A. CONTROL   B. LIDOCAINE

Conclusion: Short cycles of ischemic preconditioning resulted in less $[Ca^{2+}]_i$ accumulation and improved hemodynamic recovery. Lidocaine pretreatment induced also calcium influx, mimicking the first episode of ischemic preconditioning.

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771   Antiarrhythmic Drugs

Tuesday, March 21, 1995, 4:00 p.m.–5:30 p.m.
Ernest N. Morial Convention Center, Room 26

4:00

771-1   Role of Intracellular Calcium in the Antiarrhythmic Effect of Procainamide During Ventricular Fibrillation in Rat Hearts

Christian E. Zaugg, Shao T. Wu, Shoji Kojima, Joan Wikman-Coffelt, William W. Parmley *University of California San Francisco, San Francisco, CA*

Intracellular calcium ($[Ca^{2+}]_i$) overload is considered one of the factors that cause ventricular fibrillation (VF). In addition, VF itself causes and maintains $[Ca^{2+}]_i$ overload. We tested whether the class IA antiarrhythmic agent procainamide can reduce $[Ca^{2+}]_i$ overload during VF and if so, whether such reduction is responsible for the recovery of left ventricular function. For this purpose, we measured the effects of 0.1 mM (0.03 mg/ml) procainamide perfusion on left ventricular developed pressure (LVP), heart rate, and $[Ca^{2+}]_i$ during pacing-induced VF in isolated rat hearts. $[Ca^{2+}]_i$ was assessed by surface fluorometry after Indo-1/AM-loading. The concentration of procainamide was selected in a way that about half of the hearts would recover from VF (criteria: recovery of LVP > 67%). During perfusion with 0.1 mM procainamide, 6 hearts recovered from VF (●), whereas 8 hearts did not recover (■, recovery of LVP < 33%). In the untreated control group (O, n = 5), no heart recovered from VF. Procainamide effects on heart rate (left panel) and $[Ca^{2+}]_i$ (right panel) are shown (mean $\pm$ SEM; †p < 0.05 vs. control; *p < 0.05 vs. no recovery):
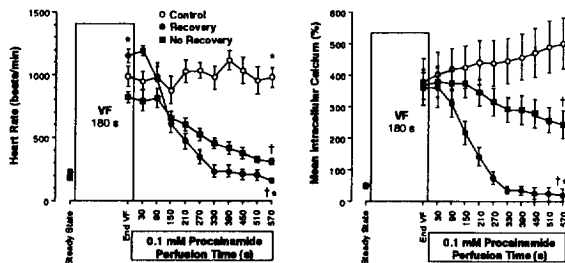
We conclude that procainamide can reduce $[Ca^{2+}]_i$ overload during VF. In addition, the reduction of the $[Ca^{2+}+]_i$ overload might be responsible for the recovery of the left ventricular function. This reduction appeared to be dependent on the fibrillation rate (use-dependent) rather than on the decrease of heart rate.

4:15

771-2   Isoproterenol Amplification of Flecainide-induced Conduction Slowing in Depolarized Canine Purkinje Fibers: Elucidation of Flecainide Proarrhythmia in CAST

Kevin T. Cragun, Susan B. Johnson, Douglas L. Packer. *Mayo Foundation, Rochester, MN*

To elucidate the potential mechanism for the flecainide (FLEC) proarrhythmia observed in CAST, the voltage-dependence of β-adrenergic modulation of impulse propagation in 10 FLEC-superfused canine Purkinje fibers was examined using a dual microelectrode technique. At physiologic membrane potentials (V_m) ($[K+]_o$ = 5.4 mM), 1 μM FLEC decreased $\dot{V}_{max}$ from 677 $\pm$

72 to 576 $\pm$ 97 V/sec (p = 0.04) and squared conduction velocity (θ^2) from 1.28 $\pm$ 0.5 to 1.04 $\pm$ 0.4 (M/s)^2. With K+ depolarization to V_m = -70 mV, FLEC further reduced $\dot{V}_{max}$ from 324 $\pm$ 100 to 241 $\pm$ 64 V/s and θ^2 from 0.90 $\pm$ 0.3 to 0.83 $\pm$ 0.5 (M/s)^2 and produced a 1.9 mV hyperpolarizing shift of apparent Na+ channel availability curves derived from θ^2. The addition of 1 μM isoproterenol (ISO) to FLEC-superfused fibers at physiologic V_m increased θ^2 by 10% to 1.14 $\pm$ 0.5 (M/s)^2 (p = 0.009) without altering $\dot{V}_{max}$. At -70 mV, the addition of ISO magnified the FLEC-induced reduction of $\dot{V}_{max}$ an additional 26% to 177 $\pm$ 49 V/s (p = 0.001) and θ^2 by 20% to 0.67 $\pm$ 0.4 (M/s)^2 (p = 0.008), producing an additional 1.8 mV (p = 0.001) and 1.9 mV (p = 0.001) hyperpolarizing shift in the apparent Na+ channel inactivation curves generated from $\dot{V}_{max}$ and θ^2, respectively. At physiologic V_m, the action potential duration (APD_{95}) was reduced from 308 $\pm$ 32 to 266 $\pm$ 25 (p < 0.001) by FLEC and subsequently to 217 $\pm$ 4 (p < 0.001) with ISO addition. With 12 mM K+, APD_{95} decreased from 193 $\pm$ 24 to 179 $\pm$ 20 ms (p = 0.001) with FLEC and to 162 $\pm$ 14 ms (p = 0.001) with ISO. Thus, at depolarized V_m, ISO amplified the FLEC-induced reduction of $\dot{V}_{max}$ and θ^2, suggesting a further adrenergic-mediated reduction of Na+ current. Consequently, the synergy between catecholamines and FLEC at depolarized V_m and the shortened APD_{95} could facilitate double-wave reentrant arrhythmias in the presence of FLEC and superimposed ischemia.

4:30

771-3   Direct Characterization of Flecainide Binding Rates from Use-Dependent Conduction Delay in Canine Purkinje Fibers

Kevin T. Cragun, Susan B. Johnson, Douglas L. Packer. *Mayo Foundation, Rochester, MN*

To quantitatively characterize flecainide-induced channel blockade from use-dependent conduction delay (CD), 12 canine Purkinje fibers were studied using a dual microelectrode technique. During 60 sec of pacing at interstimulus intervals (ISI) of 1.25–0.4 sec with 2 μM flecainide (FLEC), incremental CD followed a monoexponential time course, the rates of which were linearly related to the interpulse recovery interval (t_r = ISI — action potential duration). Steady state block was an exponential function of the recovery rates. Use-dependent block derived from incremental CD and decremental squared conduction velocity (θ^2) was characterized by the forward (k) and reverse (l) rate constants for the activated (a) and resting (r) states:

	k_a (× 10^6) (mol^{-1} s^{-1})	l_a (s^{-1})	k_r (× 10^2) (mol^{-1} s^{-1})	l_r (s^{-1})
CD	7.0 $\pm$ 2.6	12.0 $\pm$ 4.4	0.6 $\pm$ 1.7	4.01 $\pm$ 1.63
θ^2	10.0 $\pm$ 3.4	14.7 $\pm$ 2.5	2.8 $\pm$ 5.7	3.66 $\pm$ 1.40
$\dot{V}_{max}$(prox)	6.8 $\pm$ 2.3	15.9 $\pm$ 5.0	5.1 $\pm$ 10.3	4.22 $\pm$ 1.11

These rates reflect marked open state Na+ channel block and closed channel trapping at resting membrane potentials with FLEC. The addition of 1 μM isoproterenol (ISO) to FLEC-superfused fibers reversed the FLEC-induced reduction of θ^2 from 1.79 $\pm$ 0.7 to 1.89 $\pm$ 0.89 (m/s)^2 (p = 0.017) without changing $\dot{V}^{max}$. The rate constants for FLEC binding and unbinding were not altered by ISO. Thus FLEC's apparent binding rates can be quantified from its use-dependent effects on conduction. Both ISO's selective reversal of FLEC effect on θ^2 but not $\dot{V}_{max}$ and the absence of changes in the rate constants suggest that the modulation of FLEC effect is due to an alteration in passive membrane properties. These characterizations will facilitate subsequent comparisons of FLEC interactions in pathologic and hyperadrenergic states *in vivo*.

4:45

771-4   Enhancement of Delayed Afterdepolarizations (DADs) and Triggered Activity by E-4031 and Dofetilide in a Cardiac Glycoside Model of Cell Ca^{2+} Overload

Jing T. Xie, Peter M. Cunningham, Craig T. January *University of Chicago, Chicago, IL*

Hypothesis: Several new class III antiarrhythmic drugs, including E-4031 and Dofetilide, are reported to selectively block the rapidly activating delayed rectifier current (i_{KR}). These drugs increase action potential duration (APD) which should load cells with Ca^{2+} via the Na-Ca exchange mechanism and Ca^{2+} channels. Thus DADs, which occur in Ca^{2+} loaded cells, should be enhanced by these drugs. *Methods:* Action potentials were recorded from sheep Purkinje fibers at pacing cycle lengths (CL) of 990 and 690 ms. Ca^{2+} overload with DADs were induced by exposing fibers to acetylstrophanthidin (AS, 0.15 μM) for 30 min. Fibers were then exposed to AS-free Tyrode's containing E-4031 (E, 5.0 μM; Group 1, n = 5), or Dofetilide (D, 0.5 μM; Group 2, n = 5), or no drug (Group 3, n = 5) for 30 min. *Results:* 1) Both E and D enhanced DAD amplitude. With AS exposure for 30 min, mean DAD amplitude