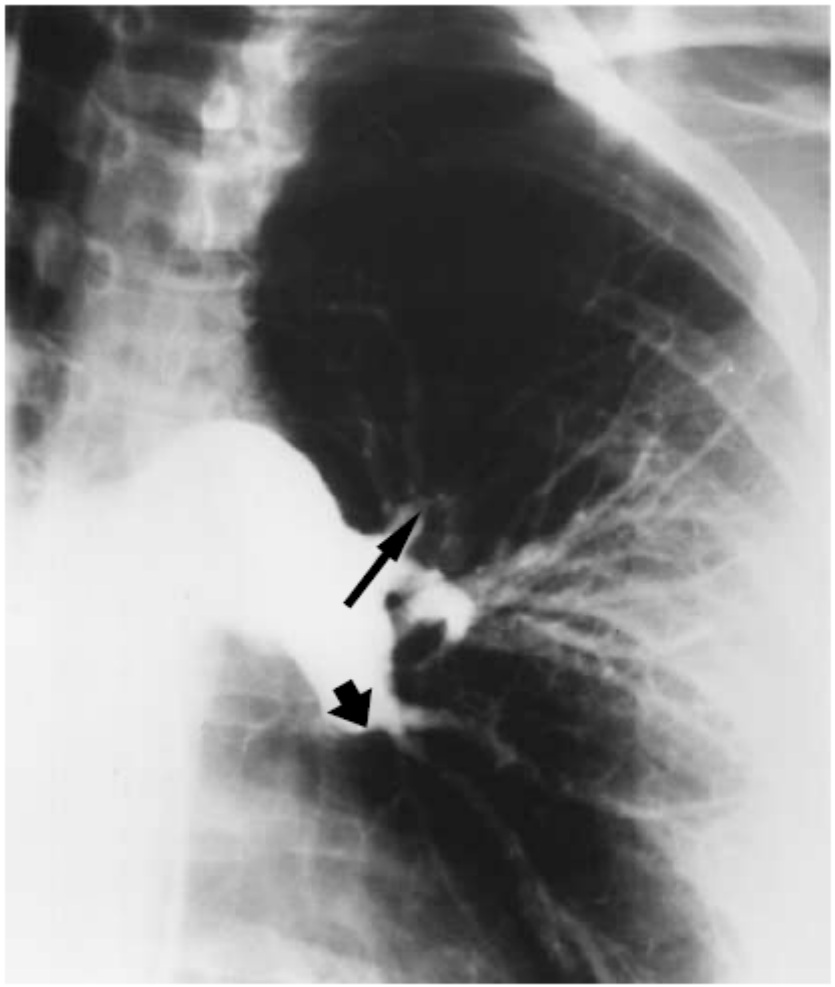
Figure 1. Representative Perfusion Lung Scan in a Patient with Chronic Thromboembolic Pulmonary Hypertension.
The ventilation study (not pictured) showed no abnormalities. The perfusion scan shows multiple, segmental, mismatched defects. Panels A and B show the posterior and anterior views, respectively. In Panel C, which shows the left lateral view, there is a segmental defect involving the lingula (arrow). In Panel D, which shows the right lateral view, areas of hyperperfusion involving the posterior aspect of the right upper lobe as well as the right middle lobe (arrowheads) are interspersed with areas of relative hypoperfusion involving the anterior aspect of the right upper lobe (arrow) and the majority of the lower lobe.

Figure 1. Ventilation–Perfusion Scans and Pulmonary Arteriograms of Patients with Primary Pulmonary Hypertension and Chronic Thromboembolic Pulmonary Hypertension.

B shows similar lung scans of a patient with chronic thromboembolic pulmonary hypertension. Panels C and D (facing page) show pulmonary arteriograms of a patient with primary pulmonary hypertension and a patient with chronic thromboembolic pulmonary hypertension, respectively. The arrows in Panel D indicate intravascular bands and abrupt cutoffs, which are typical of chronic thrombotic disease. R denotes right, L left, P posterior, A anterior, RAO right anterior oblique, LAO left anterior oblique, RPO right posterior oblique, and LPO left posterior oblique.



B



D

Treatment (general)

treatment of the causes (L heart, coagulation…)

vasodilatation
oxygenotherapy – lung diseases

nitric oxide (NO) and its donors
prostacyclin
endothelin antagonists
calcium channel blockers

anticoagulation and antiaggregation therapy
antiimflammatory drugs

lung transplantation

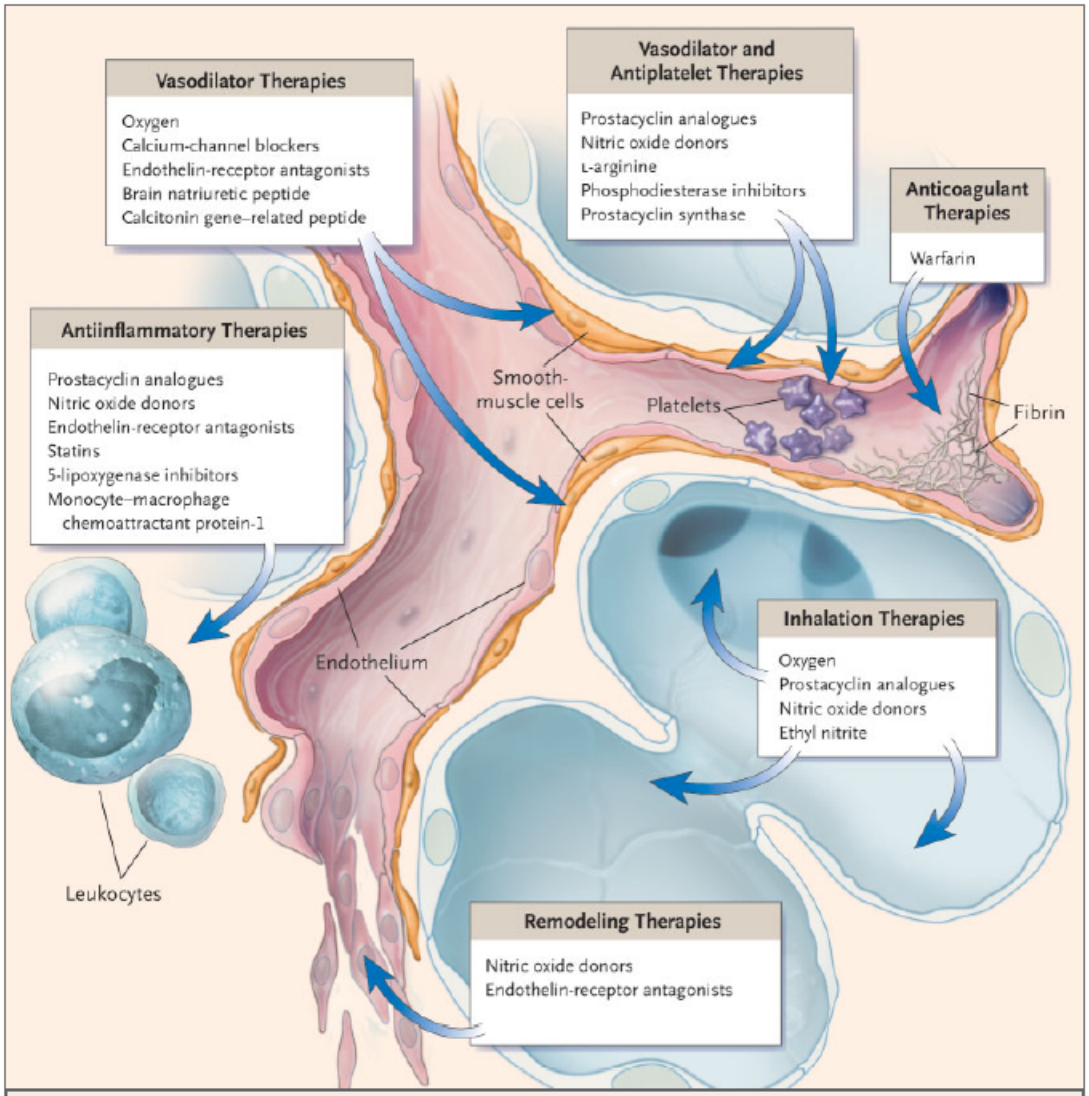


Figure 3. Therapeutic Approaches to Pulmonary Hypertension.

A model pulmonary arteriolar system and alveolus are illustrated, with the sites of action of each of six major classes of agents. Pulmonary vascular smooth-muscle cells are indicated in orange, platelets in purple, leukocytes in blue with pale nuclei, and fibrin as tan strands.

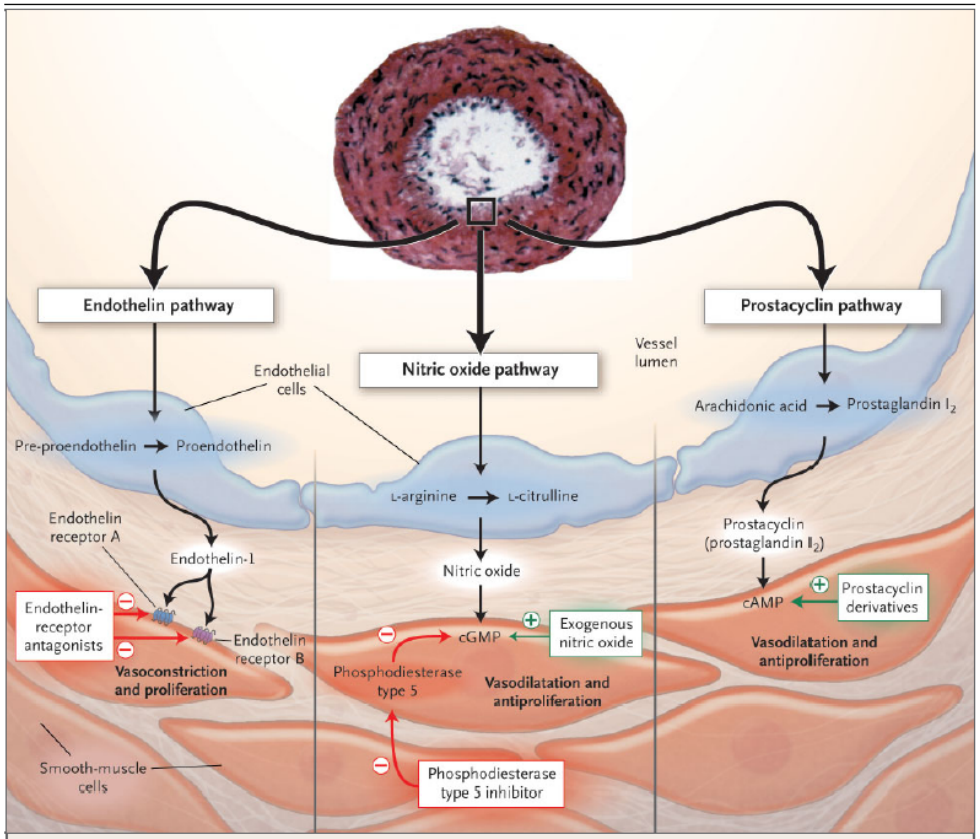


Figure 1. Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension.

Three major pathways involved in abnormal proliferation and contraction of the smooth-muscle cells of the pulmonary artery in patients with pulmonary arterial hypertension are shown. These pathways correspond to important therapeutic targets in this condition and play a role in determining which of four classes of drugs — endothelin-receptor antagonists, nitric oxide, phosphodiesterase type 5 inhibitors, and prostacyclin derivatives — will be used. At the top of the figure, a transverse section of a small pulmonary artery (<500 μm in diameter) from a patient with severe pulmonary arterial hypertension shows intimal proliferation and marked medial hypertrophy. Dysfunctional pulmonary-artery endothelial cells (blue) have decreased production of prostacyclin and endogenous nitric oxide, with an increased production of endothelin-1 — a condition promoting vasoconstriction and proliferation of smooth-muscle cells in the pulmonary arteries (red). Current or emerging therapies interfere with specific targets in smooth-muscle cells in the pulmonary arteries. In addition to their actions on smooth-muscle cells, prostacyclin derivatives and nitric oxide have several other properties, including antiplatelet effects. Plus signs denote an increase in the intracellular concentration; minus signs blockage of a receptor, inhibition of an enzyme, or a decrease in the intracellular concentration; and cGMP cyclic guanosine monophosphate.

or surgical sterilization has been proposed, but the procedures that are required can promote bleeding and may be impossible to perform in severely compromised patients. Vasectomy for the long-term male partner or spouse has also been proposed.

Many centers treating patients with pulmonary arterial hypertension recommend oral contraception with progesterone derivatives or low-dose estrogens, provided that the patient has no history of thromboembolic disease or thrombophilia.

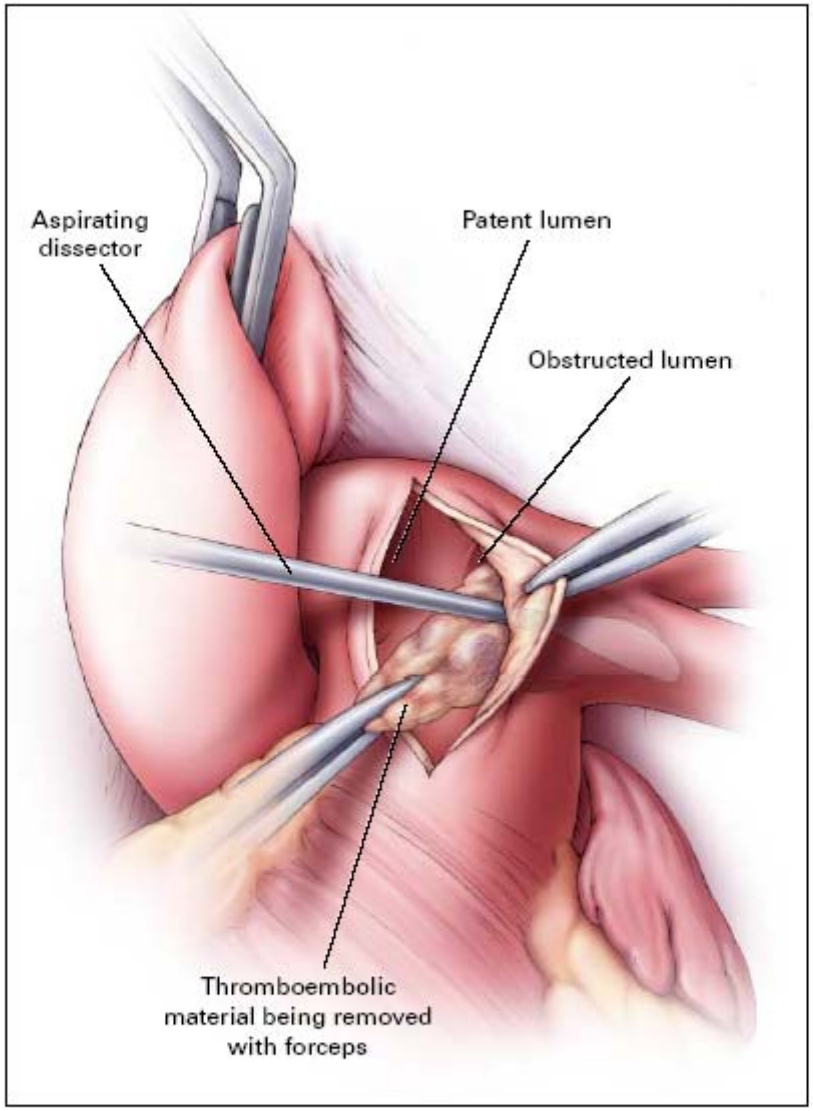
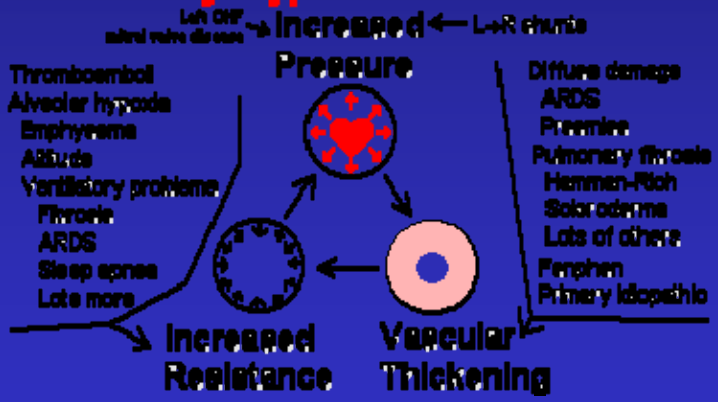


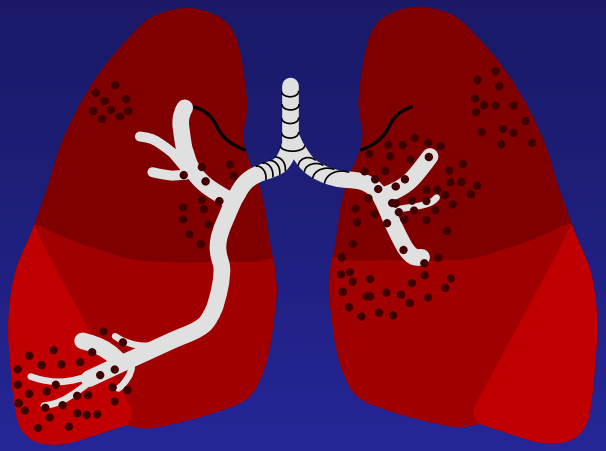
Figure 4. Intraluminal View of the Pulmonary Artery during Thromboendarterectomy.
The fibrotic, thromboembolic material is grasped with a forceps and circumferentially dissected from the vessel wall with an aspirating dissector. The material is then grasped at a more distal point, and the process is repeated until all the material has been removed and the patency of the vessel restored.

The End

Pulmonary Hypertension

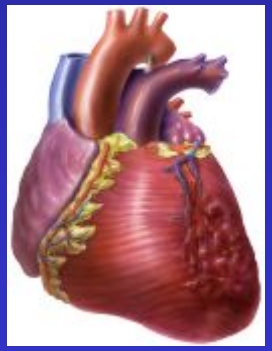


zvýšený odpor
přetížení



nedostatečné plnění

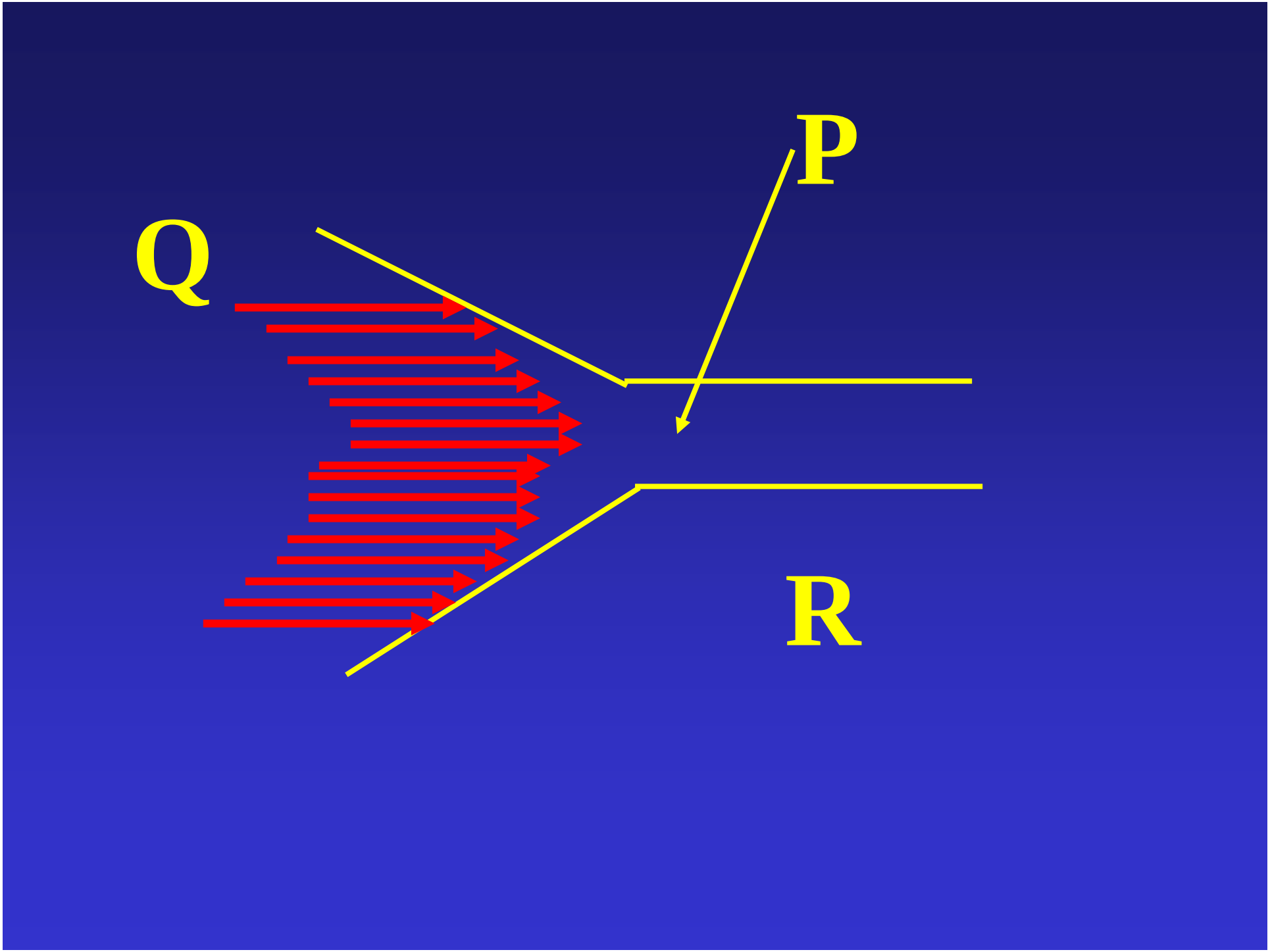
P srdeční komora

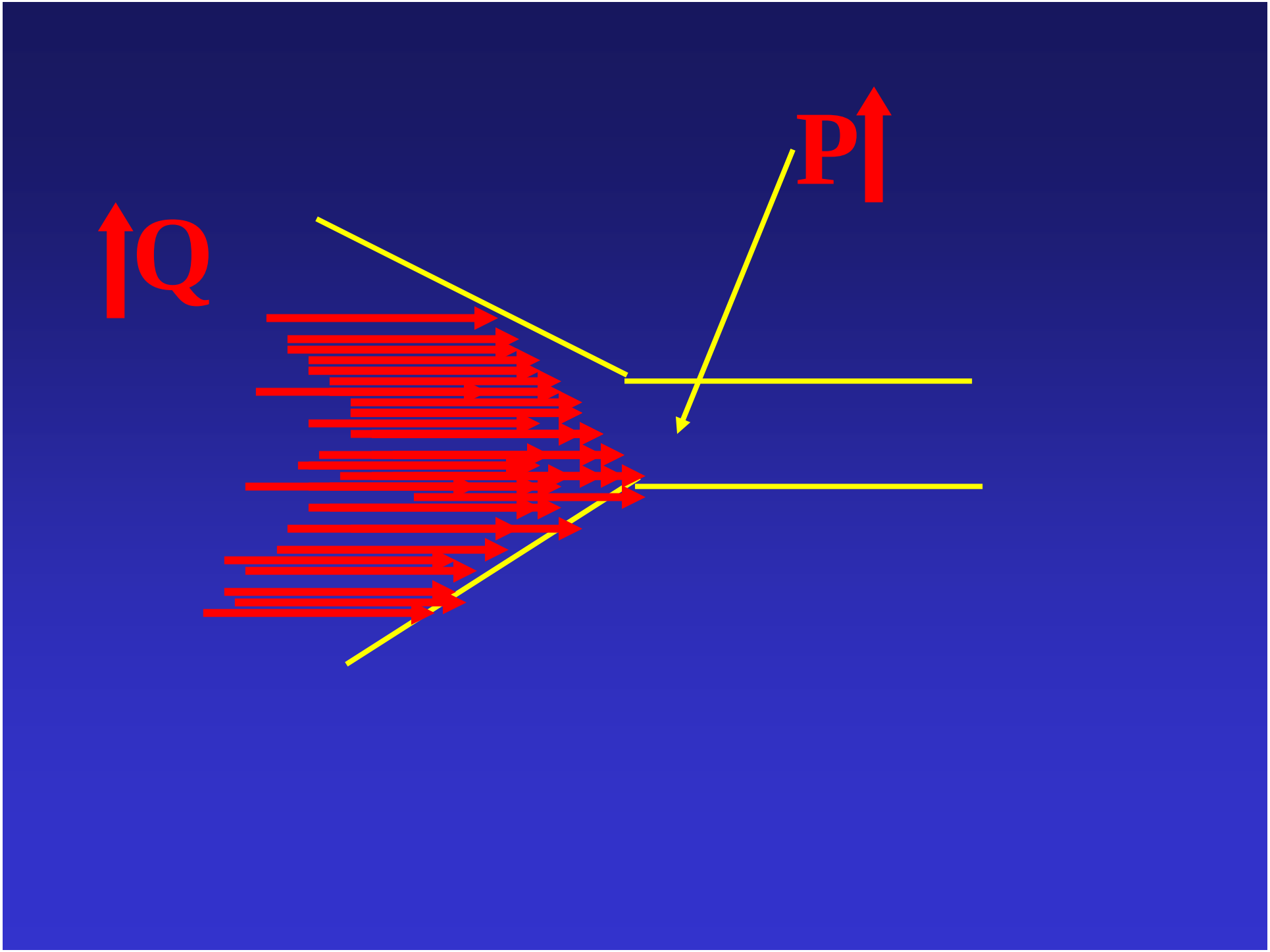


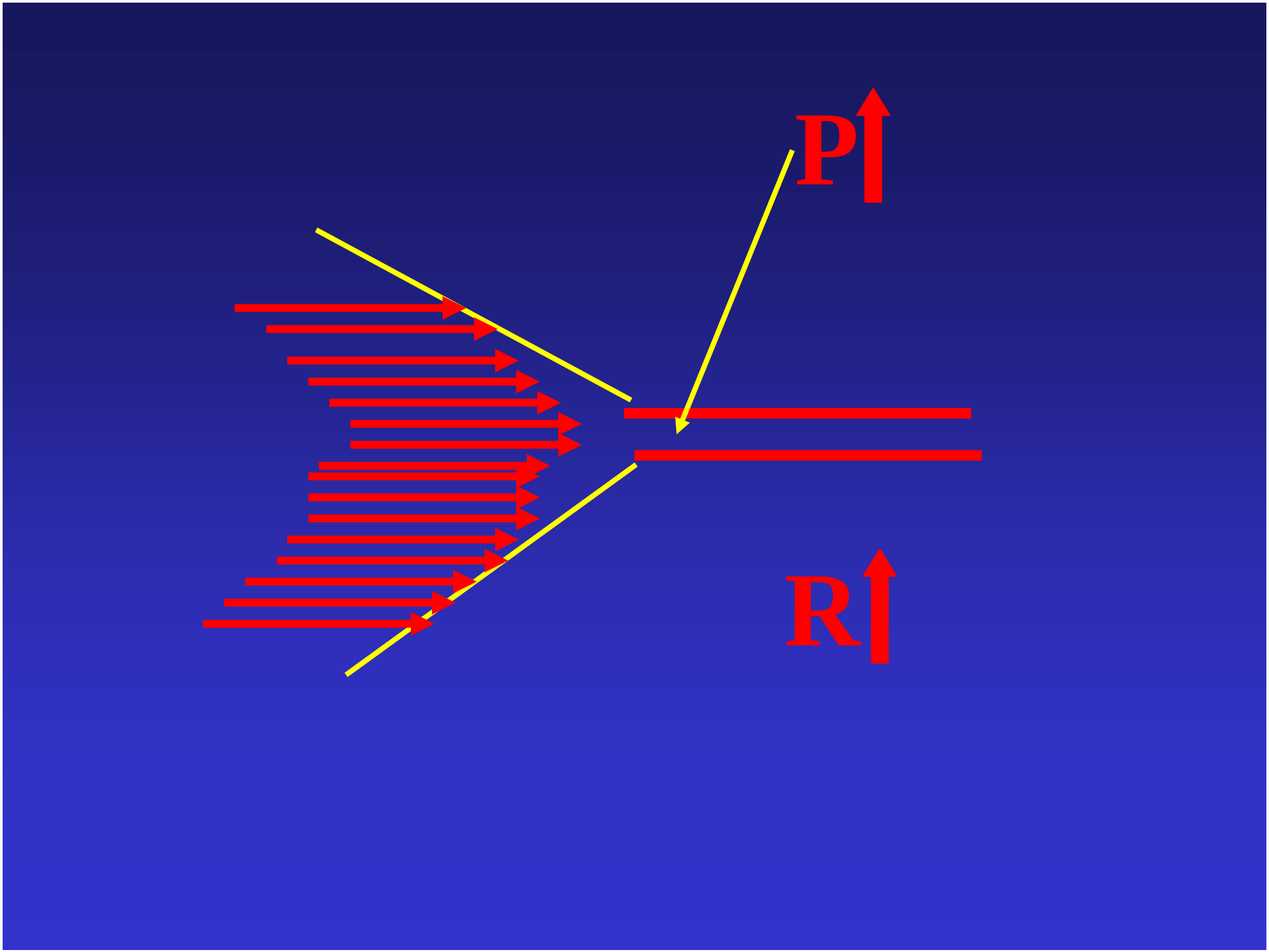
L srdeční komora

Pravostranné
srdeční selhání

Snížení
srdečního výdeje


P
Q
R


Q
P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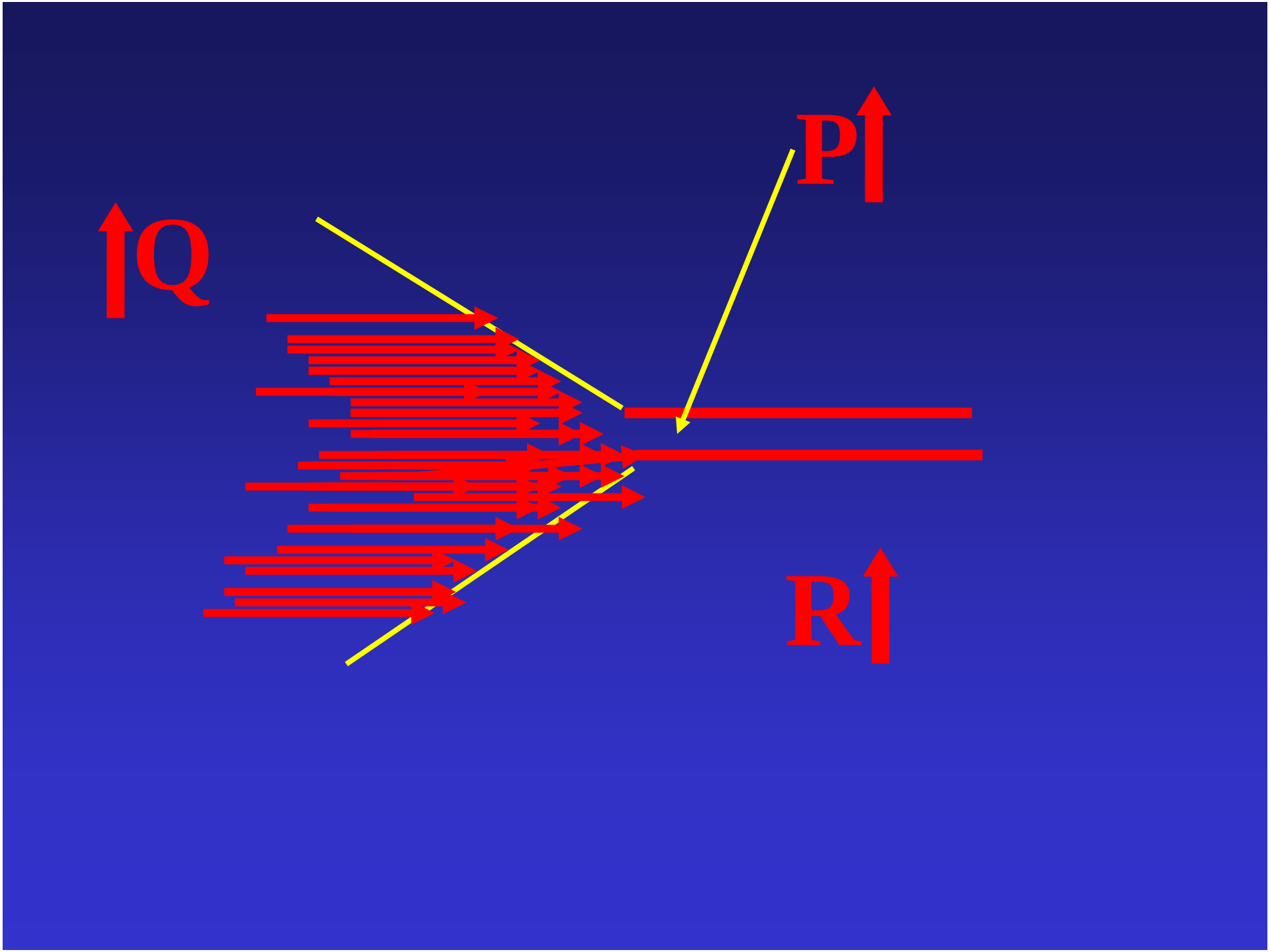
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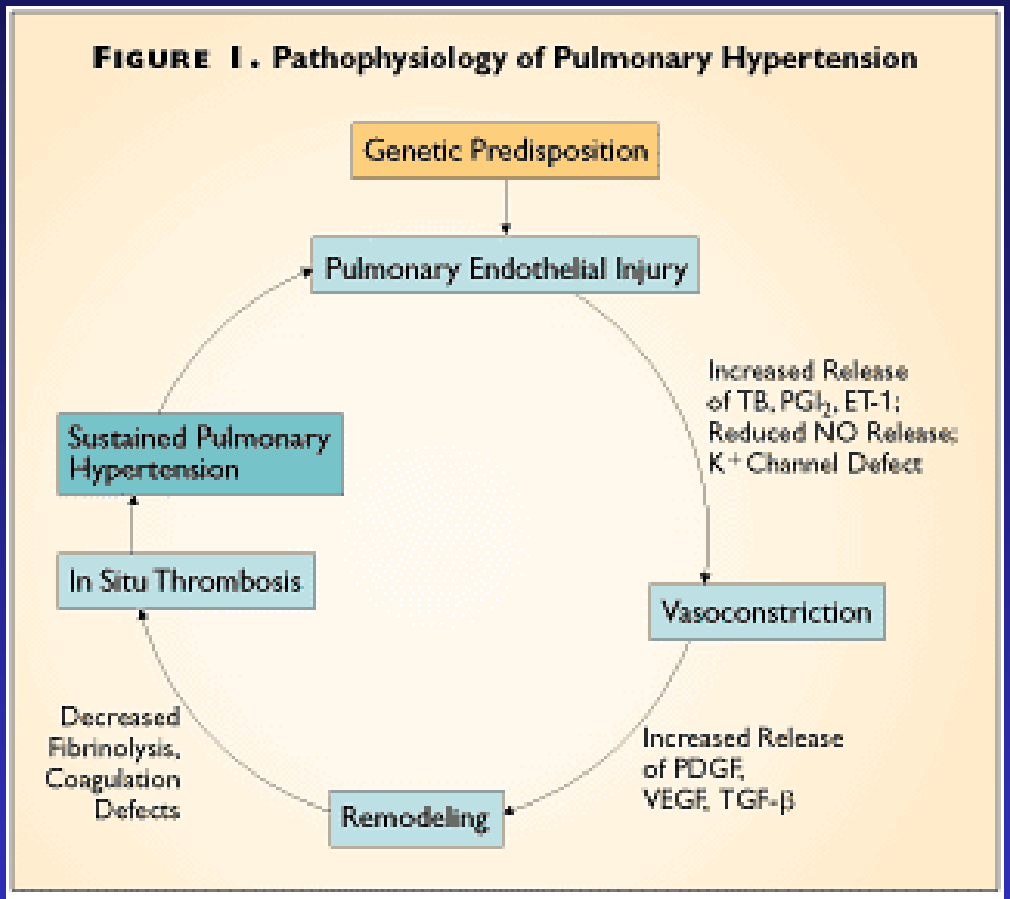

Figure 1. In genetically predisposed persons, endothelial cell injury can set off a vicious cycle leading to the development of primary pulmonary hypertension. First, the injury results in an imbalance of vasoactive mediators favoring vasoconstriction. In turn, growth factors are released, causing vessel wall thickening (remodeling). This promotes coagulation and fibrinolytic defects, which precipitate in situ thrombosis. The net effect is sustained pulmonary hypertension, causing more endothelial cell injury. TB=thromboxane, PG=prostaglandin, ET=endothelin, NO=nitric oxide, PDGF=platelet-derived growth factor, VEGF=vascular endothelial growth factor, TGF=transforming growth factor.