1089 Nitric Oxide and Angiotensin Converting Enzyme Inhibitors

Tuesday, March 31, 1998, 9:00 a.m.–11:00 a.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: 9:00 a.m.–10:00 a.m.

1089-1 Altered Endothelial Reactivity in the Postischemic Heart Is Caused by Myocardial Nitric Oxide Tolerance

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While alterations in endothelial function with impaired endothelial dependent relaxation (EDR) occur in the postischemic heart, the mechanism of this process is unknown. It was proposed that this was due to decreased nitric oxide (NO) formation, however, direct measurements have recently demonstrated that NO levels in the postischemic heart are increased, not decreased. It is possible that EDR is impaired due to a desensitization with the induction of tolerance to a given amount of NO. To determine if the vasculature of the postischemic heart is desensitized to NO, studies were performed in which hearts were subjected to ischemia and reperfusion and the dose dependent reactivity to exogenous NO was determined. The dose dependent increase in coronary flow was measured in isolated rat hearts (N = 14) after infusion of 0.1 uM, 1 uM, 10 uM, 50 uM, and 100 uM concentrations of the NO donor S-nitroso-N-acetylpenicillamine, SNAP, in the presence or absence of the constrictor U46619. Studies were performed with 5 min of infusion of each SNAP concentration both before and after 20 min of global 37°C ischemia followed by 15 min of reflow. After ischemia a marked desensitization to NO was seen with 50% decrease in maximum reactivity and at least 10 fold higher concentrations required to achieve a given vasodilatory response. In the presence of U46619 more than a 50 fold desensitization was seen. Electron paramagnetic resonance studies were performed using the NO trap Fe-MGD (1 mM) to directly measure the release of NO from SNAP in the coronary circulation and demonstrated that NO release was linearly proportional to the concentration of SNAP. Thus, in the postischemic heart a marked desensitization with tolerance to a given amount of NO is seen which is an important cause of the impairment in endothelial reactivity which occurs.

1089-2 Paradoxical Increase in Myocardial Perfusion After Nitric Oxide Synthase Blockade

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Background: Nitric oxide (NO) release in response to shear stress modulates epicardial coronary artery diameter. Its impact on the myocardial microcirculation and coronary vasodilator reserve (CVR) remains unclear.

Methods: Using O15 labeled water and positron emission tomography, myocardial blood flow (MBF, ml/min/g) was measured in 34 healthy male volunteers (45 ± 8) at rest and during iv adenosine (Ado; 0.14 mg/kg/min) in control conditions. Fifteen minutes later, resting and Ado MBF measurements were repeated during a 30 min infusion of saline (n = 9, GR1) or L-NMMA, to block NO synthase, at a dose of 3 mg/kg (n = 9, GR2) and 10 mg/kg (n = 16, GR3) L-NMMA iv.

Results: Resting heart rate decreased by 4% ($p < 0.05$) and 15% ($p < 0.01$) in GR2 and GR3. Systolic blood pressure (SBP) increased by 7% (NS) and 10% ($p < 0.05$) after L-NMMA whereas HR and SBP during Ado were comparable before and after L-NMMA.

	MBF				CVR	
	baseline		LNMMA/sal		baseline	LNMMA/sal
	rest	Ado	rest	Ado		
GR1	0.9 ± 0.1	3.3 ± 0.8	1.0 ± 0.1	3.9 ± 1.2	3.8 ± 0.7	3.9 ± 0.7
GR2	0.8 ± 0.1	3.8 ± 1.0	0.9 ± 0.1	4.2 ± 0.7	4.9 ± 1.4	4.9 ± 1.4
GR3	0.9 ± 0.1	4.4 ± 1.1	0.9 ± 0.2	5.3 ± 1.9*	5.3 ± 1.5	6.3 ± 1.9*

*p < 0.05 after vs. before

Conclusions: NO synthase blockade does not affect resting MBF in healthy volunteers. High dose L-NMMA increases Ado-induced CVR, suggesting a sensitization of the microcirculation to Ado after NO blockade.

1089-3 Effects of Felodipine and Enalapril on Coronary Hemodynamics and Myocardial Collagen Content in Aged Spontaneously Hypertensive Rats

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Background: Evidence from clinical and animal studies clearly show that the coronary circulation is adversely affected in hypertension, and that aging exacerbates this process. This study was undertaken to determine whether: (1) antihypertensive treatment prevents progressive hypertension and age-related deterioration of coronary hemodynamics, and (2) there is a different response with various antihypertensive agents.

Methods: 65 week old spontaneously hypertensive rats were given vehicle (C), felodipine (F - 30 mg/kg/day), or enalapril (E - 30 mg/kg/day) for 12 weeks. Coronary blood flow (CBF), flow reserve (CFR), and minimal coronary vascular resistance (MCVR) were measured with radiomicrospheres. Mean arterial pressure (MAP), left ventricular mass index (LVI) and hydroxyproline concentration (HYDP) (to estimate collagen) were also determined.

Results: Both agents similarly reduced arterial pressure, but enalapril appeared to reduce left ventricular mass and improve coronary hemodynamics more effectively (Table).

Index	Control	Felodipine	Enalapril
MAP (mmHg)	152 ± 4	114 ± 4[a]	111 ± 5[a]
LVI (mg/g)	3.4 ± 0.1	3.1 ± 0.1[a]	2.8 ± 0.1[a,b]
HYDP (mg/g)	6.7 ± 0.2	6.6 ± 0.2	5.3 ± 0.3[a,b]
CBF (ml/min/g)	5.1 ± 0.3	5.0 ± 0.3	4.9 ± 0.2
CFR (ml/min/g)	1.1 ± 0.3	3.1 ± 0.3[a]	4.4 ± 0.3[a,b]
MCVR (U/g)	20.2 ± 1.4	13.9 ± 0.6[a]	10.7 ± 0.4[a,b]

* ± SEM; [a]P < 0.05 compared to C; [b]P < 0.05 compared to F.

Conclusion: Both agents improved coronary hemodynamics within 12 weeks, although the angiotensin converting enzyme (ACE) inhibitor seemed more effective. In addition, the ACE inhibition decreased myocardial collagen content, suggesting that the fibrosis associated with hypertension and aging may be reversible by ACE inhibition.

1089-4 Angiotensin Converting Enzyme Inhibition With Quinaprilate Stimulates Angiogenesis in a Rabbit Model of Hindlimb Ischemia

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Background: The demonstration that angiotensin converting enzyme inhibition (ACEI) may favorably affect endothelial function suggests that ACEI might have similarly favorable effects on angiogenesis. Accordingly, we investigated the effect of Quinaprilat (Q) and Captopril (C) in a rabbit model of chronic hindlimb ischemia.

Methods: Calf blood pressure index (BPI), vasoreactivity to agonists and angiographic score of collateral formation were recorded at day 10. Animals were then randomized to receive either intra-arterial injection of Vascular Endothelial Growth Factor (VEGF) as positive control (500 μg, n = 13), or nothing (n = 13), or daily injection of Q (n = 13) or C (n = 14). At day 40, measurements were repeated after 5 days of wash-out for Q and C, and muscle samples harvested.

Day 40 (* $p < 0.01$)	control	VEGF	C	Q
BPI (% of healthy limb)	0.64	0.88*	0.61	0.94*
Acetylcholine (% of base value)	1.66	2.35*	1.64	2.61*
Nitroprusside (% of base value)	1.83	2.43*	2.01	2.58*
Angiographic score	0.55	0.91*	0.55	0.91*
Capillary density	131	212*	137	203*

Results: Equivalent ACEI levels were achieved in serum with Q and C at day 14 (49% vs. 53%). VEGF and Q induced higher increases in 1) BPI, 2) flow reserve recovery, 3) angiographic score and 4) capillary density, compared to C and control groups.

Conclusion: ACEI using Q, but not C, stimulated angiogenesis in vivo.

1089-5 Functional Effects of ACE-Inhibitors on Angiotensin I Conversion in Human Vasculature

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Background: The relevance of tissue ACE-inhibition is largely based on experimental models. The QUO VADIS (effects of QUinapril On Vascular Ace and Determinants of Ischemia) study was designed to evaluate the