

Inotropes

increase contractility of a cardiac myocyte independent of preload or afterload
 common ultimate cellular mechanism of action of these agents involves an influence on the release, utilisation or sequestration of intracellular calcium.
 two main groups based on cAMP involvement in increasing intracellular Ca

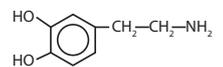
cAMP Dependent Inotropes	cAMP Independent Inotropes
Catecholamines Natural Adrenaline Noradrenaline Dopamine Synthetic Dobutamine Isoprenaline Non catecholamine sympathomimetics phenylephrine metaraminol Phosphodiesterase inhibitors Milrinone Other Glucagon	Calcium Sensitisers Levosemidan Other Digoxin Calcium Thyroid hormone

Catecholamines

act on beta1, 2 and alpha1,2 adrenergic receptors (beta1 mostly responsible for inotropy)
 beta1 receptors are numerous in the heart, they are Gs protein coupled receptors
 activation - alpha subunit swaps GTP for GDP - adenylyl cyclase activated - increased cAMP
 increased cAMP causes increased intracellular calcium leads to increased contractility
 beta effects predominate at lower doses, adrenaline has a greater beta affinity than noradrenaline and adrenaline are given at doses similar to that naturally released in shocked states
 dopamine is given at higher doses, many effects may relate to a subsequent conversion to noradrenaline
 dobutamine binds to beta1 vrs beta2 3:1. It is a potent inotrope which increases MVO2 ++
 isoprenaline is a potent non selective beta agonist, inotropy benefits are = to drop in SVR

Non catecholamine sympathomimetics

do not have two OH on their benzene rings
 phenylephrine is a potent alpha agonist with minimal beta activity
 metaraminol is a synthetic amine with both direct and indirect actions, main beta 1



Dopamine

Phosphodiesterase inhibitors

Milrinone - decreased the breakdown of cAMP by phosphodiesterase leading to increased Ca

Calcium Sensitisers

Levosemidan increases myofilament calcium sensitivity by binding troponin C, increasing inotropy

Other Glucagon increases the action of adenylyl cyclase which increases cAMP and Ca (but needs high doses)

Digoxin blocks Na.K.ATPase which decreases Na-Ca pump action increasing intracellular Ca
 infusion of calcium leads to a 10-20 minute intense +ve inotropic effect (admin at end of bypass surg)
 thyroxine mediates increases in Ca.ATPase activity increasing Ca release from the SR