# Mechanisms of inotropic effects induced by nitric oxide

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## Introduction

Nitric oxide (NO) has been shown to modulate cardiac contractility. In physiologic concentrations (0.01-1 µM) NO induces a positive inotropic effect in different mammalian species including man. In contrast, concentrations of NO exceeding physiologic levels (> 1 µM) can reduce myocardial contractility. These effects of NO have been attributed to cGMP, the second messenger generated following NO-dependent activation of soluble guanylyl cyclase. Interestingly, it is not known whether endothelial cells or cardiomyocytes are the major cellular source of inotropic NO. Although the effects of NO on myocardial contraction are moderate, they might be important in regulation of myocardial function. Both impairment of endogenous NO production by endothelial NO-synthase and increased NO production by inducible NO-synthase could result in cardiodepressive effects.

Many years before organic nitrates were known to be NO donors, several laboratories reported positive inotropic effects of glyceryl trinitrate in animals and man[1-3]. Most of the subsequent studies on the effects of exogenous NO have been performed with NO donors[4]. However, there are important differences between clinically used nitrovasodilators. This holds true for the mechanism and the kinetic of NO release and for the formation of toxic by-products. For example, organic nitrates need enzymatic bioactivation to form NO, while sodium nitroprusside generates cyanide as cardiodepressive by-product[4]. The enzyme soluble guanylyl cyclase is the most important cellular target of NO (Fig. 1). This holds true for almost any cell type responding to NO[5]. In addition, NO has been shown to directly affect other cellular structures such as transmembrane ion channels and mitochondrial enzymes[6,7], although a cGMP-independent effect of NO on potassium channels has been questioned[8]. The known mechanisms underlying the inotropic effects of NO differ with respect to the concentration of NO and the expected effect on myocardial contractility.

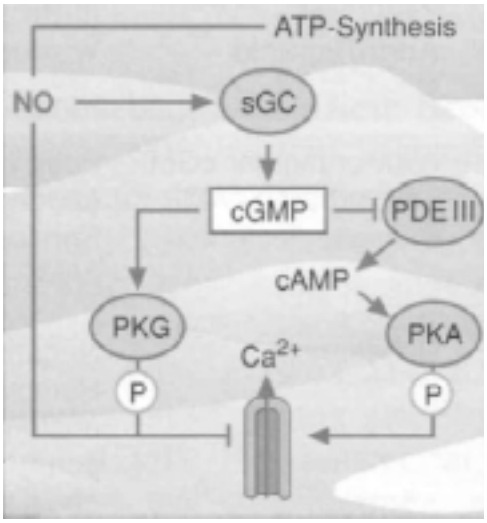


**Figure 1.** *Mechanism underlying the inotropic effects of nitric oxide (NO) on cardiac muscle. Activation of soluble guanylyl cyclase (sGC) and generation of cyclic guanosine monophosphate (cGMP) can induce inhibition of phosphodiesterase (PDE III) resulting in accumulation of cyclic adenosine monophosphate (cAMP) and activation of protein kinases (PKG) resulting in reduced transmembrane $Ca^{2+}$-current. Other mechanisms are the direct inhibition of myocardial adenosine triphosphate (ATP)-synthesis and of L-type $Ca^{2+}$-channels.*

## cGMP-dependent mechanisms

The enzyme soluble guanylyl cyclase is found abundantly in vascular smooth muscle cells, neurons, platelets and also in hu-

man cardiomyocytes[9,10]. In mammalian cardiomyocytes the most important effector proteins of cGMP are the cGMP-dependent protein kinases and the cGMP-inhibited cGMP-phosphodiesterase[11]. Stimulation of the protein kinases elicits inhibition of transmembrane $Ca^{2+}$-current through voltage-dependent $Ca^{2+}$-channels. This has been observed at high concentrations of NO (> 10 µM) in different species such as frogs, guinea pigs and rats[12-14]. The underlying mechanism is not known but might involve phosphorylation of voltage-dependent $Ca^{2+}$-channels[15]. The enzyme phosphodiesterase III hydrolyzes cAMP. It is important among phosphodiesterases in mammalian cardiomyocytes and inhibition of phosphodiesterase III has been observed at physiologic concentrations of NO donors (< 1 µM)[16]. Binding of cGMP to phosphodiesterase III results in a reduced hydrolysis and accumulation of cAMP[17]. Studies with cardiomyocytes of frogs, guinea pigs and human atrial tissue showed that inhibition of phosphodiesterase by cGMP stimulates the transmembrane $Ca^{2+}$-current[9,14,18].

## cGMP-independent mechanisms

Studies with isolated dog ventricle showed inhibition of cellular respiration by the NO donor S-nitroso-N-acetylpenicillamine which was attributed to an impairment of mitochondrial electron transport[7]. Another mechanism which has been demonstrated in cells transfected with voltage-dependent $Ca^{2+}$-channels is a cGMP-independent inhibition of transmembrane $Ca^{2+}$-current induced by high concentrations of NO donors (> 100 µM)[19].

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