Q14 Describe the mechanism of action, and adverse effects, of pulmonary vasodilators that are administered via the inhalational route. (March 2011)

PROSTACYCLINE THERAPY

- Prostacycline (PGI2) is the main product of arachadonic acid in the vascular endothelium. It stimulates cAMP production to induce smooth muscle relaxation and inhibits platelet aggregation and smooth muscle growth.
- Iloprost is a synthetic prostacycline analog delivered by inhalation which causes direct vasodilatation of the pulmonary arterial bed with improvement in PAP, PVR, CO and SvO2.
- SIDE EFFECTS → headache, cough, hypotension, bronchospasm and bleeding events

NITRIC OXIDE

- NO activates soluble guanylate cyclase, inducing vasodilatation, inhibition of platelet aggregation and inhibition of smooth muscle proliferation. When given via inhaler, it preferentially dilates the vessels of well ventilated alveoli, improving V/Q matching.
- NO is absorbed systematically but rapidly combines with haemoglobin in the pulmonary capillary bed, producing methaemoglobin and nitrate. Nitrate is cleared via renal excretion at a rate approaching to GFR.
- SIDE EFFECTS → risk of rebound PTHN on withdrawal of drug, methaemoglobinaemia, hypotension and thrombocytopaenia

OXYGEN

- Oxygen is a colourless, odourless, tasteless gas present in the atmosphere at a concentration of approximately 21%.
- The main action of oxygen in the body is to participate in oxidative phosphorylation, which produces the ATP required for cellular function. It moves down the oxygen cascade from a partial pressure of 159mmHg in atmospheric gas to approximately 105mmHg in the alveoli (dependent on PACO2 as per the alveolar gas equation), then to the mitochondria, where the PO2 may be as low as 2-3mmHg. Note the Pasteur point is the minimum mitochondrial PO2 required for oxidative phosphorylation to proceed – usually 1-2mmHg.
- SIDE EFFECTS →
    - CNS – visual changes and seizures may occur at 3 atmospheres
    - Ocular – retrolental fibroplasia has been seen in premature babies treated with oxygen, possibly due to vasoconstriction of developing retinal vessels
    - CVS – improvement in haemodynamics if oxygen is being used to correct hypoxaemia. Prolonged administration of 100% FiO2 may cause a reduction in heart rate and cardiac output, and coronary artery vasoconstriction.
    - Respiratory - Potential decrease in respiratory drive (significant in patients who are CO2 retainers and rely on their hypoxic drive to breathe). Absorption atelectasis. Tracheobronchitis. ALI/ARDS due to the production of oxygen free radicals (superoxide, hydroxide, hydrogen peroxide), which cause parenchymal damage and diffuse lung injury.