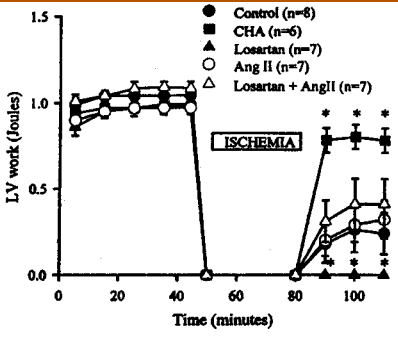

958-41 Prolonged Exposure of Canine Coronary Arteries to a Nitric Oxide Donor Desensitizes Soluble Guanylate Cyclase

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Tolerance to nitric oxide donors is postulated to result from either substrate limits on biodegradation or desensitization of soluble guanylate cyclase. The former is well characterized while the latter is controversial. Paired canine coronaries were exposed to either sodium nitroprusside (SNP) or papaverine in varying doses (10^{-9}, 10^{-7}, 10^{-5} M) for 3 hr with continuous recording of isometric tension. Solutions were exchanged every 30 min. The optimal length-tension curve was not significantly different between groups and colorimetric cyanide was undetectable (< 0.2 μg/ml). Receptor-independent contraction to KCl (5–50 mM) and receptor-dependent contraction to $PGF_{2\alpha}$ (10^{-9}–10^{-5} M) were similar between groups. Relaxations to calcium ionophore A23187 (10^{-9}–10^{-6} M) was attenuated in the 10^{-7} M and 10^{-5} M SNP groups but not with 10^{-9} M SNP (n = 7 each, $P < 0.05$, ANOVA). Relaxation to nitric oxide (3×10^{-9}–10^{-5} M) was markedly attenuated in the 10^{-7} M and 10^{-5} M SNP groups but not with 10^{-9} M SNP (n = 7 each, $P < 0.05$). Relaxation to nitric oxide was abolished with methylene blue pretreatment (10^{-5} M, n = 4). Pretreatment with SNP did not alter vascular smooth muscle contractions but markedly attenuated relaxation to both calcium ionophore and authentic nitric oxide. These studies demonstrate desensitization of soluble guanylate cyclase in the intact coronary artery upon 3 hr exposure to SNP in concentrations greater than 10^{-7} M.

958-42 Treatment of Ischemia-Reperfusion Damage to the Latissimus Dorsi Muscle After Cardiomyoplasty Mobilization

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Very often there are serious morphological changes in the latissimus dorsi muscle (LDM) used for cardiomyoplasty (CMP) that compromise CMP results. These changes are due to ischemia-reperfusion damage after subtotal LDM mobilization. We hypothesized that application of an autologous biological glue (ABG) with pharmacological agents (aprotinin, pyrrolostatin) to the LDM would prevent ischemia-reperfusion damage, as well as increase capillary ingrowth which would accelerate future angiogenesis.

Pockets were created of ischemic and nonischemic LDM to test for muscle damage and angiogenesis. One pocket was left free of ABG (control); one received ABG only; one ABG with aprotinin; and one ABG with pyrrolostatin. ABG was prepared from each animal's citrated blood. Biopsies were taken on days 0, 14, 28 and 56.

Fibrosis, calcified necrosis, fiber degeneration, and leukocyte margination were less in pockets with ABG than in the control pocket. The peak of these changes was noted on day 28 in the control pocket. No strong adhesions between the ischemic LDM and adipose tissue were noted in control pockets, but were seen in pockets with ABG.

In nonischemic LDM, capillaries occupied 4.0 ± 0.24% of the area. The results of the percent capillary area from the pockets are below:

	Control	ABG	ABG + Aprotinin	ABG + Pyrrolostatin
Day 14	3.0 ± 0.9	4.1 ± 0.4	5.2 ± 2.1	7.9 ± 1.9
Day 56	3.6 ± 0.7	5.5 ± 0.2	8.5 ± 1.1	9.4 ± 1.9

Conclusion: ABG with pharmacological agents can accelerate the healing process and angiogenesis, and provide an organic bridge between the LDM and the myocardium after cardiomyoplasty.

958-43 Suppression of Atherosclerotic Development in Watanabe Heritable Hyperlipidemic (WHHL) Rabbits Treated with an Oral Anti-allergic Drug, Tranilast

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The atherosclerotic plaque bears many similarities to chronic inflammatory conditions, and interactions between cellular components within the arterial wall are considered to be essential in the progression of atherosclerotic lesions. Tranilast, which is clinically used as an anti-allergic drug in Japan, has been reported to be effective against the thickening of the intima after endothelial injury by suppression of cell-mediated inflammatory response. We thus investigated the effects of tranilast on the development of atherosclerotic changes in WHHL rabbits. WHHL rabbits (2 month old) were orally given either 300 mg/kg/day of the tranilast (Tranilast, n = 10) or vehicle (Vehicle, n = 12) for 6 months. Tranilast-treatment suppressed percent aortic area covered with plaque (Tranilast 39 ± 5% vs Vehicle 76 ± 8%, $p < 0.01$) and decreased contents of cholesterol and cholesterol esters in the aortas. Little difference was found in serum cholesterol levels between the 2 groups. The cellular composition and phenotype of atherosclerotic plaques were analyzed in immunohistochemical study. There was no difference in the percentage of the RAM11-positive macrophage area in intimal plaques between Tranilast and Vehicle. Most of the MHC class II antigen (recognized as foreign by T cells) -positive cells were macrophages, and the ratio of MHC class II antigen-positive area to RAM11-positive macrophage area was markedly lower in Tranilast as compared with that in Vehicle (Tranilast 18 ± 7% vs Vehicle 58 ± 12%, $p < 0.01$). Furthermore, there was no difference in the number of T cells between the two groups, but the percentages of Interleukin-2 (IL-2) receptor (CD25) positive cells (activated T cells) to pan T cells was lower in Tranilast as compared with that in Vehicle. In an in vitro study, the incubation of human peripheral blood mononuclear cells with tranilast inhibited the expression of MHC Class II antigen on monocytes and IL-2 receptors on T cells activated with IFN-γ and IL-2, respectively. The results indicated that tranilast suppressed the atherosclerotic development by downregulating the immune activation in atheromatous plaque.

958-44 Long-term Cilazapril Therapy Limits Left Ventricular Diastolic Dysfunction with Depressed Systolic Function in Myocardial Infarcted Rats

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The purposes of this study were to assess the effect of angiotensin converting enzyme inhibitor (ACEI), cilazapril (1 mg/kg/day) on left ventricular diastolic dysfunction with systolic dysfunction in myocardial infarcted (MI) rats by using echocardiography and to analyze cardiac gene expression by northern blot analysis. ACEI was administered after MI. On 1 and 3 months (M) after MI, left ventricular function were measured and mRNAs in cardiac tissue were analyzed. LV end-diastolic dimension (LVDd) and ejection fraction (EF) on 1 M were 9.7 ± 0.5 mm and 34 ± 4%, respectively, and LVDd on 3 M increased to 10.4 ± 0.3 and EF decreased to 30 ± 6%. ACEI prevented an increase of LVEDV (8.2 ± 0.3 mm; $p < 0.01$) and improved FS (45 ± 8%; $p < 0.05$) on 1 M and also on 3 M. E/A velocity ratio (E/A) and E wave deceleration (E dece.) increased to 9.5 ± 2.2 and 26.3 ± 2.6 m/s^2 on 1 M after MI. ACEI prevented the increase of E/A (4.2 ± 0.5; $P < 0/05$) and E dece. (26.3 ± 2.6 m/s^2; $P < 0.05$) on 1 M after MI, and those on 3 M after MI. The left and right ventricular weight significantly increased after MI, which were prevented by ACEI. The gene expressions of β-myosin heavy chain (MHC), α-skeletal actin, atrial natriuretic peptide (ANP), collagen I, III, in the nonischemic left ventricular myocardium increased by 1.8-, 2.9-, 4.2-, 3.0-, 2.6-fold on 1 M, respectively ($p < 0.01$) and RV also increased. ACEI significantly suppressed these increased gene expressions of nonischemic LV and RV. On contrary, SR Ca-ATPase in nonischemic and RV decreased to 0.7- and 0.5- fold, respectively, on 3 M after MI and ACEI prevented them. In conclusion, ACEI prevented the change of the properties of the myocardium and progressive diastolic and systolic dysfunction by left ventricular remodeling after MI.