ELECTROPHYSIOLOGICAL CHANGES DURING MYOCARDIAL ISCHAEMIA

1. Definition of myocardial ischaemia
"The blood supply to the myocardium is inadequate" (Opie)
"The absence of arterial blood flow" (Jennings)
"Supply-demand imbalance" (Schelbert)

"Ischo" = "to hold back" "haima" = "blood"

The fundamental concept:
Imbalance between blood supply and blood demand of the myocardium (the oxygen supply is not able to keep up with the oxygen demand of the myocardium)

"Reversible" phase - when it is sufficiently severe to cause characteristic metabolic, mechanical, electrocardiographic changes that are diminished when the ischaemia ceases

"Irreversible" phase - as ischaemia progresses
→ infarction (= stuffed in)
→ cell death (= necrosis; "necro" = death)

Reperfusion (eg. thrombolysis) as early as possible - benefit for cells that are reversibly damaged
stenosis

critical ischaemia

mild ischaemia

severe ischaemia

occlusion
Coronary stenosis/spasm/occlusion

Physical/emotional stress

O$_2$ supply $\downarrow$/ O$_2$ demand $\uparrow$

Reduced perfusion

Metabolic changes

Electrophysiological changes

Impaired contractility
(little blood, little work)
Mild ischaemia

**Metabolic changes**

- ATP, CP breakdown $\uparrow$, Pi $\uparrow$
- phosphofructokinase $\uparrow$
  - (rate-limiting enzyme)
- phosphorylase $\uparrow$
- Glycolysis, glucose uptake $\uparrow$
- Glycogen breakdown $\uparrow$
- PYRUVATE $\rightarrow$ LACTATE
Severe ischaemia

Metabolic changes 1

• Accumulation of the products of anaerobic glycolysis (lactate, Pi, H+, NADH₂)
  
  glycolysis ↓ • ischaemic damage ↑

  acylCoA ↑ • ATP/ADP transport ↓

• Impaired mitochondrial function

• Impaired mitochondrial function

membrane damage
Severe ischaemia

Metabolic changes 2

Acute pain

catecholamines ↑

Plasma free fatty acid (FFA) ↑

acylCoA ↑

membrane damage

Intracellular FFA ↑

Triglyceride (TG)

O₂ demand ↑

ATP ↓
Membrane damage

- enzyme loss
- Ca²⁺ overload
- arrhythmias

Lack of ATP → uptake of Ca²⁺ into the SER ↓
→ Ca²⁺ pump activity ↓

ROS, CA, FFA

Ca²⁺

phospholipases

ATP production ↓
ATP utilisation ↑

Mitochondria (MITO)

ROS formation

Ca²⁺

ADP

ATP utilised

2

Ca²⁺

ATP

Ca²⁺

SER

Hypercontraction

Impaired diastolic relaxation

ROS, ATP, ADP, FFA

↑↑ ↑↑ ↑ ↑↑

Ca²⁺
Endothelium

Activated xanthine oxydase

hypoxanthine

O₂⁻

inosine

arachidonic acid

AMP

ADP

AMP

Cytosol

Reduced state

Neutrophils

ischaemia

H₂O₂

O₂⁻

OH⁻

CATECHOLMINES

ADRENOCHROME

H₂O₂

O₂⁻
ischaemia

poor O₂ delivery

Depressed mitochondrial metabolism

ATP↓

glycolysis, protons↑
glycolitic ATP

Ca²⁺↑
cell swelling

contracture

increasing ischaemia

poor washout

FFA metabolites

Ion pumps inhibited

NE↑
cAMP↑

ROS formation

Phospholipase activation

Lactate, H⁺, CO₂↑

severe cellular acidosis

cell swelling

membrane damage

lysosomal activation

ATP↓

enzyme loss

infarction

proteolysis

irreversible

reversible
Electrophysiological changes

- **K⁺ loss**
- **Ca²⁺ overload**

**EKG alterations:**
- ST-segment deviations (elevation, depression)
- peaked T wave

**Arrhythmias:**
- extrasystole (ES)
- tachycardia (VT)
- fibrillation (VF)

normal EKG
Rhythm disturbances (Arrhythmias)

Place of origin
• atrial
• junctional
• ventricular

Effects on heart rate
• tachycardia
• bradycardia

Mechanism
• disturbance in impulse generation
• disturbance in impulse conduction

early (EAD) and delayed (DAD) afterdepolarisations

„re-entry”
arterial blood pressure

left ventricular pressure

LV contractility (+/-dP/dt)

inhomogeneity of electrical activation

epicardial EKG 1

epicardial EKG 2

coronary blood flow

limb lead EKG

reperfúzió
OCCLUSION-INDUCED VENTRICULAR ARRHYTHMIAS IN ANAESTHETISED DOGS

Number of Arrhythmias

CONTROL

Single VEB
Salvo
Tachycardia
REPERFUSION-INDUCED VENTRICULAR ARRHYTHMIAS IN ANAESTHETISED DOGS
Consequences of acute myocardial infarction

- **ventricular arrhythmias**
  - early arrhythmias (within 24 h) ES, VT, VF
  - sudden cardiac death

- **atrial fibrillation**
  - often occurs after MI, especially in severe coronary artery disease, bad prognosis

- **heart failure**
  - Impaired LV pump function due to muscle loss

Treatment of arrhythmias (antirrhythmic manoeuvres)

Present

1. Pharmacological treatment → Antiarrhythmic drugs
2. Special pacemakers
3. Cardioverter defibrillators (ICD)

Future

1. Ischaemic preconditioning
2. Gene therapy
Ischaemic preconditioning

Short periods of ischaemia (coronary occlusions) protect the heart against the severe consequences of a subsequent, more prolonged ischaemia/reperfusion insult.

**Preconditioning stimulus**
- Coronary occlusion/stenosis
- Volumen overload
- Increased heart rate
  - electrical stimulation
  - physical exercise

**Protective effect**
- Preserved metabolism (ATP utilisation ↓, lactate production ↓)
- Ischaemic injury (infarct size) ↓
- Enhanced recovery of myocardial function during reperfusion
- Protection against ischaemia and reperfusion-induced ventricular arrhythmias
- Protection against endothelial dysfunction
PRECONDITIONING PROTOCOL

CONTROL

PRECONDITIONED

Occlusion  Reperfusion

5 min 5 min 25 min

Preconditioning

20 min 20 min
DISTRIBUTION OF VPBs DURING A 25 min OCCLUSION OF THE LAD

*n = 110*
VENTRICULAR ARRHYTHMIAS IN DOGS SUBJECTED TO CORONARY ARTERY OCCLUSION AND REPERFUSION

Duration of occlusion (min)

- VPBs
- VT
- VF
- REPERFUSION
ANTIARRHYTHMIC PROTECTION BY BRIEF CORONARY ARTERY OCCLUSIONS

 phase Ia

 phase Ib

 CONTROL (n = 110)  PRECONDITIONED  (n = 77)
TIME-COURSE AND INTENSITY OF PROTECTION INDUCED BY PRECONDITIONING

EARLY PROTECTION

„FIRST WINDOW”
„CLASSIC PRECONDITIONING”

ONSET: IMMEDIATE
DURATION: From minutes to 1 or 2 hours
INTENSITY: STRONG PROTECTION

DELAYED PROTECTION

„SECOND WINDOW”
„SWOP”

ONSET: 12 - 24 HOURS
DURATION: From 12 to 72 hours
INTENSITY: Milder Protection