933-91 Nitric Oxide Contributes to Bradykinin-Induced Vasodilation of Human Epicardial Coronary Arteries In Vivo

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It has been shown that Bradykinin induces endothelium-dependent relaxation of isolated human coronary arteries in vitro. To investigate whether nitric oxide (NO) release contributes to bradykinin-induced vasodilation of human epicardial coronary arteries in vivo, we studied the effect of inhibition of NO synthesis by N^G-monomethyl-L-arginine (L-NMMA) on intracoronary infusion of bradykinin in 11 patients with normal coronary arteries. After baseline angiography, incremental doses of bradykinin (0.5, 1.5, and 2.5 μg/min for 2 min) were infused into the left coronary artery. After intracoronary administration of L-NMMA (60 μmol/min), repeat baseline angiography was performed. Then, incremental doses of bradykinin were infused again, followed by infusion of nitroglycerin (NTG, 200 μg). Changes in diameter of the proximal and the distal left anterior descending and circumflex coronary segments were measured by quantitative angiography. Percent changes in coronary diameter were as follows (mean ± SD):

	Bradykinin (μg/min)		
	0.5	1.5	2.5
Proximal (n = 18)			
Before L-NMMA	+4 ± 8%**	+5 ± 9%**	+8 ± 9%*
After L-NMMA	0 ± 4%	+1 ± 3%	+2 ± 4%
Distal (n = 18)			
Before L-NMMA	+7 ± 7%*	+12 ± 13%*	+13 ± 12%*
After L-NMMA	−1 ± 6%	+2 ± 4%	+2 ± 6%

*p < 0.01, ** p < 0.05 vs Baseline

At baseline, L-NMMA reduced epicardial coronary diameters by 5 ± 9% and 5 ± 10% in the proximal and the distal coronary segments, respectively. Although bradykinin-induced coronary vasodilation was observed before L-NMMA infusion in dose-dependent manner, it was reduced by L-NMMA. Endothelium-independent dilation with NTG was significantly observed (p < 0.01). Thus, bradykinin-induced vasodilation of human epicardial coronary arteries is mediated by the action of endothelium-derived NO in vivo.

933-92 Role of Endothelium-Derived Nitric Oxide in the Vasodilator Response to Mental Stress

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Endothelium-derived nitric oxide (NO) plays a central role in regulating basal arterial tone, as well as in modulating vascular reactivity to a variety of stimuli. The aim of this study was to determine whether endothelial NO may contribute to the vascular response to mental stress. To this purpose, we compared the effect of saline and L-NMMA (4 μmol/min for 15 min), a blocker of NO synthesis, on forearm vascular dynamics during mental arithmetic test (MAT) (repeated subtraction of 7 from a three-digit number for 3 min) in 15 normal subjects (9 males; age 44 ± 12 years) who underwent 2 tests 3 hours apart. The effect of L-NMMA on endothelium-independent vasodilation was studied during the infusion of sodium nitroprusside (SNP) (0.4, 0.8 and 1.6 μg/min) in 11 of the 15 subjects. Drugs were infused into the brachial artery and forearm vascular responses were measured by plethysmography. L-NMMA did not modify mean arterial pressure and heart rate during MAT (98.7 ± 11.3 vs. 98.1 ± 10.1 mmHg, and 75.9 ± 12.8 vs. 76.9 ± 15 bpm, respectively; both p = NS). Basal blood flow was significantly lower during L-NMMA than during saline (1.66 ± 0.62 vs. 2.14 ± 0.69 mL/min/100 mL; p < 0.01). L-NMMA significantly blunted the increase in blood flow induced by MAT (from 116 ± 70% to 36 ± 16%, p < 0.001), but did not modify the maximum flow increase induced by SNP (173 ± 71% during saline vs. 232 ± 89% during L-NMMA; p = NS). These findings indicate that endothelial release of NO plays a role in the vasodilator response to mental stress. This may help explain the abnormal vascular responsiveness to this stimulus in conditions associated with impaired endothelial vasodilator function.

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934-77 Acute Anti-Ischemic Effect of Estradiol 17β in Menopausal Women With Coronary Artery Disease

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Previous studies have suggested that estradiol 17β improves effort-induced myocardial ischemia in female pts with coronary artery disease (CAD). Recent studies, however, have questioned this effect. Aim of the present study was to evaluate the effect of acute administration of estradiol 17β upon pacing-induced myocardial ischemia by means of continuous monitoring of coronary sinus pH in 16 female menopausal pts with CAD. Pts underwent incremental atrial pacing starting at a rate of 100 bpm and increments of 20 bpm every 2 min up to 160 bpm before and 15 min after either estradiol 17β (1 mg sublingual, 9 pts) or placebo (sublingual, 7 pts). The time of onset of myocardial ischemia during pacing was significantly increased by estradiol 17β (254 ± 36 vs 298 ± 23 sec; p < 0.01) but not by placebo (262 ± 45 vs 256 ± 34 sec; p = NS) The pH shift was significantly reduced by estradiol 17β but not by placebo at every step of the pacing protocol. The maximum pH shift at peak pacing was significantly reduced by the administration of estradiol 17β by 0.022 pH Units (95% C.I. 0.001, 0.043; p < 0.04) but not by sublingual placebo (−0.002 pH Units, 95% C.I. −0.0073, 0.0021; p = NS). The maximum pH shift at maximum comparable pacing was also reduced by estradiol 17β by 0.015 (95% C.I. 0.012, 0.017; p < 0.001) but not by placebo −0.0022 (95% C.I. −0.006, 0.0015; p = NS). The reduction of pacing-induced coronary sinus pH shift are consistent with an anti-ischemic effect of the hormone and are not due to preconditioning as suggested by the absence of improvement after placebo. In conclusion estradiol 17β reduces the degree of pacing-induced myocardial ischemia in menopausal pts with CAD.

934-78 Efficacy and Safety of Once-Daily Monotherapy With Coat-Core Nisoldipine in Patients With Stable Angina Pectoris: Dose Response Studies

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Nisoldipine (NIS) is a potent dihydropyridine calcium channel blocker but the standard formulation requires multiple daily dosing for optimal efficacy and may occasionally produce proischemic effects. We therefore evaluated the safety and efficacy of an extended release formulation (Coat Core) of NIS, in 271 patients with reproducible exercise (EX) induced angina. After therapy with single-blind placebo for 2 weeks, patients were randomized in a double-blind manner to once daily therapy with either placebo (PLA), or NIS 10, NIS 20 or NIS 30 mg. Symptom limited EX tests were repeated after 2 weeks of therapy at 4–8 hours (peak) and 24 hours (trough) post dose. Changes in seconds from baseline (single-blind placebo) EX variables were:

	PLA	NIS QD		
		10 mg	20 mg	30 mg
Time to EX Termination	(n = 62)	(n = 64)	(n = 58)	(n = 61)
Peak	27	53*	75*	63*
Trough	34	34	53	65*†
Time to 1 mm ST↓	(n = 44)	(n = 43)	(n = 40)	(n = 42)
Peak	37	47	56	57
Trough	9	30	49	71*†

*P < 0.05 vs PLA; †p < 0.05 vs 10 mg NIS

Coat Core NIS was well tolerated without proischemic effects and the most frequently occurring adverse events were peripheral edema and headache. Results show that once daily therapy with NIS 10, 20 and 30 mg increased EX time at 4–8 hours post dose and the 30 mg dose increased EX time and time to ischemia 24 hours post dose. Thus in patients with exercise induced angina pectoris monotherapy with 30 mg NIS Coat Core once a day is safe and effective throughout the dosing interval.

MONDAY POSTER