917-118 ET_A Antagonist BQ123 Inhibits Endothelin-1-Induced Vasoconstriction in Flow-Loaded Rabbit Carotid, Diabetic Rat, and Atherosclerotic Human Coronary Arteries

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The roles of endothelin-1 (ET-1) and its receptors (ET_A, ET_B) in mediating altered arterial reactivity in arteries undergoing atherosclerotic changes and/or collateral hyperperfusion, processes of occlusive arterial disease, were evaluated in isolated arteries. Use of normo- (C–) and hypercholesterolemic rabbits (C+) with normal (F–) or high carotid artery flows (F+) induced by contralateral carotid transection yielded 4 groups (C–F–, C–F+, C+ F–, C+ F+; 30 arteries from 6 rabbits per group). Contractions induced by ET-1 (10 pM–50 nm) were 100% inhibited by ET_A-selective antagonist BQ123 at 10 μM (IC_{50} = 200 nm). No inter-group differences were demonstrated. Non-selective antagonist bosentan induced similar but less potent inhibitions (IC_{50} = 500 nM). ET_B-selective antagonist BQ788 (10 μM) was inhibitory at low ET-1 (< 3 nM), but paradoxically potentiated contractions at higher ET-1 concentrations. Paradoxical responses were uninfluenced by blockade of nitric oxide synthesis with nitroarginine (1 mM). In aortas from streptozotocin-diabetic rats (n = 4) and atherosclerotic human coronary arteries (n = 4), BQ123, bosentan, and BQ788 exerted similar effects as in rabbits. Thus, constrictor responses to ET-1 were mediated predominantly by ET_A in all arteries tested. Efficacy of BQ123 was not modified by high flow, hypercholesterolemia, atherosclerosis, or diabetes. Paradoxical potentiations of ET-1-induced contractions by BQ788 suggest direct smooth muscle relaxing effects of ET-1 acting on ET_B receptors.

917-119 Nitroglycerin (NTG), but Not Sodium Nitroprusside (SNP), Increases Vascular cGMP Levels via an L-Arginine Dependent and L-NAME Sensitive Pathway

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The purpose of our study was to determine mechanistic differences between NTG and SNP. NTG and SNP have different vasodilator profiles and clinically relevant tolerance develops only to NTG. We have investigated the involvement of nitric oxide synthase (NOS) in the vascular actions of NTG and SNP. Intact rat aortic rings pretreated with supplemental L-arginine (10^{-5} M) for 30 min were incubated with NTG (10^{-7} M) or SNP (10^{-5} M). Accumulation of cGMP was measured in the presence of the phosphodiesterase inhibitor, IBMX. Similar experiments were performed in the presence of the NOS inhibitor, nitro-L-arginine methylester (L-NAME, 5×10^{-4} M). With no added L-arginine, NTG increased cGMP levels from 2.6 ± 0.2 to 3.5 ± 0.6 pmol/mg wet wt/15 min. With added L-arginine, NTG increased cGMP production from 2.6 ± 0.7 to 5.3 ± 0.4. SNP, in the absence and presence of additional L-arginine, raised cGMP production from 2.3 ± 0.7 to 7.8 ± 1.1 and 4.0 ± 0.1 to 8.2 ± 0.9, respectively. L-NAME inhibited the cGMP elevation to NTG by 85%, but SNP-induced cGMP accumulation was not affected by L-NAME.

In other aortic strips preconstricted with phenylephrine, NTG relaxed tone with an EC_{50} of 1.2×10^{-8} M; following 2 hr exposure of these same vessels to NTG (5.5×10^{-5} M), the EC_{50} for relaxation was 1.8×10^{-6} M (141 × more). Addition of L-arginine (1 or 2×10^{-5} M) to the bath 0.5 hr prior to the second NTG dose-response curve resulted in $EC_{50's}$ of 6.3×10^{-8} M and 7.1×10^{-8} M, respectively (only 5.6 or 5 × more). Similar experiments with SNP revealed little or no tolerance with 2 hr exposure.

In conclusion, unlike SNP, the mechanism of action of NTG is L-arginine dependent and is L-NAME sensitive. Development of tolerance to nitroglycerin can be partially reversed by L-arginine.

918 Hypertension

Monday, March 25, 1996, Noon–2:00 p.m.
Orange County Convention Center, Hall E
Presentation Hour: 1:00 p.m.–2:00 p.m.

918-65 LV Remodelling and LVH Regression Are Related to Ambulatory (Not Casual) BP Control in Hypertension

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Studies of LVH regression have generally emphasized the class of antihypertensive agent used, rather than level of blood pressure reduction achieved. To clarify how BP control *per se* affects LVH regression or LV remodelling in hypertension (HTN), 51 patients (pts) with mild-moderate HTN and elevated LV mass (LVM) by screening echo were treated for 16 months. Pts received lisinopril and/or hydrochlorothiazide with addition of calcium channel or beta blocker as needed to normalize 95% of ambulatory (ABP) readings for 12 months. Sector-guided M-mode echos were read in scrambled coded sets by two MDs with adjudication by 2 others. 35/51 pts completed the protocol and had technically acceptable baseline and 1-yr Rx echos for comparison. The mean LVM of 3 baseline vs 2 final echos for the entire group was 262 ± 69 vs 244 ± 65 gm p = 0.025. *Office* BP control was similar among pts whose LV mass did or did not change. However, *ABP* reduction was greatest in those pts with LVM decrease vs no change (BP difference = 18 ± 16 vs 9 ± 11 mm Hg, p = 0.04). Both LVM and relative wall thickness (RWT) decrease were significantly related to the extent of 24 hr ABP decrease (R = 0.59 p = 0.0002 and R = 0.40 p = 0.017), but the office BPs *failed* to predict either LVM or RWT decrease (both p = NS for SBP and DBP). The data confirm for the first time the importance of continuous blood pressure control for LV remodelling and LV mass reduction to occur in hypertensive individuals.

918-66 Left Ventricular Longitudinal Shortening in Hypertension

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Purpose: To evaluate the interaction between left ventricular (LV) longitudinal (l) and circumferential (midwall, m) fiber shortening (FS) in normal loading conditions and in arterial hypertension.

Methods: Echocardiograms (2D and M-mode) were obtained in 50 normotensive (nmls, 49 + 12 years, 14 women) and 50 untreated hypertensive subjects (hpts, 49 + 11 years, 5 women). Ejection fraction (EF) was calculated by 2D-echo as a measure of LV chamber performance.

Results: Hpts exhibited higher LV mass (p < 0.001) and relative wall thickness (p < 0.0001). Seven of 50 hpts (14%) had LV hypertrophy. mFS was reduced in hpts (16.8 ± 2..3% vs 18.3 ± 2.1%, p < 0.001), but lFS was normal (15.9 ± 3.4 vs 16.1 ± 2.7%). EF was also normal in hpts (68.2 ± 6.3% vs 68.6 ± 5.6). lFS was related to meridional wall stress (ESS) in hypertensive patients (r = – 0.49), but not in normal controls, whereas mFS was related to circumferential ESS in both groups (r = –0.28 in hpts and –0.46 in nmls). EF was more closely related to mFS in nmls (r = 0.78) than in hpts (r = 0.63, p < 0.05), whereas it was more related to lFS in hpts (r = 0.77) than in nmls (r = 0.66, p < 0.05). In nmls, variance of EF was mainly influenced by mFS (β = 0.60, p < 0.0001), with minor, additional contribution for lFS (β = 0.26, p < 0.03, R-multiple = 0.80, SEE = 3.4%). In contrast, in hpts, the whole variance of EF was explained by lFS (β = 0.77, p < 0.0001, SEE = 4).

Conclusions: Thus, 1) LV EF is normal in arterial hypertension with mild abnormalities in LV geometry, although mFS is depressed; 2) Longitudinal contraction helps to keep EF normal in the presence of reduced circumferential function; 3) In normal subjects, lFS is only weakly related to myocardial afterload.

918-67 Early Involvement of Left Ventricle in Adolescents With Upper Percentile of Blood Pressure (BP) — The Rio de Janeiro Study

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We analyzed the relationship of Left Ventricular Mass (LVM), accessed by echocardiography, and Maximal Systolic BP (MSBP), obtained in the Bruce treadmill stress test, in adolescents (13 to 19 yrs.) with different percentiles of blood pressure. We evaluated 3906 children and adolescents (10 to 15