mRNA levels of both genes were 0.97 in controls, 0.96 in FH. Although the genes were coordinately regulated in FH fibroblasts, there was a marked up-regulation of the HMG CoA red. gene compared with the LDL-R gene in FH subjects. Peak mRNA levels of the LDL-R gene was approximately 5.31 fold over LPDS in controls, 1.73 fold in FH. $^{125}$I-LDL binding studies confirm that FH subjects increase the amount of LDL receptors in response to Lova, 5 $\mu$M. We conclude that the LDL-R and HMG CoA reductase genes are expressed in coordinate regulation in fibroblasts from subjects with FH due to the > 10 Kb deletion, but with a proportionately greater up-regulation of the HMG CoA reductase gene. Some subjects with FH due to the > 10 Kb deletion of the LDL-R gene who fail to respond to HMG CoA red. inhibitors have abnormal LDL-R gene up-regulation in response to Lova *in-vitro*.

## 1028-76 Linkage of the Apo CIII Microsatellite With Isolated Low High Density Lipoprotein Cholesterol

Cecilia M. Devlin, Karen I. Zeller, Valerie L. Prenger, Michael Miller. *Baltimore Veterans Affairs Medical Center; University of Maryland Medical Center, Baltimore, MD*

Low levels of high density lipoprotein cholesterol (HDL-C) ( < 35 mg/dL) and its primary apolipoprotein, apo AI, are associated with premature coronary artery disease (CAD) even with desirable total cholesterol levels ( < 200 mg/dL). To evaluate the familial basis of isolated low HDL-C, a nationwide search of normocholesterolemic subjects with HDL-C < 20 mg/dL was conducted. Seven unrelated probands (mean HDL-C = 9 ± 5 mg/dL) and 96 biological family members were identified. Five probands developed premature CAD (mean age = 45 ± 4). Extracted genomic DNA from each subject was used to determine whether a highly polymorphic region within the apolipoprotein AI-CIII-AIV gene complex segregated with isolated low HDL-C. The size of the alleles of the $(C_aT_b)_c$ microsatellite within intron 3 of the apo CIII gene was assessed following PCR amplification and denaturing polyacrylamide gel electrophoresis. Using quantitative sib-pair analysis there was strong evidence for linkage of this microsatellite with the reduced HDL-C phenotype ($P < 0.005$). These results suggest a potentially important role for the apo CIII microsatellite region in the genetic screening of families with isolated low HDL-C associated with premature CAD.

# 1029 Myocardial Infarction: Basic II

Wednesday, March 27, 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.

## 1029-37 Can Lactate, Per Se, Induce Cardiac Preconditioning?

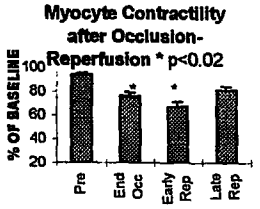
Francesca Aresta, Gary Gerstenblith, Konrad Vandegaer, Robert G. Weiss. *The Johns Hopkins Hospital, Baltimore, MD*

The contractile benefits associated with cardiac "preconditioning" (IPC) induced by exposure to brief periods of ischemia, hypoxia, and to adenosine may be related to activation of $K_{ATP}$ channels. Lactate also activates $K_{ATP}$ channels. To test whether repeated transient lactate exposures, resulting in tissue lactate levels similar to IPC, but in the absence of ischemia, can provide similar "preconditioning" benefits, isolated, retrogradely perfused rat hearts were subjected to either a "lactate-preconditioning" protocol (LP) consisting of two 5-minute exposures to 15 mM lactate and two 5-minute periods of reflow with normal buffer ($n = 6$), to a previously reported IPC protocol composed of two 5-minute ischemia reperfusion cycles (IP, $n = 5$), or control perfusion (C, $n = 5$). Subsequently all hearts underwent 30 minutes of normothermic, total ischemia (I) followed by 30 minutes of reflow. Tissue levels of lactate (10.5 ± 0.3 versus 10.5 ± 0.5 mmol/gWW) and contractile dysfunction (developed pressure (DP) 89.2 ± 4.4% and 89.8 ± 3.9% of initial) were similar in LP and IPC hearts, respectively, before the prolonged ischemia period. The recovery of DP after 30 min of I, however, was higher in IPC hearts than in C and LP reaching, respectively, 56.8 ± 3.4%, 14.2 ± 6.8%, and 9.5 ± 3.6% of the baseline values. EDP was lower during reperfusion in IPC hearts than in LP and C hearts, and there were no significant differences between the latter two groups (36.2 ± 3.5, 82.0 ± 2.9, and 81.2 ± 0.5 mmHg, respectively). Thus, transient lactate exposure resulting in tissue lactate levels similar to IPC does not improve contractile recovery after prolonged ischemia and therefore cannot be a mechanism which explains the protective effects observed in preconditioned myocardium.

## 1029-38 Release of Soluble Myocardial Depressant Activity by Reperfused Myocardium

Rupinder Brar, Anand Kumar, Gary Schaer, Steven Hollenberg, Tony Hursey, Yifan Sun, Joseph Parrillo. *Section of Cardiology, Rush Medical College, Chicago, IL*

Myocardial ischemia followed by reperfusion is associated with injury and myocardial stunning. Circulating cytokines may play a role in reperfusion injury. *Methods:* We examined effect of serum from dogs undergoing LAD occlusion and reperfusion on contractility of beating myocytes. Anaesthetized dogs ($n = 3$) were subjected to 3 hours of LAD occlusion and 3 hours of reperfusion. Control dogs ($n = 3$) underwent sham occlusion. Coronary sinus serum from each dog was collected preocclusion (PRE), end occlusion (END OCC 170 min), early reperfusion (EARLY REP, 5 min) and late reperfusion (LATE REP, 170 min). Myocardial depressant activity in eac.: sample ($n = 6$) was evaluated using a previously described assay employing incubation of serum with isolated contracting cultured rat cardiac myocytes. Myocyte contractility was assayed by measuring the amplitude of displacement of a latex bead embedded in the cell membrane at baseline and at 30 minutes following incubation with serum. Results are mean ± SEM of the baseline displacement. *Results:* Significant myocardial depressant activity was seen at END OCC ($p = 0.02$), and EARLY REP ($p = 0.001$). The effect was largely reversed at LATE REP (see figure). Control dogs showed no significant depression.




*Conclusions:* These findings demonstrate circulating myocardial depressant activity in efferent blood after coronary occlusion, with the greatest depression occurring during early reperfusion. Soluble circulating mediators may be important in the pathogenetic mechanisms causing reperfusion associated myocardial depression (stunning).

## 1029-39 High Extracellular K$^+$ During Hypoxic Preconditioning Episodes Attenuates the Post-Ischemic Contractile and Ionic Benefits of Preconditioning

Keith M. Baumgarten, Gary Gerstenblith, Robert G. Weiss. *The Johns Hopkins Hospital, Baltimore, MD*

Hypoxic preconditioning (PC) improves contractile recovery and decreases calcium loading following ischemia (I) and reperfusion (R). This may be mediated via activation of $K_{ATP}$ channels and a resulting decrease in the trans-sarcolemma K gradient. To test whether changing the trans-sarcolemma K gradient during the PC period changes its benefits, isolated isovolumic rat hearts were subjected to two, 5 min intervals of hypoxia, separated by 5 min of normoxic reflow, in the presence of normal K (5 mM, NmlK-PC) and of high K (10.3 mM, HlK-PC). Developed pressure (DP) and cellular Ca and K, by atomic spectroscopy using KCoEDTA as an extracellular marker, at 45 min of R after 30 min of total I were compared to those of control hearts (C), which did not undergo any PC. (Results at 45 min of R: mean ± SD; $Ca_i^{++}$ before I = 4.1 ± 2.0)

| | DP as % of initial | $K_i^+$ ($\mu$mol/g dry) | $Ca_i^{++}$ ($\mu$mol/g dry) |
|---|---|---|---|
| C | 14.1 ± 8.0 (n = 14) | 166 ± 46.5 (n = 9) | 19.4 ± 6.8 |
| NmlK-PC | 72.2 ± 20.7 (n = 12) | 231 ± 17.7 (n = 5) | 12.9 ± 3.3 |
| HlK-PC | 31.7 ± 19.6 (n = 12) | 186 ± 54.6 (n = 4) | 22.9 ± 1.6 |

Thus, the trans-sarcolemmal K gradient during the PC period influences PC effects; decreasing the gradient decreases preconditioning's favorable influences on contractile recovery and calcium loading during reperfusion.