933 Coronary Vascular Physiology/Clinical Studies I

Monday, March 25, 1996, 3:00 p.m.–5:00 p.m.
Orange County Convention Center, Hall E
Presentation Hour: 3:00 p.m.–4:00 p.m.

933-86 Deficiency in Nitric Oxide Bioactivity at Spasm Sites of Epicardial Coronary Arteries in Patients With Coronary Spastic Angina

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The aim of this study was to determine nitric oxide bioactivity at baseline and at the stimulated condition with acetylcholine (ACH) at the spasm sites of epicardial coronary arteries. N^G-monomethyl-L-arginine (L-NMMA; 10, 25, and 50 μmol/min), an inhibitor of nitric oxide synthase, or L-arginine (125 mg/min) was infused into coronary arteries for 4 min in 21 patients with coronary spastic angina (CSA) and in 28 control patients. Coronary spasm was induced by intracoronary injection of ACH and was angiographically documented in all patients with CSA but not in any control patients. The luminal diameter of epicardial coronary arteries was determined by computer-assisted quantitative angiography. L-NMMA dose-dependently constricted all segments of coronary arteries in control patients (percent diameter changes from baseline at 25 μmol/min: proximal sites −5.6 ± 1.8*, distal sites −12.5 ± 2.9*, *p < 0.01 vs the baseline), while L-NMMA had no effect in the spasm arteries (−0.5 ± 1.2 at 50 μmol/min, p = NS vs the baseline, p < 0.01 vs control patients). L-NMMA abolished the dilator response to ACH in control arteries, while it had no effect on the constrictor response to ACH. L-arginine was inactive on the diameter in the spasm arteries as well as in the control arteries. The dilator response to the infusion of nitroglycerin was greater in the spasm arteries than that in the control coronary arteries (+43.7 ± 5.1 vs +17.8 ± 3.2, respectively, p < 0.01). The results indicate that nitric oxide bioactivity is deficient in the spasm arteries through the mechanism(s) independent of L-arginine availability, possibly leading to supersensitive response to the exogenous nitrovasodilator as well as to vasoconstrictor effect of ACH in patients with CSA. Deficient NO bioactivity in the spasm arteries may play an important role in the genesis of coronary artery spasm.

933-87 Hormone Replacement Therapy Does Not Protect Women Against the Age-Related Decline in Endothelial Function

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Estrogens seem to protect women against coronary artery disease possibly due to a beneficial effect on the age-related decline in endothelial function. Most postmenopausal women who are on hormone replacement therapy (HRT) receive a combination of estrogen and progesterone. The addition of a progestin may however negatively influence the endothelium and thus reduce the positive effect of unopposed estrogens.

We studied 100 healthy postmenopausal women aged 53 ± 3 years randomized to either combined HRT (n = 46) or no HRT (n = 54) 3 years earlier. 55 were life-long non-smokers and 45 current or ex-smokers. Using high-resolution ultrasound, flow-mediated dilation (FMD, endothelium-dependent dilation) and nitroglycerine (NTG) induced dilation (endothelium-independent dilation) were measured in the brachial artery.

Vessel size, degree of reactive hyperemia, total cholesterol, HDL-cholesterol and years post menopause were similar in all groups. In the non-smokers, FMD was 3.2 ± 3.2% in the HRT group and 2.8 ± 2.2% in the control group (p = 0.55). NTG induced similar vasodilation in both groups (18.4 ± 5.8% vs 16.1 ± 6.3%, p = 0.17). In the smokers, FMD was 2.1 ± 2.4% in the HRT group and 2.0 ± 2.2% in the control group (p = 0.9). NTG responses were not different (19.1 ± 6.3% vs 18.2 ± 6.0%, p = 0.66).

Combined long-term HRT does not protect healthy postmenopausal women against the age-related impairment of endothelial function. This lack of protection seems independent of smoking habits.

933-88 Antioxidants Are Vasodilators

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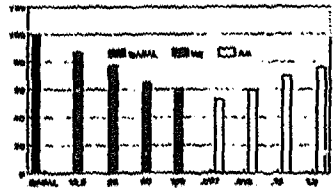
Superoxide radical (O_2^-) combines with nitric oxide (NO^*) to form the peroxynitrate ($ONOO^*$) radical and therefore provides a metabolic pathway for NO removal. Thus, the removal of O_2^- may increase the bioavailability of NO, thereby causing NO induced vasodilatation. We therefore tested the effect of ascorbic acid and N-acetylcystine (N-AC), two known antioxidants on the luminal diameter of the cephalic vein at wrist, using echovenography. Norepinephrine (NE) was infused into the right cephalic vein at wrist at four serial concentrations (12.5, 25, 50 and 100 ng/min). Cephalic vein diameter was measured by echovenography using a 7.5 MHz detector. NE induced dose dependent constriction. When ascorbic acid (doses: 0.007, 0.013, 0.13, 1.3 ng/min) was infused with the maximum dose of NE (100 ng/min), a dose dependent vasodilatory (anticonstrictive) effect was observed. A similar significant vasodilatory effect of N-AC was also observed (×: p < 0.05).



These data show for the first time that ascorbic acid and N-AC are vasodilators, that this effect of antioxidants is consistent with the hypothesis that antioxidants may increase the bioavailability of NO. The use of antioxidants may be important in restoring normal vascular responses in diseases like diabetes mellitus which are associated with increased O_2^- generation.

933-89 Is Coronary Microvascular Endothelial Dysfunction Reversible? Six Month Effects of Quinapril on Coronary Flow

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Acetylcholine (ach) causes vasodilation by release of nitric oxide (NO) from healthy endothelium to increase coronary blood flow (CBF) but induces paradoxical vasoconstriction in patients (pts) with no or minimal coronary artery disease (CAD) and risk factors. There are limited studies regarding the reversibility of macro- or microvascular ED. We postulated that treatment with the angiotensin converting enzyme inhibitor, quinapril (Q), would improve CBF in pts with impaired NO release. In pts with angiographic evidence of epicardial ED (vasoconstriction to ach) and minimal CAD (≤ 40% stenosis by quantitative coronary angiography [QCA]), functional coronary angiometry was performed at baseline study using intracoronary (IC) Doppler, measuring responses to IC infusions of ach (10^{-6}, 10^{-4} M) and adenosine(ado, 14 μg bolus). Volumetric CBF was determined using velocity and coronary diameters by QCA. Pts were randomized to placebo (P) or Q; 14 were evaluable at 6 months.

Results: At follow-up, CBF response to ach (10^{-4} M) improved in Q pts (73 ± 45.7% to 101.8 ± 56.8%), but deteriorated in P pts (39.0 ± 20.1% to 17 ± 18.1%). Likewise, the percentage of maximal CBF that was endothelial-dependent (ach/ado ratio) was highest in patients treated with Q compared to P (44 ± 0.15 vs 0.25 ± 0.16).

Conclusions: In this pilot study of pts with minimal CAD and ED, data suggest a potential role for quinapril in restoring microvascular endothelial function to improve blood flow.

933-90 Effect of Treadmill Exercise on Flow-Mediated Brachial Artery Vasoactivity

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Coronary and peripheral vasoactivity is improved by alterations in serum lipids and cessation of smoking. To determine the effect of acute exercise on vascular health, we assessed flow-mediated (endothelium-dependent) brachial artery vasoactivity at pre-exercise baseline and one hour following (post) treadmill exercise (3.4 mph at 6% elevation for 30 minutes) in 10 healthy males aged 41 ± 10 years. Brachial artery vasoactivity was measured using 7.5 MHZ ultrasound and expressed as percent diameter change from baseline to hyperemic conditions (1 minute post 5 minutes blood pressure cuff arterial occlusion). Although resting brachial artery diameter and flow did not vary from pre to post, post-exercise flow-mediated vasoactivity increased substantially over pre-exercise FMV in 9 of 10 subjects. Flow-mediated vasoactivity (FMV increased from 9.0 ± 4.2% to 17.8 ± 5.7 (p < 0.001) 1 hour post exercise.

These data suggest that 30 minutes of mild treadmill exercise markedly improves endothelium-dependent brachial artery vasoactivity at one hour of recovery. The duration of this improvement is under investigation. Thus, acute mild exercise appears to have a substantial beneficial effect on subsequent flow-mediated vasoactivity.

MONDAY POSTER