• Freely diffusible gas that acts as a signalling molecule
• Very short half-life 6-30s = local activity
• Activity in blood limited by circulating haemoglobin α
• Prevents thrombosis – inhibits platelets adhesion to vessels and activation
• Anti-inflammatory – inhibits leukocyte adhesion and migration
• Antioxidant
• Inhibits smooth muscle cell proliferation and migration
• Atheroprotective

Relaxation of vascular smooth muscle (vSMC)
• Mechanism of vSMC relaxation
  o cGMP reduces [Ca^{2+}]
  o regulates phosphodiesterase
  o Activates PKG → limit activation of myosin-light chain kinase (MLCK) essential for myosin-actin cross bridge formation → smooth muscle relaxation

Prostacyclin synthesis
• Phospholipase A2 activity leads to prostacyclin – rate limiting step – activated by Ca^{2+} & PKC
• Cyclooxygenases
  o COX-2 – inducible
  o COX-1 – constitutive (predominant isoform in endothelium)
• Endothelial cells express prostacyclin synthase (PGCIS)
• Platelets use thromboxane synthase to produce thromboxane

Prostacycline (PGI2) and vSMC relaxation
• Prostacyclin binds IP receptors (GPCRs)
  o Activates adenylate cyclase
  o Increasing [cAMP] activates PKA
  o Decreases [Ca^{2+}] limiting vSMC contraction

Endothelium-derived hyperpolarising factors (EDHF)
• The phenomenon of endothelium-dependent hyperpolarisation and relaxation
• Ach stimulation of artery preparation in the presence of NO scavengers (e.g. haemoglobin) & COX inhibitors (indomethacin) indication an additional endothelial-dependent vasodilatory activity
• Small molecule with a short half-life
• EDHF effects are blocked with endothelial K+ (e.g. IKca2+) channel inhibitors
• EC become hyperpolarised and signal to vSMCs resulting in hyperpolarisation to produce vasodilation
• EC hyperpolarisation transmitted to myocytes via myo-endothelial gap junctions OR
• EDHF is K+ exciting EC through K+ channels to activate myocyte K+ channels & Na+/K+ ATPases

Endothelium dysfunction/activation
• Shift in EC function to reduced vaasodilation & more pro-inflammatory & pro-thrombotic state
• Classically associated with reduced bioavailability of NO & reduced vasodilation
• Blood vessels may become damage and leaky with loss of EC