Coronary Circulation

- PDA supplied by the RCA – **right dominance** (70%), by the CX – **left dominance** (10%), by both RCA and CX – **co-dominance** (20%)
- **Capillary density** in the human heart > 3000/mm² (skeletal muscle has only ~ 400/mm²)
- **Thebesian veins** drain capillary beds within the ventricular wall
Epicardial, Intramuscular, and Subendocardial Coronary Vasculature
Anastomoses in the Coronary Arterial System

- Collateral vessels among branches of the arterial vessels and throughout the venous system act as anastomoses.

- They provide alternative routes for blood flow should a primary vessel become occluded.

- Collateral vessels originate from existing branches that undergo remodeling with the proliferation of endothelial and smooth muscle cells (arteriogenesis).
**Angiogenesis**

- **Angiogenesis** = *de novo* formation of capillary-like vessels, connecting the existing coronary arteries (genesis of subendocardial collaterals)

- Factors involved in angiogenesis: **FGFs** – fibroblast growth factors, **VEGFs** – vascular endothelial growth factors, **HGF** – hepatocyte growth factor, **HIF-1** – hypoxia inducible factor-1, angiopoietin-1 (ANGPT1)
Coronary Flow

- 5% of the resting cardiac output (225 ml/min), although heart weight represents 0.5% of body weight)
- Depends on
  - **Perfusion pressure** = Ao pressure
  - **Resistance** of the coronary vasculature, given by
    - Blood viscosity and the **inertia** of the blood column (10 - 15%)
    - **Autoregulated** changes of the vascular diameter (60 – 70%)
    - **Extrinsic compression** during myocardial contraction (25 – 35%)

\[ Q = \frac{\Delta p}{R} \]
Extravascular Compression Impairs Coronary Blood Flow During Systole

- Approximately 80% of total left coronary blood flow occurs during diastole.
  - In the early systole, blood flow may even reverse transiently (red pannel).

→ A high heart rate (= a short diastole) can be dangerous when coronary artery obstruction restricts blood flow.

- In the right coronary artery, the systole contributes substantially to the total flow.
Coronary Blood Flow in Depth of the Ventricular Wall

- **Systole:** the endocardium is less perfused than the epicardium due to a higher intramuscular pressure near the endocardium

- **Diastole:** the endocardium has a lower intrinsic vascular resistance → a better perfusion during diastole, compensating the effect of systole

  Nonetheless any condition that compromises coronary blood flow usually causes damage first in the subendocardial regions
Regulation of Coronary Blood Flow

- Done mainly by adjusting the **resistance** of coronary vasculature by relaxing/contracting the vascular smooth muscle in several manners:
  - **Autoregulation**
    - Metabolic
    - Myogenic
  - **Neural control**
  - **Humoral control**
Autoregulation

It is governed by the fundamental relationship that myocardial oxygen supply rises and falls in response to myocardial oxygen demands.

Autoregulation – the ability to maintain myocardial perfusion at constant levels over a wide range of driving pressure values (mean Ao pressure between 130 and 40 mmHg)
Myogenic Control

- Arterial smooth muscle reacts to increased intraluminal pressure by contracting → increased resistance → blood flow returns toward normal despite the higher perfusion pressure

- How?
  Increased length of vascular smooth muscle cells (VSMCs) activates **mechanical gated channels** anchored at the cytoskeleton of the vascular wall, determining an increase of the vascular tone
Metabolic Control

- A sum of mechanisms allowing a prompt adaptation of oxygen supply to the energetic needs of the myocardium.

- Necessary because:
  - The myocardium depends almost entirely on aerobic metabolism.
  - The myocardial oxygen extraction is very high (70 – 80%, compared to 25% in systemic circulation).
  - Oxygen stores in the heart are meager.

- Mediated by adenosine, NO, vasodilator prostaglandins, ATP-sensitive K+ channels, myocardial O$_2$ and CO$_2$ tensions.
**Adenosine**

- The principal metabolic mediator
- Formed by degradation of adenine nucleotides when ATP consumption exceeds cell capacity to resynthesize high energy phosphate compounds, due to:
  - increased heart activity
  - insufficient coronary blood flow
  - fall in myocardial pO$_2$

=> From myocardial cells adenosine diffuses into VSMCs → vasodilation → increased O$_2$ supply
Neural Regulation

- **Sympathetic** nerves stimulation
  - On myocardium, increases the metabolism (contractility, heart rate by $\beta_1$-stimulation) and indirectly produces metabolic vasodilation.
  - On VSMCs, through $\alpha$-receptors activation produces vasoconstriction.
  - Under normal circumstances, the metabolic vasodilation prevails the $\alpha$-mediated vasoconstriction.

- **Vagus** nerve stimulation
  - Has a mild vasodilatatory effect, due to the meager vagus nerve distribution into the heart,
  - While acetylcholine administered directly elicits a pronounced vasodilation.
Humoral Regulation

- **Endothelium-derived factors**

  Vascular endothelium has a very intense biologic activity, performing an array of homeostatic functions in normal blood vessels

  - **Endothelium-derived relaxing factors:** NO, PGI₂, EDHF (endothelium-derived hyperpolarizing factor)
  - **Endothelium-derived constricting factors:** endothelins (ET-1)

- **Others**
  - Angiotensin II, vasoconstrictor
  - Bradikinin, vasodilator
  - Serotonin, vasodilator
Measuring Coronary Blood Flow

- **Quantitative methods** - accurate but invasive $\rightarrow$ limited clinical use
  - Electromagnetic flowmetry (A)
  - Ultrasound flowmetry (B)

The movement of an electrical conductor (i.e., blood in a vessel) through a magnetic field induces a voltage between two points along an axis that is mutually perpendicular to both the axis of the field and the axis of the blood flow.
• **Semiquantitative methods** – show the distribution of myocardial perfusion; noninvasive, therefore widely used in clinics

- **Myocardial scintigraphy** – determines the distribution of radioactive isotopes (Thalium201, Technetium99) with access only in perfused areas, using scintillation cameras
Positron emission tomography (PET)
- based on the detection of gamma rays emitted by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule
- for myocardial perfusion assessment, are used N13, Rb82, O15
Myocardial Oxygen Supply and Demand

- CORONARY BLOOD FLOW: 60-90 ml/min / 100 g tissue
- DIASTOLIC FLOW
- Resisance

OXYGEN TRANSPORT AND DELIVERY

DEMAND: 10 ml O₂ / 100 g tissue

O₂ balance in myocardium

MAJOR DETERMINANTS

MINOR DETERMINANTS
Myocardial Oxygen Demand

- **Major determinants** reflect the *active* state of the myocardium:
  - Wall stress (preload, afterload)
  - Heart rate
  - Myocardial contractility

- **Minor determinants** are linked to the *basal* myocardial oxygen needs:
  - Cell structure maintenance
  - Electrical activity
  - Transmembrane transport of metabolites (fatty acids, glucose etc.)
Wall Stress

- Shortening of the contractile fibers generates tension within the ventricular walls
- Stress develops when tension is applied to a cross-sectional area; is expressed in force per unit area
- The geometry of ventricular cavity is important in determining the wall stress, as shown by the Laplace law:

\[
\text{Wall stress} = \text{pressure} \times \text{radius} / (2 \times \text{wall thickness})
\]

- Wall stress is an important determinant of myocardial oxygen demand → ventricular geometry influences the myocardial energetics
Wall Tension, Wall Stress

- Wall tension – the force acting on a hypothetical myocardial slice, tending to pull its borders one towards the other

- Wall stress – the force acting on surface unit

\[ T = \frac{p \times R}{2h} \]

- \( p \) – pressure
- \( R \) – radius
- \( h \) – wall thickness
Major Determinants

**Wall stress**
- According to the Laplace law
  \[
  \text{Wall stress} = \frac{pr}{2h}
  \]
- Ventricular systolic pressure \((p)\) depends on the pressure in the Ao and PA, that is the **afterload**
- Ventricular radius \((r)\) depends on the ventricular filling, which represents the **preload**
The Laplace law (Wall stress = pressure x radius/2 x wall thickness) helps understanding O₂ demand, which is
- Increased by:
  - High afterload (hypertension, aortic stenosis)
  - A dilated heart
- Decreased by:
  - Myocardial hypertrophy (thick wall)
  - Low ventricular pressure (low afterload)
Heart rate
- Tachycardia
  - Increases the myocardial oxygen demand
  - Decreases the coronary flow due to diminution of diastolic filling

Myocardial Contractility
- Positive inotropic agents increase the myocardial oxygen demand due to increased energy costs of enhanced excitation-contraction coupling
Myocardial Oxygen Supply

Oxygen transport and delivery
- Require an adequate
  - inspired quantity of oxygen (good air, healthy lungs)
  - amount of red blood cells
  - healthy hemoglobin

Coronary blood flow
- Continuously adapted to the metabolic needs of the myocardium in order to avoid underperfusion that would lead to ischemia or infarction
Acute Coronary Occlusion

A. Diagram of a **myocardial infarction** of the tip of the anterior wall of the heart (an *apical infarct*) after occlusion (1) of a branch of the left coronary artery (LCA, right coronary artery = RCA).

B. Cross section through a human coronary artery at the level of a **thrombotic atherosclerotic lesion** causing fatal myocardial infarction.
Coronarography
Computed tomography angiography (A)
Magnetic resonance angiography (B)

A. **CT** combines the use of x-rays with computerized analysis of the images; projection images obtained from different angles are assembled by computer into a three-dimensional picture of the area being studied.

B. **MRI** provides a better contrast and uses no ionizing radiation. Instead, it causes the atomic nuclei to produce a rotating magnetic field detectable by a scanner. It is more expensive, less accessible and slower than CT. Has a limited spatial resolution.
Coronary Artery Reperfusion

- Thrombolytic therapy
- Percutaneous coronary intervention (PCI)
- Coronary artery bypass graft (CABG) surgery

Thrombus material (in a cup, upper left corner) removed from a coronary artery during a PCI to abort a myocardial infarction.
Characteristics of Myocardial Metabolism

• Predominantly aerobic

• ATP providing the fuel for myocardial contraction is generated by – oxydative phosphorylation
  - anaerobic glycolysis

• Sources of energy – major: fatty acids, glucose, lactat;
  - during starvation or diabetic ketoacidosis: ketone bodies

• Normal oxygen supply: breakdown of fatty acids → high levels of ATP and citrate → inhibit anaerobic glycolysis
Myocardial Energetics in Ischemic Myocardium

- **Low oxygen supply** $\rightarrow$ low ATP and citrate $\rightarrow$ accelerated glycolysis $\rightarrow$ lactate production, pH lowering

- Increased lactate and H+ concentration inhibit glycolytic enzymes $\rightarrow$ depletion of high energy phosphates $\rightarrow$ cell membrane disruption and cell death

- Therefore, in ischemic hearts glycolysis can provide energy only as long as the blood flow is sufficient for preventing lactate and protons accumulation = borderline between mild and severe hypoperfusion
Better prevent than cure...