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Differential effects of nitric oxide donors and phosphodiesterase 5 inhibitors on vascular function in humans

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Although organic nitrates continue to be widely used in the therapy of cardiovascular disease there is increasing evidence that their long-term use is associated with adverse vascular effects. The phenomenon of tolerance, whereby the vascular, hemodynamic and clinical effectiveness of the nitrates is lost during sustained therapy, has been recognized for almost 30 years. Recent studies have documented that sustained therapy with glyceryl trinitrate (GTN) is associated with increased vascular free radical formation and the development of endothelial dysfunction. These findings have been documented in animal models as well as in the human coronary and forearm circulation. Paradoxically the acute and short-term administration of organic nitrates appears to have beneficial effects on vascular function. When given in very low doses GTN augments the effects of endothelium-dependent vasodilators. Furthermore, there is now clear evidence that short-term (1–2 hours) exposure to GTN provides protection from ischemic injury at time points 24 to 48 hours later. This pharmacologic preconditioning effect appears to be mediated by the production of reactive oxygen species as it can be blocked by the co-administration of vitamin C. The finding that administration of sildenafil affords protection from the impact of ischemic insults emphasizes the importance of cyclic GMP in the mediation of pharmacologic preconditioning. In order to address this question we used a human forearm model of ischemic vascular injury where the impact of 15 minutes of forearm ischemia followed by reperfusion on flow-mediated radial artery dilation is used as the marker of ischemic injury. This ischemia reperfusion insult causes almost complete loss of flow mediated brachial artery dilatation. In a double blind, placebo controlled trial we have documented that the administration of sildenafil just prior to ischemia reperfusion provides complete protection from the impact of ischemia on flow-mediated dilatation (figure 1). This effect appears to be dependent on mitochondrial potassium ATP channels as the protective effect of sildenafil could be completed inhibited by the co-administration of the sulfonylurea glibenclamide.

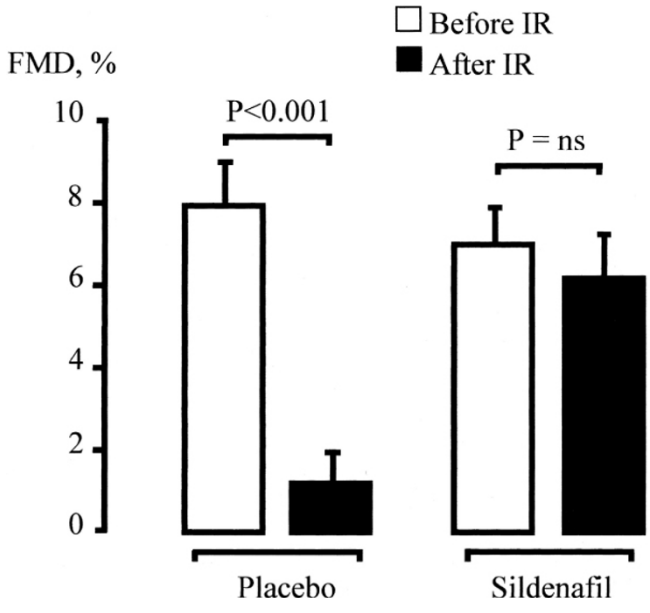

Figure 1
Flow-mediated dilatation of the radial artery (FMD %) before and after 15 min. of forearm ischemia and reperfusion (IR) in the presence and absence of sildenafil.