Results: Typical changes in the antegrade recovery curve produced by R are shown in the figure. There was a concentration dependent decrease in ΔAH from the pre-drug value of 56 ± 15 ms to 29.2 ± 16.9 ms and 13.7 ± 5.9 ms by 3 and 6 × 10^{-6} M respectively (n = 6). A reciprocal increase in the AV node effective refractory period was observed from 91 ± 15 ms (pre-drug) to 139 ± 16 ms (3 × 10^{-6} M) and 170 ± 16 ms (6 × 10^{-6} M). AH_{∞} was unchanged at any concentration of R.

Conclusions: These results suggest that class III antiarrhythmic agents may increase action potential duration and the refractory period of the structure(s) limiting AV conduction and thereby eliminate a majority of the "slow" AV node conduction. These findings may have important implications for a pharmacologic approach to the treatment of AV node reentry tachycardias.

947-112 Has the Inotropic Effect of the Class-III Antiarrhythmic Drug Amiodarone a Frequence-dependency In Vivo?

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The prolongation of the action potential duration (APD) by class-III antiarrhythmic drugs causes in vitro a positive inotropic effect. On the other side a frequence-dependency of the APD-prolongation ("reverse use-dependence") was described. This would mean, that a heart rate reduction should have a positive effect on myocardial contractility after administration of class-III drugs.

We examined the hemodynamic effects of amiodarone (10 mg/kg, 20 mg/kg i.v.) in thoracotomized rats vs. saline controls (NaCl) without and with bradycardia. Heart rate reduction was produced by vagal stimulation (reduction about 50%). Besides measurements in the intact circulation isovolumic maximum registrations (isovol. LVSP, isovol. dp/dt_{max}) were performed to determine myocardial contractility.

	spontaneous heart rate			vagal stimulation	
	10 mg/kg	20 mg/kg	NaCl	20 mg/kg	NaCl
isovol. LVSP	93 ± 2	88 ± 1*	98 ± 1	80 ± 5*	100 ± 2
isovol. dp/dt_{max}	81 ± 3*	73 ± 3*	94 ± 3	54 ± 5*	82 ± 4
cardiac output	90 ± 7	75 ± 7	93 ± 8	57 ± 6	68 ± 4

Means ± SEM in % of preinfusion values, *p < 0.01

Conclusion: The prolongation of the action potential duration by the class-III antiarrhythmic drug amiodarone does not cause in vivo a positive inotropic effect since the cardiodepressive effects of the drug (e.g. sodium- and calcium-channel blockade) are stronger. A reverse use-dependence of the inotropism of this drug is not detectable in vivo.

947-113 Aprotinin Produces Ion Channels in Lipid Bilayers

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Aprotinin, a 58 Amino Acid peptide protease inhibitor, is used clinically to prevent postoperative blood loss and reduce transfusion requirements in those procedures which employ extracorporeal circulation. Its mechanism of action is unknown. We have observed that Aprotinin has produced channel-like artifacts in other experimental systems. We tested the hypothesis that Aprotinin could form ion channels in lipid bilayers. Lipid bilayers were created on the tips of patch clamp pipets using phosphatidylethanolamine, phosphatidylserine and cholesterol in a 5:3:2 ratio respectively. Single channel currents were recorded in symmetric solutions of KCl + Tris/HEPES, pH = 7.2, as well as asymmetric solutions. Aprotinin was added to the bath solution. Data were digitized and recorded on video tape for off-line analysis using custom software. 8 μM Aprotinin produced typical ion channel currents in symmetric solutions of KCl at concentrations of 50 mM, 100 mM, 150 mM, and 250 mM, with resultant peak currents of 7.33 pA. The conductance of the Aprotinin channel was 31.8 pS in 250 mM KCl. Aprotinin exhibited multiple conductance levels and complex kinetics. In 250 mM potassium, the channel had a steady state Popen of 0.5. Popen was not voltage dependent. The channels were saturable, selective, and highly specific for potassium ions over sodium ions. No definite blockers of the channel have yet been identified. Our experiments show that Aprotinin produces ion channels in lipid bilayers, and this in turn may lead to better understanding this drug's mechanism of action.

947-114 Effects of Azimilide (NE-10064) on Cardiac K Channels

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To understand the cellular mechanism of action of azimilide (Azim), a novel class III antiarrhythmic agent, we studied its effegts on K currents in guinea pig and canine ventricular myocytes: slow (I_{Ks}) and rapid (I_{Kr}) delayed rectifier, inward rectifier (I_{KI}) and transient outward (I_{to}) currents. To facilitate the quantification and comparison of drug potencies, the recording conditions were designed to "isolate" these K currents from other ionic currents and from each other. In particular, since it is difficult to separate I_{Kr} and I_{Ks} under normal physiological conditions, a Na- and Ca-free external solution was used to dissect the two. This was confirmed by the selective action of dofetilide. Azim blocked I_{Ks} concentration dependently (0.2–10 μM) and reversibly. Block was potentiated by more positive V_t. At +30 mV, 2 μM Azim blocked I_{Ks} by 58 ± 13% (n = 6). Azim caused a time-dependent reduction of I_{Ks} during depolarization and slowed I_{Ks} deactivation, suggesting that block and unblock occurred mainly in the open state. Azim also blocked I_{Kr} concentration dependently (0.1–2 μM) and reversibly. At −20 mV, 1 μM Azim blocked I_{Kr} by 86 ± 10% (n = 3). On the other hand, I_{to} (IC_{50} > 10 μM, n = 6) and I_{KI} (IC_{50} > 50 μM, n = 2) were much less sensitive to Azim than I_{Kr} or I_{Ks}. In conclusion, blockade of both delayed rectifiers makes important contributions to the class III action of Azim.

947-115 Comparative Effects of D-Sotalol, Quinidine and Amiodarone on Dispersion of Ventricular Repolarization in the Isolated Intact Rabbit Heart

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It has been hypothesized that antiarrhythmic as well as proarrhythmic effects of antiarrhythmic drugs (AA) can be linked to changes in dispersion of ventricular repolarization (DISP). The influence of d-sotalol (D-SOT), quinidine (QUIN) and amiodarone (AMIO) was studied in isolated Langendorff-perfused rabbit hearts. Between 5–7 monophasic action potentials were recorded simultaneously from both ventricles at steady-state cycle lengths (CL) between 300 and 1200 msec and measured at 90% repolarization (APD_{90}). DISP was defined as APD_{90}max − APD_{90}min. The protocol was repeated after infusion of D-SOT (n = 12, 10^{-6} M, 10^{-5} M and 5 × 10^{-5} M) and QUIN (n = 8, 10^{-6} M and 10^{-5} M). AMIO was given chronically po. for 4 weeks (n = 9) and compared to n = 18 normal hearts. DISP change compared to the respective baseline (values ranged between 20–27 msec) is shown in the table at selected CLs (all values mean ± SEM in msec, * p < 0.05). AMIO tissue levels correlated with APD duration but not with DISP.

CL	300	600	900	1200
D-SOT 10^{-6} M	+2 ± 3	+5 ± 3	+4 ± 2	+4 ± 3
D-SOT 10^{-5} M	+11 ± 2*	+14 ± 3*	+10 ± 3*	+11 ± 3*
D-SOT 5 × 10^{-5} M	+18 ± 2*	+22 ± 3*	+24 ± 3*	+45 ± 10*
QUIN 10^{-6} M	+14 ± 5*	+22 ± 6*	+18 ± 4*	+28 ± 4*
QUIN 10^{-5} M	+22 ± 5*	+15 ± 5*	+29 ± 5*	+31 ± 6*
AMIO	+3 ± 2	−4 ± 2	−3 ± 2	+3 ± 3

Conclusions: Neither of the three drugs with class III-action shows a reduction of DISP. While QUIN and D-SOT show dose-dependent increases in DISP, especially at long CLs, AMIO tissue concentrations are not related to DISP and no increase is seen at long CLs. These effects on DISP may explain the different clinical incidence of torsade de pointes between the three drugs.

948 Heart Failure: Renal and Adrenal Characteristics

Tuesday, March 21, 1995, 9:00 a.m.–11:00 a.m.
Ernest N. Morial Convention Center, Hall E
Presentation Hour: 9:00 a.m.–10:00 a.m.

948-46 Preserved Cardiac Baroreflex Control of Renal Cortical Blood Flow in Advanced Heart Failure Patients: A Positron Emission Tomography Study

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Cardiac baroreflex (CBR) control of forearm blood flow (FBF) is blunted or reversed in humans with heart failure (HF), but little is known about CBR control of renal cortical blood flow (RCBF) in HF due to technical limitations. Positron emission tomography (PET) 0-15 water is a new, precise method to measure RCBF quantitatively. We compared CBR control of RCBF and FBF (venous plethysmography) in 8 patients with HF (mean age, 47 ± 3 y, ejection fraction 0.25 ± 0.02) and 10 normal humans (mean age 35 ± 5 y) during CBR unloading with phlebotomy (450 ml). In 5 normals, cold pressor test was