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Hector O Ventura
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RESEARCH INTEREST

Arterial hypertension following cardiac transplantation, the effect of digitalis on mortality in heart failure, Lipid profiles after cardiac transplantation.
Pulmonary Arterial Hypertension: histopathological features

- **Normal**
  - Intima
  - Endothelium
  - Media and smooth muscle
  - Adventitia

- **Intimal and medial thickening**
  - Endothelial proliferation
  - Intimal fibrosis
  - Medial and smooth muscle cell hypertrophy

- **Intimal fibrosis and in situ thrombosis**
  - In situ thrombosis
  - Intimal fibrosis

- **Direction of blood flow**
  - Media
  - Intimal fibrosis
  - Collateral flux
  - Plexiform lesion

- **Diagram**
  - Arterial blood flow direction
Pulmonary Arterial Hypertension

Primary Pulmonary Hypertension (PPH)
- Sporadic
- Familial

Pulmonary Hypertension Associated with:
- Collagen Vascular Disease
- Congenital Systemic to Pulmonary Shunts
- Drugs/Toxins
- Portal Hypertension
- HIV Infection
Pulmonary arterial hypertension - a hypothetical mechanism -

- Proliferation of SMC and EC
- Phenotypically altered and transdifferentiated (SM-like) EC
- Muscularization of arterioles
- Complex vascular lesion

- Medial and intimal thickening
- Apoptotic EC
- Surviving EC
- CD34+ precursor cell
- SMC
- SM-like cell

- Release of factors
- Proliferation
- Expansion of precursor cells
- Transdifferentiation
BMPR2 haploinsufficiency

Other genetic factors:
- ALK1  SMAD1
- CAV1  SMAD4
- ENG   SMAD9

Environmental factors:
- Hypoxia
- Infection
- Appetite suppressant drugs (dex/fenfluramine)
- Toxic oil

Tunica adventitia
Tunica media
Tunica intima

Lumen

Medial and smooth muscle cell hypertrophy
Endothelial proliferation
Intimal fibrosis

In situ thrombosis
Intimal fibrosis

Pulmonary arterial hypertension

Thrombosis
Lipid mediator dysregulation
Extracellular matrix
Nitric oxide chemistry
Autoimmunity
Potassium channel disruption
Endothelin-1 dysregulation
Serotonin dysregulation
Inflammation
Decreased BMP signalling
Increased TGF-β signalling
The mechanism by which nicorandil attenuates MCT-induced pulmonary arterial hypertension

Dilatation of systemic veins and epicardial coronary arteries

Caspase-inhibitor

Vasodilation
Platelet aggregation↓
Anti-inflammation
Anti-SMC proliferation

PAEC protection

Anti-PAEC apoptosis

PAEC protection

Anti-PAH

Nitrate-effect

NO↑

Nitrater-effect

L-NAME

K<sub>ATP</sub> opener

Glibenclamide

eNOS↑

PI3k-Akt↑

MAPK-RSK↑

Survival Factors↑

PASMC stabilized

Intracellular Ca<sup>2+</sup>↓

Dilatation of peripheral and coronary resistance arterioles
Diverse Pathophysiology of Pulmonary Arterial Hypertension

- Pulmonary Vasoconstriction
- Fibrosis
- Hypertrophy
- In situ thrombosis
- Right ventricular strain and dysfunction
Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension

SIGNATURE

Hector O Ventura
Drug Designing

Drug Metabolism & Toxicology

Bioequivalence & Bioavailability
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