1219 Vascular Dysfunction: Mechanisms

Wednesday, April 1, 1998, 3:00 p.m.–5:00 p.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: 3:00 p.m.–4:00 p.m.

1219-1 Hypothermia Induces Nitric Oxide Release From the Arterial Endothelium: Mechanism of Early Hypotension Following Institution of Cardiopulmonary Bypass

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Background: The onset of hypothermic cardiopulmonary bypass is initially associated with a decrease in peripheral resistance resulting in hypotension. Nitric oxide is an endogenous vasodilator produced by the arterial endothelium. Experiments were undertaken to determine if hypothermia induces the release of endothelium-derived nitric oxide (EDNO) from arterial conduits.

Methods and Results: Segments of contracted (prostaglandin $F_{2\alpha}$, 2 × 10^{-6}M) canine coronary, femoral and renal artery, with and without endothelium, were exposed to progressive hypothermia (from 37 to 20°C). Hypothermia induced vasodilation of arterial segments with endothelium (to 93 ± 4% of the initial contraction for femoral artery segments, means ± SEM, n = 5, each group, $P < 0.05$). In all groups, endothelium-dependent vasodilation to hypothermia was blocked by L-NMMA or NO-ARG (10^{-5}M), two competitive inhibitors of nitric oxide synthesis from L-arginine (n = 5, each group, $P < 0.05$). Vasodilation was also inhibited by hemoglobin (2×10^{-6}M) (n = 6, $P < 0.05$). Vasodilation to hypothermia was completely inhibited by the addition of atropine or pirenzepine (10^{-6}M) (n = 5, each group, $P < 0.05$).

Conclusions: Endothelium-dependent vasodilation to hypothermia in systemic and coronary arteries, presumably mediated by the M_1 muscarinic receptor, could be the mechanism for the decrease in peripheral vascular resistance and hypotension associated with the onset of hypothermic cardiopulmonary bypass.

1219-2 Adrenomedullin Induces Vasodilation in Porcine Coronary Conductance and Resistance Arteries In Vivo

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Background: Adrenomedullin (ADM) is a newly discovered vasodilator peptide found in the heart, lung, adrenals and vascular endothelium. Its physiological role is unknown. Although vasoactive effects have been described, its role in the coronary circulation is unclear.

Objectives: We examined the acute vasodilator effect of intracoronary (IC) ADM on epicardial and resistance coronary arteries in 15 pigs.

Methods: Epicardial coronary cross-sectional area (CSA) and average peak flow velocity (APV) were assessed using simultaneous intracoronary two-dimensional and Doppler ultrasound. Coronary blood flow (CBF) was calculated. Amplification by RT-PCR was performed to demonstrate the expression of the ADM receptor gene.

Results: ADM (0.01nM to 0.1 μM/L IC) induced a significant increase in coronary CSA (8.93 ± 1.23%), APV (16.63 ± 4.67%) and CBF (26.65 ± 4.62%). Following preconstriction with endothelin-1 (10 nM/L IC), there was no increase in ADM-induced vasodilation. Pretreatment with "nitro-L-arginine methylester (100 μ/L IC) significantly attenuated ADM-induced increase in CSA ($P < 0.0001$), APV ($P = 0.0046$) and in CBF ($P = 0.0001$). By RT-PCR, the intensity of the ADM receptor gene signal was greater in epicardial coronary arteries than in lung tissue (used as control).

Conclusions: ADM induces vasodilation in coronary conductance and resistance arteries in pigs, in part mediated via nitric oxide. ADM receptor gene is expressed in coronary conductance arteries.

1219-3 Short-term Exposure to Second Hand Smoke Induces Vascular Dysfunction in Normocholesterolemic Rabbits

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Background: Second hand smoke (SHS) contributes to about 37,000 out of a total 53,000 heart disease deaths in the US. We have previously shown that chronic (10 weeks) SHS exposure causes endothelial dysfunction in normocholesterolemic rabbits. We hypothesized that short-term exposure to SHS would also cause endothelial dysfunction.

Methods: Ninety six normocholesterolemic rabbits (16/group) were exposed to SHS in smoking chambers (4 cigarettes/15 minutes) for 0 (control), 1/2, 1, 2, 4 and 6 hours. Vascular reactivity was examined in vitro in aortic rings. Vasoconstriction was assessed in response to the alpha$_1$-adrenoceptor agonist phenylephrine (Phe). Following preconstriction with the EC50 dose of Phe, vasorelaxation responses were assessed using the endothelium-dependent vasodilator acetylcholine (Ach) and the endothelium-independent vasodilator nitroglycerin (Ntg).

Results: Short-term SHS exposure caused a decrease in maximal response and sensitivity to Phe, but an increase in the rate of vasoconstriction (slope $p = 0.001$). Following 1/2 and 1 hours of SHS exposure there was a trend towards depressed maximal endothelium-dependent relaxation with Ach, that was significant at 2 hours (66% ± 4 Vs 71% ± 4 at 0 hrs, $p < 0.05$). However, at 4 and 6 hours Ach-induced vasorelaxation appeared to be restored. Short-term SHS exposure caused no change to Ntg-induced vasodilation.

Conclusions: Short-term exposure to SHS influences adrenoceptor-mediated vasoconstriction and causes transient endothelial dysfunction in normocholesterolemic rabbits.

1219-4 Effect of Passive Smoking on Arterial Wave Reflection: An Additional Detrimental Effect

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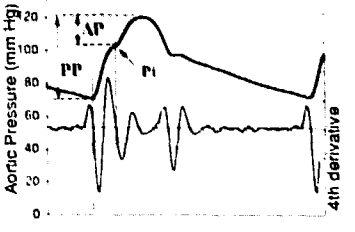
Background: We have previously shown that active smoking deteriorates function the human aorta (Circulation 1997;95:31-38). However, wave reflection along the arterial bed, an important index of arterial stiffening and cardiac afterload, has not been studied during passive smoking.

Methods: High-fidelity pressure waveforms of the thoracic aorta were obtained before and for 20 min. after the initiation of passive smoking (exposure for 5 min, CO: 30 p.p.m. 10 pts), or sham smoking in 10 pts with an intravascular catheter-tip micromanometer (Millar Instr.) during diagnostic catheterization. In all pts, an inflection point (Pi) defined by computer algorithm (4th derivative) divided aortic pressure waveform into early and late systolic phase (fig). Augmentation index was defined as: AP/PP (fig).



Results: Both systolic and diastolic pressures increased with passive smoking (peak at min. 4, from 126 ± 14 to 137 ± 12 and from 74 ± 8 to 80 ± 7 mmHg, respectively, $P < 0.001$). Augmentation index increased with passive smoking (from 0.29 ± 0.12 to 0.33 ± 0.14, $P < 0.05$, peak: min. 4) indicating increased wave reflection in the periphery.

In contrast, no changes were observed with sham smoking.

Conclusions: Wave reflection is increased with passive smoking. This effect may contribute in the multiple adverse consequences of passive exposure to tobacco smoke in the cardiovascular system.

1219-5 Raman Spectroscopy Provides Chemical Mappings of Atherosclerotic Plaques in APOE*3 Leiden Transgenic Mice

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Background: The chemical composition of the arterial wall may change during plaque development and determines whether a plaque will progress, regress or rupture. APOE*3 Leiden transgenic mice, which overexpress a dysfunctional human apolipoprotein E variant, develop hyperlipidemia and diet-induced atherosclerotic plaques, similar to those in humans. To map the chemical composition of atherosclerotic plaques we used near-infrared Raman spectroscopy.

Methods: APOE*3 Leiden transgenic mice (n = 14) were fed either a high saturated-fat/high-cholesterol/0.5%-cholate (HFC/0.5%-cholate) diet or normal chow for 5 or 6 months. The mice were sacrificed, and their aortas (~3.5 mm in circumference) were flushed and cut open for spectroscopic examination. Raman spectra were obtained from locations across the luminal surface