interquartile range 0.09–0.21 mU/mg; p = 0.0019). Thus, in plaques of patients with unstable coronary syndromes, the higher content of tissue factor may be related to the thrombotic response to rupture.

11:30

839-5 ATP-sensitive Potassium (K_{ATP}) Channel Blockers Suppress Monophasic Action Potential Shortening and Abolish the 'Second Window of Protection' Induced by Ischemic Preconditioning in Rabbit Hearts

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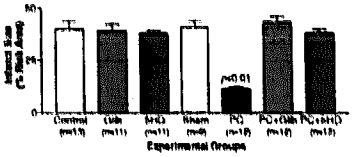
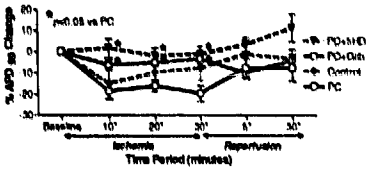
Background: Ischemic preconditioning (PC) brings about a delayed phase of myocardial protection 24 hours later. We hypothesized that this 'second window of protection' (SWOP) involves the opening of K_{ATP} channels.

Methods: Seven groups of rabbits were studied using the *in vivo* model of myocardial infarction. *1.* Control. *2.* Glibenclamide (G) 0.3 mg/kg IP 30 min before ischemia/reperfusion (I/R). *3.* 5-hydroxydecanoate (5HD) 5 mg/kg IV 15 min before I/R. *4.* Sham operated 24 hrs prior to I/R. *5.* PC - preconditioned with four 5-min coronary occlusions, each separated by 10 min of reperfusion, 24 hrs before I/R. *6.* PC + G. *7.* PC + 5HD. All rabbits underwent 30 min of coronary occlusion followed by 3 hrs of reperfusion. Risk area was delineated by Evan's blue dye and infarct size was determined by tetrazolium staining. Monophasic action potential duration (APD) was measured by an epicardial electrode.





Results: A significant reduction in infarct size was observed in PC which was blocked by G and 5HD. These specific K_{ATP} channel blockers significantly suppressed APD shortening in PC hearts.

Conclusion: The 'SWOP' afforded by PC is mediated via the opening of K_{ATP} channels.

840 Optimizing Heart Failure Therapy: Latest Strategies

Tuesday, March 31, 1998, 10:30 a.m.–Noon
Georgia World Congress Center, Lecture Hall 1

10:30

840-1 Irbesartan Combined With Conventional Therapy, Including Angiotensin Converting Enzyme Inhibitors, in Heart Failure

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Irbesartan (IRBE; BMS/Sanofi) efficacy and tolerability, combined with conventional therapy including angiotensin converting enzyme inhibitors (ACE-Is), was evaluated in a double-blind, placebo-controlled (PBO), pilot study of patients (pts) with mild-to-moderate heart failure (HF; NYHA Class II or III) and left ventricular ejection fraction (LVEF) ≤40%, on diuretic (≥2 wks) and ACE-I (≥6 wks) therapy. Pts with 2 consistent Modified Naughton exercise tolerance tests (ETTs) were randomized to IRBE (n = 57) [starting doses: 12.5 mg, 37.5 mg, or 75 mg; titrated to 150 mg as tolerated] or PBO (n = 52) QD. ACE-I therapy continued. Angiotensin II (AII) and plasma renin activity (PRA) were studied in 20 pts. Pts were mainly NYHA Class II (79%), male (76%), white (82%), with ages equally ≥ and <65.

PRA and AII increases were consistent with AII receptor blockade. IRBE was well tolerated; serious adverse events were rare in both groups; no deaths occurred. More PBO pts required supplemental diuretics than did IRBE pts (21% vs 12%).

	ETT (sec) median change	LVEF (units) mean change	AII (pg/mL)	PRA (ng/ml-hr)
IRBE	63.5, 21–109*	5.2 (3.2–7.3)	pre: 3.5, post: 6.9	pre: 9.4, post: 21.3
PBO	47.0, −6–131*	2.4 (−0.4–5.1)	pre: 0.8, post: 2.0	pre: 7.0, post: 14.1

*25th–75th quantiles; values in () represent 95% confidence limits.

Conclusion: IRBE, combined with conventional therapy including ACE-I, produced favorable trends in ETT and LVEF and was well tolerated in pts with mild-to-moderate HF.

10:45

840-2 Angiotensin II Receptor Blockade Combined to ACE-Inhibition Improves Left Ventricular Dilation and Exercise Ejection Fraction in Congestive Heart Failure

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Angiotensin II type 1 receptor antagonist losartan (LOS) has recently emerged as a valuable alternative to ACE-inhibitors (ACEI) in the management of congestive heart failure (CHF). Aim of this study was to determine if the association of LOS and ACEI in pts with CHF may enhance the well-recognized beneficial effects of ACEI alone on left ventricular (LV) dimensions and function as assessed by 2D echocardiography at rest and during submaximal supine bicycle exercise (SBE). Seventy-three pts (74% male, age 64 ± 6 yrs) with impaired systolic LV function (EF 28 ± 9%) and stable mild to moderate CHF (NYHA class 2.1 ± 0.4) were randomized in a double blind fashion to receive LOS 50 mg/d (n = 42) or placebo (P, n = 31) in addition to ACEI (enalapril, mean dose 29 mg/d or captopril, mean dose 86 mg/d) for 3 months. All pts were on digoxin and diuretics. The two groups were comparable in age, gender, EF, LV end-diastolic (EDVI) and end-systolic (ESVI) volume index at rest and during SBE. After three months, both groups showed improved EF and LV volumes with respect to values at randomization ($p < 0.01$). However, treatment with LOS resulted in significantly greater improvement of LV dimensions and function with respect to P, as shown in the Table.

	ACEI + LOS		ACEI + P	
At 3 months	Rest	SBE	Rest	SBE
EF (%)	31 ± 10*	36 ± 12†	28 ± 12	32 ± 9
EDVI (ml/m²)	79 ± 13*	71 ± 10†	87 ± 14	76 ± 11
ESVI (ml/m²)	69 ± 10*	58 ± 8†	72 ± 10	66 ± 9

Mean ± SD. *p < 0.05 vs ACEI + P Rest; †p < 0.05 vs ACE + P SBE

In conclusion, these results indicate that LOS combined to ACEI may confer incremental functional benefit as compared to ACEI alone in pts with CHF.

11:00

840-3 Clinical Benefits of Long-term Angiotensin II Receptor Blockade in Patients With Severe Symptoms of Congestive Heart Failure Despite Full Angiotensin Converting Enzyme Inhibition

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After initial improvement, symptoms tend to recur in patients with congestive heart failure (CHF) despite angiotensin converting enzyme (ACE) inhibition at maximally recommended or tolerated dose, digoxin and loop diuretics. The present study was undertaken to determine if the addition of AII type 1 (AT1) receptor blockade to full ACE inhibition would improve functional class (FC, NYHA) and maximal exercise capacity (peak VO2, ml/kg/min) in patients with severe CHF, i.e. peak VO2 <16 and FC III–IV at baseline (BL). Thirty-two patients (mean age 61 yrs, ejection fraction 26%) were randomized to placebo (P) or losartan (L) 50 mg daily. They were evaluated at 3 and 6 mos. Results were as follows:

	BL		3 mos		6 mos	
	L	P	L	P	L	P
FC	3.2	3.0	2.9	3.0	2.5*	3.0
Peak VO2	13.1	14.5	14.7	14.7	15.1*	14.2

* = p < 0.05 L vs P; L (n = 15); P (n = 14)

L at a daily dose of 50 mg was well tolerated by all patients. Three patients were lost to follow up. In conclusion, long-term AT1 receptor blockade improves symptoms and exercise capacity in patients with CHF who are severely symptomatic despite full ACE inhibition, digitalis and diuretics.