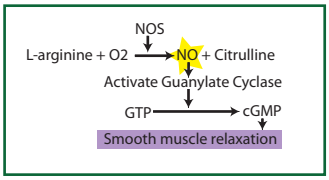
DRUG CLASS & APPLICATION	MODE OF ACTION	PHARMACOKINETICS	VARIABILITY / SIDE-EFFECTS
Endothelin Receptor Antagonists Dual action - (Bosentan) is used for patients who are New York Heart Association II-III. Drugs selective for ETA (sitaxsentan) are not currently in use.	In addition to exerting a direct vasoconstrictor effect, endothelin-1 stimulates proliferation of vascular smooth muscle cells, acts as a co-mitogen, induces fibrosis and acts a proinflammatory mediator by enhancing adhesion molecule expression. Bosentan is a dual action ET_A / ET_B endothelin receptor antagonist with a higher affinity for ET_A.	Bosentan is delievered orally and achieves approximately 50% bioavailability. It has a volume of distribution of 18 litres. Hepatic metabolism via CYP3A4 and 2C9 into three metabolites, one with 10-20% pharmacological activity. The time to peak plasma concentration is 3-5 hours and the half life is 5 hours although this may be prolonged in heart failure patients. Most of the metabolites are excreted in the faeces.	The major issue with Bosentan is there is dose dependent deranged liver function with transaminitis of up to eight times the normal levels. This necessitates monthly monitoring of LFTs in patients on Bosentan. It strongly induces CYP3A4 and 2C9 and therefore may reduce the efficacy of other drugs metabolised by this pathway.
Phosphodiesterase type 5 inhibitor Sildenafil is used for patients who are NYHA II-III other PDE 5 inhibitors include vardenafil and tadalafil	Like theophylline, Sildenafil is a phosphodiesterase inhibitor, however sildenafil is selective for type 5 (PDE5) inhibition. This results in a reduction in hydrolysis of cyclic GMP, and a subsequent increase in pulmonary vasculature relaxation through increased sensitivity to nitrous oxide actions. It uses the same mechanism when used for erectile dysfunction.	Sildenafil is taken orally and has an onset of action within 60 minutes and duration of 2-4 hours. It is absorbed rapidly with a bioavailability of 40%. There is a large volume of distribution of 105 litres. It undergoes hepatic metabolism via CYP3A4 and forms an active metabolite. Half life is around four hours and it is excreted 80% in the faeces and the remainder in the urine.	Due to its action in sensitising the vasculature response to NO, it is contraindicated in patients taking nitrates as this may lead to a dramatic loss in tone and subsequent profound hypotension. The most common side effect with this treatment is headaches which may occur in up to half of all patients.
Prostacycline therapies Prostaglandin I_2 (prostacycline) is delivered in several different forms and has the most beneficial effect in patients with PAH even those which have failed other therapies and is thus used in patients with NYHA III-IV. Unfortunately the pharmacokinetics limits the use of this class of drugs. IV Epoprostenol, IV or SC Treprostinil and Inhaled Iloprost are the main drugs in this class.	Prostacycline is the main product of arachidonic acid in the vascular endothelium, induces relaxation of vascular smooth muscle by stimulating the production of cAMP and inhibits the growth of smooth muscle cells. In addition it is a powerful inhibitor of platelet aggregation.	Epoprostenol may only be delivered by IV infusion, it has a very short half life of only 3-6 minutes, and is often delivered via infusion pump through a central line. It is rapidly metabolised by hydrolysis and mostly exceted in the urine. Iloprost is a chemically stable prostacycline analogue delivered by inhaler. It has a short half life of approximately 30 minutes therefore requiring frequent dosing (q2hr).	Common side effects include jaw pain and cramps. Sudden or abrupt withdrawal of the prostacyclines may lead to rebound pulmonary hypertension. Prostacyclines are inhibitors of platelet aggregation and caution may be required in patients with a bleeding diathesis.

Nitric Oxide therapy Nitric oxide is a powerful modulator of many aspects of bodily function. It is synthesised from L-arginine and molecular O2 by NO synthase (NOS). There is usually an abundance of L-arginine so it is the NOS that limits the reaction. NOS exists in three isoforms endothelial - eNOS (also found in platelets), inducible - iNOS (induced by macrophages and interferon gamma) and neuronal - nNOS. The main action of nitric oxide is to activate soluble guanylyl cyclase, which in turn activates cGMP. This leads to the main effects which include vasodilation, inhibition of platelet and monocyte adhesion and aggregation, as well as inhibition of smooth muscle proliferation.



Inhaled Nitric Oxide Is used as to test response in patients with PHTN. It is also used in paediatric popluations to improve oxygenation when paitents have respiratory distress. There may be an indication in patients with acute respiratory failure.	As stated above Nitric Oxide works by increasing the expression of guanylate cyclase which inturn increases production of cGMP. The result is increased smooth muscle relaxation. Other effects include decreased platelet aggregation and angiogenesis. When inhaled it preferentially dilates the vessels of the well perfused alveoli which leads to an improvement of V/Q matching.	Nitric oxide is rapidly inactivated by haemoglobin in blood (hence its limited systemic effects). NO forms methemoglobin and nitrate on reaction with oxyhemoglobin. Almost 70% of inhaled NO is excreted as nitrate in the urine within 48hrs. When high conc O2 is combined with NO it forms the toxic NO2, therefore delivering it with a high FiO2 is not recommended.	The response of the patient to inhaled NO is dependent on the degree of VQ mismatching is contributing to decreased oxygenation. Doses need to be titrated with worsened oxygenation at both high and low doses. There is some concern about environmental contamination to health care professional although this is minimal in a well ventilated room. Very high doses may lead to significantly increased methemoglobin levels.

Pharmacology of oxygen oxygen may be regarded as a drug. It is a colourless, odourless and tasteless drug which is present in normal air at a approximately 21% of the total pressure. The delivery of oxygen is determined primarily by a decrease down the oxygen cascade from a normal pO2 at sea level of 158 mmHg down to the mitochondrial level where the partial pressure may be as low as 2-3 mmHg. Oxygen is primarily transported throughout the body bound to Hb but a small percentage is dissolved in the blood. The dissolved component may be increased at supranormal pressures such as those observed in hyperbaric oxygenation. The main purpose of O2 in the body is to participate in oxidative phosphorylation which produces the high levels of energy required for cellular function. Oxygen may delivered in a range of methods, either via nasal prongs or a face mask where the inspired amount is variable on tidal volumes and rates, or in fixed amounts via closed circuits or fixed intake valves such as venturi valves which entrain air at a set proportion. Oxygen has a range of therapeutic uses, by far the most common is treatment of hypoxia. Other less common treatments are usually delivered at increased pressures and include treatment of air embolism, non healing diabetic foot ulcers, osteoradionecrosis of the jaw, and infections such as myonecrosis. Delivered at high doses results in several physiological and potentially harmful changes. From a respiratory perspective there may be a decrease in respiratory drive, which is usually only significant in patients with a desensitised hypercapnic drive such as those with CO2 retention. Breathing high doses of oxygen also leads to the washout of nitrogen which may lead to absorption atelectasis and a subsequent shunt with a paradoxical decrease in oxygenation. Longer term high dose may also lead to oxygen toxicity, which is characterised by parenchymal damage and diffuse lung injury and is likely due to increased reactive oxygen species (Lorraine Smith Effect). Cardiovascular changes are minor and consist of a slight reduction in heart rate and cardiac output. CNS effects are noted at very high levels are characterised by seizures (Paul Bert Effect) and visual changes.

Oxygen Is used to primarily to treat hypoxia. Alternative uses include treatment of CO posioning, diabetic foot ulcers, infections such as clostridial myonecrosis, air gas embolism, decompression sickness and radiotherapy injury.	Oxygen diffuses passively throughout the body down a concentration gradient. It reverses hypoxia by increasing the partial pressure and improving O2 delivery to mitochondria. It is believed to improve chronic ulcers by creating a steep oxygen gradient at wound margins similar to an acute wound. In decompression illness is replaces nitrogen bubbles with O2 bubbles which are consumed.	Oxyen is inhaled by passive diffusion in the lungs and is bound to Hb and dissolved in plasma. Extracorporeal oxygenation is an alternative delivery method. O2 is metabolised with gluclose to form energy, CO2 and H2O. The precise mechanism is a three step process of glycolysis, the krebs cycle which are anaerobic (and produce 4 ATP) and finally oxidative phosphorylation in the mitochondria which results in 34 ATP units.	Harmful effects of hyperoxia include include dry mucous membranes, absorption ateletasis, acute lung injury, depressed respiratory drive, and seizures and visual changes at hyperbaric doses. Delivery may be impaired in patients with reduced haemaglobin capacity either due to anaemia, or dysfunctional Hb such as the thalassaemias or posioning due to CO, or damage to the oxidative phophorylation process seen in cyanide posioning.

Pharmacology of Surfactant is formed from type II alveolar cells. It is mostly phospholipid with the principle component DPPC which equates to roughly 80% content. There are also four surfactant protiens "SP" A to D. These are believed to be important in the stabilisation of the surfactant, its activation and release from alveolar cells. Surfactant forms a mono layer due to its structure with a hydrophilic head adjacent to the cell wall and the hydrophobic tail facing inwards towards the air. Surfactant has a 15-30 hour half life and in addition to its primary role of reducing surface tension also prevents transudation into in the the alveolus (less pressure inside alveolus) and has an immunological role. The exact mechanism of how it reduces surface tension is unknown but the main hypothesis is that as it packs closer together when the alveolus reduces in size the action is accentuated, causing a greater decrease in surface tension with decreases in radius.

Surfactant Is currently only indicated in neonatal resipartory distress syndrome and severe meconium aspiration syndrome in newborns. There is some research supporting its use in ARDS although no benefit in outcome has yet been proven. Most surfactant in use are bovine or porcine derived. Artifical surfactant also exists.	It is believed that surfactant acts by packing closer together and causing a paradoxical decrease in surface tension as the radius of the alveolus decreases. It also has immunological role and reduces exudation into the alveolus due to the decrease intra alveolar pressure.	The half life of human surfactant is 15-30 hours. Surfactant replacement therapy is currently delivered via endotrachael tube although it is possible to deliver in a aerosolised form. Upon delivery much of the surfactant becomes 'lung associated' and not recoverable by BAL. It is believed that exogenous delivered surfactant is enters the normal recycling pathways and provides substrate for endogenous production.	The main issues with surfactant administration are the transient hypoxia, hypotension and bradycardia and the risk of blockage of the ETT. There is some association with pulmonary haemorrhage.