Abstract: P180

Transition from post- to combined pre-/post-capillary pulmonary hypertension: key role of endothelin

Authors:
RWB Van Duin¹, K Stam¹, Z Cai¹, DJ Duncker¹, IK Reiss², D Merkus¹, ¹Erasmus Medical Center, experimental cardiology - Rotterdam - Netherlands, ²Erasmus Medical Center, Sophia children's hospital, Neonatology - Rotterdam - Netherlands,

Topic(s):
Hypertension, Pulmonary Hypertension

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S48

Funding Acknowledgements:
Netherlands CardioVascular Research Initiative CVON PHAEDRA 2012/08 and Sophia Foundation S13-12

Background: Pulmonary hypertension (PH) is a pathophysiological disorder that is defined by a mean pulmonary artery pressure (mPAP) of >25mmHg at rest. By far the most prevalent form (65 – 80% of all cases) is PH due to left heart disease. When left untreated, this ‘passive’ isolated post-capillary PH (IpcPH) can progress to active combined pre/post-capillary PH (CpcPH) characterized by chronic pulmonary vascular constriction and remodeling which can eventually result in right heart failure and death. Endothelin (ET), a potent vasoconstrictor and inducer of vascular remodeling, has been shown to be elevated in patients with PH secondary to left heart disease. However, it is currently unknown whether ET contributes to the development of pulmonary microvascular remodeling in CpcPH.

Purpose: To test the role of the vasoconstrictor endothelin in the progression from IpcPH to CpcPH.

Methods: Piglets underwent banding of the confluent of both inferior pulmonary veins (PVB n=7), or sham-operation (SH n=6). Four weeks after surgery, all animals were chronically instrumented to longitudinally assess hemodynamics for an additional 8 weeks at rest and during exercise, before and after administration of ET-A+B receptor antagonist tezosentan. Plasma was collected over time. At sacrifice, the lungs were harvested for histology and RT-qPCR, and pulmonary small arteries were isolated for wire-myograph experiments.

Results: PVB swine gradually developed PH with increased mPAP (40±7 vs 18±4mmHg) and pulmonary vascular resistance (tPVRi: 250±62 vs 105±15mmHg·L⁻¹·min⁻¹·kg⁻¹ both p<0.01). RT-qPCR showed increased expression of endothelin converting enzyme (ECE-1) and endothelin (ET-1), unchanged expression of the ET-A, and downregulation of the ET-B receptor which is also the clearance receptor. This resulted in increased ET plasma levels from week 10 onward (8.0±1.0 vs 4.0±0.9pg/ml p<0.05), and a more pronounced vasodilation to in vivo administration of tezosentan at week 10 at rest (tPVRi: -33±9 vs -12±8mmHg·L⁻¹·min⁻¹·kg⁻¹ P<0.05), and at week 12 at rest and during exercise. Isolated vessel experiments showed decreased vasodilation to substance P (endothelial dysfunction) in PVB lower lobes vs SH lower lobes (50±5 vs 70±12%) and increased vasoconstriction to KCl in PVB swine (13.4±0.7 vs 7.9±0.7mN both p<0.05), consistent with increased muscularization seen with histology. Moreover, maximal vasoconstriction to ET was increased (17.5±0.7 vs 9.9±0.7mN) whereas ET sensitivity was decreased (LogEC50: -7.5±0.2 vs 8.3±0.2M).

Conclusions: PVB swine gradually developed pulmonary hypertension with structural and functional vascular remodeling. From week 10 onward, ET-activity was increased, initiating pre-capillary aspects to the originally isolated post-capillary PH. Early inhibition of the ET pathway could be an interesting pharmacotherapeutic approach to stop progression of post-capillary PH.
Abstract: P180
Transition from post- to combined pre-/post-capillary pulmonary hypertension: key role of endothelin

Authors: RWB Van Duin 1, K Stam 1, Z Cai 1, DJ Duncker 1, IK Reiss 2, D Merkus 1
1 Erasmus Medical Center, experimental cardiology - Rotterdam - Netherlands, 2 Erasmus Medical Center, Sophia children's hospital, Neonatology - Rotterdam - Netherlands

Topic(s): Hypertension, Pulmonary Hypertension

Citation: Cardiovascular Research (2018) 114 (Supplement 1), S48

Funding Acknowledgements: Netherlands CardioVascular Research Initiative CVON PHAEDRA 2012/08 and Sophia Foundation S13-12

Background: Pulmonary hypertension (PH) is a pathophysiological disorder that is defined by a mean pulmonary artery pressure (mPAP) of >25mmHg at rest. By far the most prevalent form (65 – 80% of all cases) is PH due to left heart disease. When left untreated, this 'passive' isolated post-capillary PH (IpcPH) can progress to active combined pre/post-capillary PH (CpcPH) characterized by chronic pulmonary vascular constriction and remodeling which can eventually result in right heart failure and death. Endothelin (ET), a potent vasoconstrictor and inducer of vascular remodeling, has been shown to be elevated in patients with PH secondary to left heart disease. However, it is currently unknown whether ET contributes to the development of pulmonary microvascular remodeling in CpcPH.

Purpose: To test the role of the vasoconstrictor endothelin in the progression from IpcPH to CpcPH.

Methods: Piglets underwent banding of the confluent of both inferior pulmonary veins (PVB n=7), or sham-operation (SH n=6). Four weeks after surgery, all animals were chronically instrumented to longitudinally assess hemodynamics for an additional 8 weeks at rest and during exercise, before and after administration of ET-A+B receptor antagonist tezosentan. Plasma was collected over time. At sacrifice, the lungs were harvested for histology and RT-qPCR, and pulmonary small arteries were isolated for wire-myograph experiments.

Results: PVB swine gradually developed PH with increased mPAP (40±7 vs 18±4mmHg) and pulmonary vascular resistance (tPVRi: 250±62 vs 105±15mmHg·L⁻¹·min⁻¹·kg⁻¹, both p<0.01). RT-qPCR showed increased expression of endothelin converting enzyme (ECE-1) and endothelin (ET-1), unchanged expression of the ET-A, and downregulation of the ET-B receptor which is also the clearance receptor. This resulted in increased ET plasma levels from week 10 onward (8.0±1.0 vs 4.0±0.9pg/ml, p<0.05), and a more pronounced vasodilation to in vivo administration of tezosentan at week 10 at rest (-33±9 vs -12±8mmHg·L⁻¹·min⁻¹·kg⁻¹, P<0.05), and at week 12 at rest and during exercise. Isolated vessel experiments showed decreased vasodilation to substance P (endothelial dysfunction) in PVB lower lobes vs SH lower lobes (50±5 vs 70±12%), and increased vasoconstriction to KCl in PVB swine (13.4±0.7 vs 7.9±0.7mN, both p<0.05), consistent with increased muscularization seen with histology. Moreover, maximal vasoconstriction to ET was increased (17.5±0.7 vs 9.9±0.7mN) whereas ET sensitivity was decreased (LogEC50: -7.5±0.2 vs 8.3±0.2M).

Conclusions: PVB swine gradually developed pulmonary hypertension with structural and functional vascular remodeling. From week 10 onward, ET-activity was increased, initiating pre-capillary aspects to the originally isolated post-capillary PH. Early inhibition of the ET pathway could be an interesting pharmacotherapeutic approach to stop progression of post-capillary PH.

---

Expression of genes in endothelin signaling

Vasodilation to ET-receptor antagonist

At rest

During exercise

Week

Week