Method: BIO was treated with amlodipine (10 mg/kg/day) or nifedipine (30 mg/kg/day) from 5 to 20 week of age, and the aortic smooth muscle contractile responses to phenylephrine (Phe), angiotensin II (A II) and high K^+ were examined.

Results: The aortic contractions induced by Phe, AII and high K^+ in BIO were significantly enhanced compared with F1b ($p < 0.001$). Treatment with amlodipine significantly suppressed the contractile responses to Phe, AII and high K^+ in BIO ($p < 0.05$). In contrast, treatment with nifedipine was without effect.

Conclusion: These results indicate that chronic treatment with amlodipine but not nifedipine improves the hypercontractility of aortic smooth muscle in BIO. Amlodipine may improve the prognosis of nonischemic cardiomyopathy by its properties to be able to modify the vascular contractility in heart failure.

1121-31 Adenosine Inhibits Immediate Cardiodepressive Effects of Tumor Necrosis Factor-alpha in Adult Cardiomyocytes

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Background: Various studies suggest that tumor necrosis factor-alpha (TNF) contributes to cardiac dysfunction. It has recently been recognized that TNF has a biphasic effect. Delayed negative inotropy occurs after hrs. to days and is nitric oxide dependent. Immediate negative inotropy occurs after 30 min. and may be sphingosine dependent. We have previously shown that adenosine inhibits lipopolysaccharide (LPS)-mediated delayed cardiac depression in neonatal myocytes. The aim of this study was to determine whether adenosine suppresses immediate TNF effects.

Methods: We studied the effect of adenosine (1–10 μM) on contracting adult rat ventricular myocytes stimulated for 30 min. with TNF (200 u/ml), sphingosine (10 μM) or LPS (10 μg/ml). Myocyte contraction was measured with video edge detection.

Results: In controls, fractional shortening (FS) was 14.3 ± 0.4%. After exposure to TNF, sphingosine and LPS, FS decreased by 36%, 31% and 33%, respectively ($n = 28$, $p < 0.05$). Co-treatment with adenosine (10 μM) significantly ($n = 28$, $p < 0.05$) improved FS which returned to adenosine baseline in the TNF, sphingosine and LPS group. Baseline adenosine (10 μM) FS was 12.9 ± 0.5, 13% below controls, probably through activation of the A_1 receptor. Adenosine (1 μM) completely normalized TNF induced effects, presumably because of loss activation of the A_1 receptor.

Conclusion: Adenosine inhibits the immediate negative inotropic effect of TNF in adult cardiomyocytes.

1121-32 Energetic Effects of Protein Kinase C Inhibition During Calcium Induced Inotropy in the Isolated Perfused Mouse Heart

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Background: Protein kinase C, a Ca^{2+} dependent intracellular messenger, effects the Ca^{2+} sensitivity of the contractile apparatus. By modulating the amount of Ca^{2+} handling required for a given developed pressure, this may in turn effect O_2 consumption (MVO_2) (energetic efficiency).

Methods: In the isolated, Langendorff perfused mouse heart, we determined the effects of protein kinase C inhibition (PKCi) by the specific inhibitor, chelerythrine, on developed pressure (DP, mmHg) and MVO_2 (μmoles/min/g.dry weight) during increases in inotropy produced by increasing the concentration of perfusate Ca^{2+}. At a paced rate of 8 Hz, and with a balloon situated in the left ventricle, hearts were perfused for a 30 minute control period (Ca^{2+} 2.5 mM), and then received either Ca^{2+} 3.5 mM (N = 6), or PKCi (chelerythrine 10.0 μM) + Ca^{2+} 3.5 mM (N = 7) for a further 30 minutes. All values mean ± SD.

Results: Increasing [Ca^{2+}] from 2.5 to 3.5 mM increased DP from 54 ± 9 to 66 ± 9, though this was significantly attenuated by the addition of PKCi to Ca^{2+} 3.5 mM (50 ± 5 to 56 ± 5, $p < 0.05$ vs Ca^{2+} 3.5 mM). However, MVO_2 was not effected by PKCi (Ca^{2+} 3.5 mM: 49 ± 4 to 58 ± 3 vs Ca^{2+} 3.5 mM + PKCi: 51 ± 3 to 58 ± 3, p = NS). Thus, the energetic efficiency associated with Ca^{2+} induced inotropy ($\Delta DP/\Delta MVO_2$) was decreased by PKCi (0.9 ± 0.4 vs 1.5 ± 0.6, $p < 0.05$). In separate experiments, no effects of PKCi were seen when increasing [Ca^{2+}] from 1.5 to 2.5 mM.

Conclusions: PKC mediates Ca^{2+} induced inotropy and plays an important role in determining energetic efficiency at higher levels of perfusate [Ca^{2+}] in the isolated perfused mouse heart.

1121-33 Progressive Molecular and Physiologic Remodeling in Murine Hearts After Myocardial Infarction

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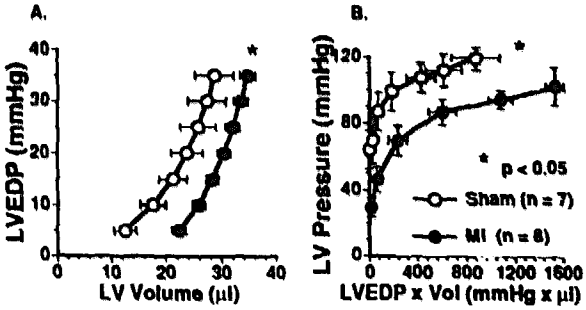
The molecular mechanisms that mediate myocardial remodeling and failure are not known. Our goal was to characterize a chronic heart failure model in CD-1 mice subjected to myocardial infarction (MI) by coronary ligation. Myocardial function was assessed by pressure-volume analysis in isolated hearts and ANF and SERCA-2 mRNAs were measured by northern blot 2 and 4 weeks after MI ($n = 12$) or sham operation ($n = 9$). MI size was 40 ± 3%. Post-MI hearts were hypertrophied vs. Shams (HW/BW = 5.5 ± 0.2 vs. 4.9 ± 0.2 mg/g; $p < 0.05$). Post-MI hearts were dilated at 2 weeks (figure A) and progressed at 4 weeks. Post-MI hearts showed decreased contractile function as assessed by LV developed pressure at any given preload (figure B). At 2 weeks ANF mRNA was increased 5-fold in the non-infarcted remote myocardium and 13-fold in the borderzone. SERCA-2 was unchanged in the non-infarcted myocardium.



Thus, in the mouse a MI of moderate size results in progressive LV remodeling at 2 and 4 weeks with chamber dilation, compensatory hypertrophy, reexpression of a fetal gene (ANF), and both systolic and diastolic myocardial dysfunction. This model will allow the use of genetically-engineered mice to study the mechanism of myocardial remodeling.

1121-34 Beneficial Effect of Phosphodiesterase Inhibitor, Milrinone on Left Ventricular Relaxation in Heart Failure

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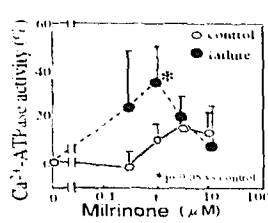
Background: Milrinone (Mil) has been shown to improve LV systolic function by its positive inotropic action in heart failure (HF). However, it is unclear whether Mil also exerts positive lusitropy in HF. Here, we assessed the effect of Mil on LV contractility and relaxation in comparison with that of dobutamine (Dob).

Methods: HF was produced by rapid RV pacing (250 bpm) over 4 weeks in 5 dogs. Mil (2–20 μg/kg) or Dob (2–10 μg/kg/min) was stepwisely administered and LV pressure was measured by 8F Millar's catheter.

Results: As compared with normal group (N, 5 dogs), LV end-diastolic pressure was elevated in HF (6 vs 22 mmHg, $p < 0.01$). The LV peak + dP/dt was decreased by 18% ($P < 0.01$), while time constant (τ) of LV pressure decay during isovolumic relaxation period was increased by 36% ($p < 0.01$). Either by Dob or Mil, the LV peak + dP/dt was less increased in HF than in N, while τ decreased to a similar extent as N by Dob and even more than N by Mil. In HF, the τ decreased to a greater extent ($p < 0.05$) by Mil (8%) than by Dob (1%) when compared at a dose by which similar increase of +dP/dt (5% vs 6%, respectively, ns) was obtained. Thapsigargin-sensitive Ca^{2+}-ATPase activity was measured in crude homogenate prepared from LV. The Ca^{2+}-ATPase activity decreased in HF compared with N (0.14 vs 0.07 μmol/min/mg, respectively, $p < 0.01$). Mil increased the Ca^{2+}-ATPase activity in a dose-dependent manner and % increase in Ca^{2+}-ATPase activity by Mil was larger in HF than in N (Fig).



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