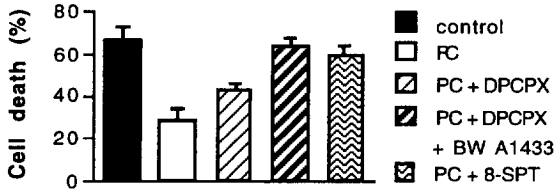
containing (mM) 2'-deoxyglucose (20), NaCN (1), Na-lactate (20), $K^+$ (10) at $pH_o$ 6.6 (37°C). Changes of myocyte length were monitored with an optical-video edge recording system, and hypercontracture was used as the index of irreversible cell injury (cell death). *Results:* PC (2 min ischemia followed by 15 min reperfusion) significantly reduced cell injury resulting from the subsequent extended ischemia (10 min) and reperfusion (15 min), as indicated by a reduction in cell death from 67 ± 6% (cells = 110, control) to 29 ± 5% (cells = 101, with PC, $p < 0.001$). PC-induced cardioprotection was only partially blocked by the maximally effective dose of the adenosine $A_1$-receptor antagonist DPCPX (100 nM) (cell death = 43 ± 3%, cells = 88, $p < 0.05$ vs control) but completely blocked by either the combination of DPCPX (100 nM) with the adenosine $A_3$-receptor antagonist BW A1433 (1 μM) (cell death = 64 ± 4%; cells = 82; p = NS vs control), or the non-selective adenosine receptor antagonist, 8-SPT (100 μM) (cell death = 59 ± 5%; cells = 86; p = NS vs control), as shown in the Figure. *Conclusion:* PC-induced cardioprotection is mediated in part through the activation of adenosine $A_3$-receptors.




## 1005-81 Myocardial Protection by $Na^+/H^+$ Exchange Inhibition in Ischemic, Reperfused Porcine Hearts

Hermann H. Klein, Sibylle Pich, Rainer M. Bohle, Jutta Wollenweber, Klaus Nebendahl. *Universities of Marburg and Göttingen, Fed. Rep. of Germany*

The protective effect of the $Na^+/H^+$ exchange inhibitor HOE 694 was tested in porcine hearts subjected to 45 min of regional ischemia and 24 h of reperfusion. The compound (3 mg/kg) was intravenously injected in 6 pigs each either 10 min before ischemia (group A) or 10 min before reperfusion (group B). Six animals served as controls. Apart from the main end-points, infarct size and regional systolic shortening, the effect of HOE 694 on global hemodynamic parameters which included coronary blood flow and coronary venous oxygen saturation was evaluated. Although the $Na^+/H^+$ exchange inhibitor did not affect global hemodynamics, preischemic treatment with HOE 694 decreased infarct size from 65 ± 18% (control group) to 12 ± 9% ($p < 0.01$) and improved systolic shortening from 8 ± 6% (control group) to 28 ± 9% $p < 0.02$). In addition, increase in heart rate and myocardial contracture during early reperfusion were significantly attenuated in group A. Treatment of group B did not exhibit protective effects.

*Conclusion:* $Na^+/H^+$ exchange inhibition is a very protective means in myocardial ischemia and reperfusion when administered before ischemia. In this model, it was ineffective when given before reperfusion.

## 1005-82 Myocardial and Coronary Vascular Protection After Coronary Occlusion and Reperfusion by Selective Sinoatrial Node Inhibition

Roger Williams, Wilmer W. Nichols, Liying Chen, Michael S. Stalvey, Linda V. Thompson, Tiffany D. Boyd, Jawahar L. Mehta, Carl J. Pepine. *University of Florida and VA Medical Center, Gainesville, FL*

Improved regional myocardial function and abnormal flow reserve resulting from myocardial ischemic injury has been observed with β-blockade. To determine if heart rate reduction alone would offer similar protection, anesthetized dogs were subjected to left anterior descending (LAD) occlusion and given a selective SA node inhibitor (ZD7288 0.5 mg/kg, n = 5 or buffer, n = 7). After 1 hour of occlusion they were reperfused. ZD7288 decreased heart rate by 28 ± 2% (153 ± 14 to 120 ± 11 bpm, $p < 0.05$) at 1 hr after reperfusion. In buffer-treated dogs, peak reactive hyperemic (RH) response after 20 sec LAD occlusion, (index of coronary flow reserve), fell from 276 ± 22% to 135 ± 18% and LAD regional shortening fraction (SF, by ultrasonic crystals) decreased from 9.7 ± 1.5% to 0.6 ± 0.1% after reperfusion (both, $p < 0.001$). In ZD7288-treated dogs, peak RH and SF after reperfusion (227 ± 19% and 4.2 ± 0.8%, respectively) were preserved ($p < 0.05$) vs buffer-treated dogs. Despite similar area of left ventricular (LV) at risk, infarct area (as % of LV), was also smaller in ZD7288-treated vs. buffer-treated dogs (14.0 ± 0.5 vs 23.0 ± 1.10%, $p < 0.05$). Heart rate was maintained constant with atrial pacing in five other ZD7288-treated dogs and neither peak RH or SF were preserved compared with buffer-treated dogs.

Thus, selective SA node inhibition alone, induced after coronary occlusion, results in myocardial and coronary vascular protection after reperfusion. Selective SA node inhibition may have clinical utility in acute myocardial patients who are not candidates for beta blockers.

# 1006 Counteracting Thrombin and Lipids in Acute Coronary Syndromes

Wednesday, March 22, 1995, Noon–2:00 p.m.
Ernest N. Morial Convention Center, Hall E
Presentation Hour: Noon–1:00 p.m.

## 1006-41 Effect of Previous Treatment with Aspirin or Nitrates on the Clinical Manifestation of Acute Coronary Syndrome

David Garcia-Dorado, Juan Oliveras, Pilar Tornos, Gaietà Permanyer, Antonia Sambola, Maite Santos, Pierre Théroux, J. Soler-Soler. *Hospital Vall d'Hebron, Barcelona, Spain; Montreal Heart Institute, Canada*

Aspirin (ASA) and nitrates inhibit platelet aggregation by different mechanisms, and it has been suggested that their antiaggregating effects could be additive. To analyze the influence of previous treatment with aspirin (ASA) or nitrates on the clinical manifestations of acute coronary syndrome, a series of 323 pts consecutively admitted to the cardiology emergency room with unstable angina (UA) or acute myocardial infarction (MI), and with a previous history of coronary heart disease, was prospectively characterized.

A standardized questionnaire was used to determine risk factors, previous cardiac history, and use of drugs preceding the index event. Previous use was defined as any dose of ASA during the week before, or of oral or transdermal nitrates during the 24 h before the onset of the event.

The final diagnosis by serial ECGs and enzyme determinations, was UA in 226 pts, and MI in 95. Fifty-one pts had received previous treatment with ASA but not with nitrates, 51 had received nitrates but not ASA, 105 had received both drugs and 94 had received neither ASA nor nitrates. The final diagnosis was MI in 12 (24%) pts who had received ASA, 12 (24%) in pts who had received nitrates, 21 (20%) in pts on both ASA and nitrates, and 43 (46%) in those receiving neither ASA nor nitrates ($p = 0.0003$). Multiple logistic regression analysis identified prior ASA and prior nitrates, but not age, sex, risk factors, previous myocardial infarction, or prior treatment with betablockers or $Ca^{++}$ entry blockers, as independent predictors of UA vs MI. The regression model did not detect any interaction between ASA and nitrates.

These results suggest that both prior treatment with ASA and with nitrates modify the clinical manifestations of acute ischemic syndrome reducing its severity, and that these effects are compatible with their effects being additive.

## 1006-42 What Beyond Aspirin and Anticoagulation Improves Outcome in Unstable Angina? Effect of Medical Therapy

Steven Borzak, Phillip L. Kraft, Lori Douthat, Christopher P. Cannon, Elliott Antman, Joe Massaro, Sebastian T. Palmeri, Judith S. Hochman, Carolyn T. McCabe, Joanna Fuchs, Burt Adelman, TIMI-7 Investigators. *Henry Ford Hospital, Detroit, MI; Brigham and Women's Hospital, Boston, MA*

Medical treatment consisting of beta-blockers (BB), calcium blockers (CB) and nitrates (N) is recommended and frequently employed in patients (pts) before and during hospitalization with unstable coronary syndromes (UA), but the benefit is unclear in the setting of combined aspirin and anticoagulation. To study the effect of each of these drugs on in-hospital events, we examined 410 pts with UA entered in the TIMI-7 trial in which all pts received aspirin and one of 4 doses of the direct thrombin inhibitor, hirulog.

Prior to hospitalization, 44% of pts received BB, 50% CB, and 51% N. Compared to pts not on these drugs, pts on each medication were older (average 62 vs 59 yrs), had a higher incidence of prior MI (BB, CB, N), revascularization (CB, N), hypertension (BB, CB, N), and diabetes (CB, N), and were more likely to be receiving aspirin (BB, CB, N). Stepwise regression showed that prior treatment with any of the 3 drugs was not predictive of in-hospital death, MI or documented recurrent ischemia.

After enrollment and during hospitalization, 71% of pts received BB, 66% CB, and 95% N at the discretion of their physicians. The in-hospital occurrence of death (4%), MI (6%), recurrent ischemia (8%) or their combined incidence (14%), the number or severity of in-hospital anginal episodes, or the incidence of catheterization (64%) or revascularization (38%) were not significantly related to treatment with any of the 3 drugs. The combined incidence of in-hospital death, MI or recurrent ischemia was best predicted by the presence of ECG changes on admission (multivariate adjusted odds ratio [OR] 2.83, $p < 0.01$) and advanced age (OR 2.38, $p < 0.01$) but not by other factors.

Prior or newly instituted anti-ischemic medical therapy, administered in a nonrandomized fashion in this trial, may have contributed to clinical stability. During hospitalization for UA, aspirin and anticoagulation play a primary role in determining clinical outcome.