Myocardial mitochondrial dysfunction in obesity/diabetes

*WG2 – heart people*

**Canada** - Hélène Lemieux, Ted Han  
**Estonia** – Kersti Tepp, Marju Puurand, Tuuli Kääambre  
**Latvia** – Marina Makrecka-Kuka, Edgars Liepinsh  
**Netherlands** – Rob Wust  
**Norway** – Neoma T Boardman, Terje Larsen  
**Portugal** – Carlos Palmeira  
**Romania** – Danina M. Muntean, Adrian Sturza  
**UK** – Andrew Murray, Katie O’Brien
Metabolic flexibility in IR and diabetes
Rob C.I. Wüst, Amsterdam UMC, University of Amsterdam, NLs

1. Brief intro on metabolic flexibility and in the heart
2. Substrate utilization: in vivo methods to assess fatty acid and glucose oxidation by PET/SPECT
3. Diabetes and metabolic flexibility: shift towards more FFA
4. Short intro on lipotoxicity, causing mito dysfunction
5. Bio-energetic status by 31P MRS – PCr/ATP ratio and link with Delta G
6. Discussion of 31P MRS literature in diabetes and IR

(Already written, 700 words)
Metabolic flexibility in IR and diabetes
Edgars Liepinsh, Marina Makrecka-Kuka, Latvian Institute of Organic Synthesis

Fasted

- Glucose 3%
- Fatty acids 95%
- Lactate 2%

Fed

- Glucose 28%
- Fatty acids 59%
- Lactate 13%
1. Summarize importance/consequence of altered mitochondrial energetics.
   • Evidence that improving the energetics of cardiac cells leads to improved clinical status in heart failure
   • Mitochondria are central to efficient energy production in the heart – and mitochondrial energetics are defined by the ATP produced in the mitochondria per molecule of nutrient, mitochondrial respiration rate, uncoupling and ROS production.

2. Characterize mitochondrial energetics in obesity/IR – what we know from the literature so far:
   • OXPHOS rates, uncoupling, ROS emission in cardiac mitochondria
   • FA/nutrient oversupply – consequences for energetics (ie higher ROS emission – uncoupling)
   • Altered mitochondrial calcium in obesity/IR may impact mitochondrial energetics

3. Brief summary of recent evidence of what can alter mitochondrial energetics in obesity/IR:
   1. The role of the redox environment on altered mitochondrial energetics in obesity/IR:
      • Glutathione redox and ROS production
      • Antioxidant treatment in mitochondria

   1. The role of mitochondrial fusion-fission dynamics on altered mitochondrial energetics in obesity/IR:
      • Nutrient overload and ROS have been shown to lead to fragmented mitochondria and downregulation of the fusion proteins. Mitochondria may reduce their efficiency to protect themselves – ensure survival.
      • OPA1 effects on mitochondrial dynamics and morphology in obesity/IR, the effects of OPA1 reduction on energetics
Role of MAO-related oxidative stress in diabetes
Danina M. Muntean, Adrian Sturza, Dept. of Pathophysiology-Functional Sciences, University of Medicine and Pharmacy of Timișoara, RO

1. Brief intro on MAO in cardiovascular system
2. The role of MAO-related oxidative stress in vasculature in the setting of experimental diabetes
3. The role of MAO-related oxidative stress in diabetic patients subjected to revascularization procedures
Mitochondrial respiratory supercomplexes as regulators of mitochondrial performance

Kersti Tepp, Marju Puurand, Tuuli Kääambre

Laboratory of Chemical Biology, National Institute of Chemical Physics and Biophysics, Tallinn, Estonia.

1. Brief introduction
2. Supercomplexes (SC) of electron transport system (ETS).
   1) Composition/stoichiometry, solid/plasticity model.
   2) Advantages/Influence of SC on ETS formation, electron transport efficiency, ROS production, maximal oxygen consumption rate etc.
   3) Alterations during aging, pathology (obesity).

Metabolic regulation in supercomplexes can be followed by method of metabolic control analyses (MCA).
Flux control coefficient (FCC), calculated from results of MCA, shows fractional change in an overall metabolic flux that is caused by 1% change in the rate of an enzyme in this pathway.
In a linear, unbranched system sum of the FCC is 1
Higher sum indicates higher organizatory levels between the proteins
3. Mitochondrial Interactosome model as regulator of mitochondrial work
   1) Effective energy flux to ATPases and signaling (transfer of information) back to mitochondrion
   2) Alterations in these supercomplexes during aging and pathology (obesity).

4. Directions of future study

Regulation of mitochondrial respiration in heart muscle - model of Mitochondrial Interactosome.

- In cardiomyocytes transport of ATP and ADP through the voltage dependent anion channel (VDAC) in mitochondrial outer membrane (MOM) is impeded.

- Regulatory linker protein(s) (LP) (heterodimeric tubulin ?), bound to the VDAC regulates it’s permeability.

- Main part of the ATP, transported through mitochondrial inner membrane (MIM) by adenine nucleotide carrier (ANC) is directly channeled to mitochondrial creatine kinase (mtCK); synthesized phosphocreatine (PCr) moves out of the mitochondrion. PIC - phosphate carrier

Exercise training and cardiometabolic health
Andrew Murray and Katie O’Brien, University of Cambridge, UK

1. Brief intro on exercise and training principles
2. Brief overview of morphological changes to heart following exercise training – eccentric vs concentric hypertrophy in endurance and resistance training
3. Metabolism during acute exercise [may omit this section if space is tight or wrap it into the introductory paragraph]
4. General effects of training on cardiac metabolism
5. Specific effects of endurance v resistance, and medium intensity vs high intensity interval training
6. Beneficial effects for cardiometabolic disease

Possible diagram highlighting differences (metabolic and morphological) between different training modalities.
Lifestyle intervention to target mitochondrial function
Hélène Lemieux and Ted Han, University of Alberta, Canada

1. Brief introduction on the aging component in T2DM and insulin resistance.
2. Lifestyle adjustment to reduce aging and T2DM
   1. Caloric restriction.
   2. Protein or specific amino acid restriction
   3. Alternate day fasting
   4. High-fiber low fat diet and the Nile rat model of T2DM

Physical activity (covered in the next section by Murray and O’Brien)
Pharmacologic strategies to target mitochondrial dysfunction (altered function)
Edgars Liepinsh, Marina Makrecka-Kuka, Latvian Institute of Organic Synthesis

- Mito targeting compounds
- Energy metabolism targeting compounds
Suggested journals

- American Journal of Physiology (Endocrinology and Metabolism)
- Physiology
- Physiol Reviews