rate-dependent AP prolongation, other currents aside from I_{Ks} seem to be responsible for frequency-dependent AP shortening.

1200-169 Effects of Chromanol 293B on Outward Currents and Action Potentials in Human Atrial Myocytes

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Background: The role of I_{Ks} in the human atrium is unclear. Therefore, the effect of Chromanol 293 B (Chrom), a recently described highly selective I_{Ks} blocker in guinea pig ventricular myocytes, was investigated in human atrial myocytes.

Methods: Specimens of human atrial appendages were obtained from patients undergoing coronary bypass surgery. Patients had stable sinus rhythm and received no antiarrhythmic drugs. Freshly enzymatically isolated myocytes were studied by whole cell patch clamp techniques.

Results: Chrom (10 μM) prolonged action potential duration at 80% depolarisation in cells of 8 patients with 16.7 ± 2.7 ms (mean + SEM) at 1 Hz, with 15.4 ± 2.4 ms at 2 Hz and with 17.3 ± 2.5 ms at 3 Hz stimulation frequency. APD 30% remained unchanged in the presence of 10 μM chrom. A small IKtail current (5ndash;40 pA) was infrequently observed at a potential of −40 mV after depolarizing pulses from −80 mV to −30 until +60 mV. 1 μM dofetilide was used to block I_{Kr}. Chrom blocked the dofetilide-insensitive tail current with 68 ± 7% after short depolarizing pulses (200 ms) to +60 mV and almost completely suppressed this I_{Ktail} current after long pulses (2000 ms). For the investigation of I_{to1}, 2 mM $CoCl_2$ was used in order to suppress I_{Ca} and I_{Na}. Chrom (10 μM) blocked peak I_{to1} with 26 ± 5% at pulses to +70 mV, while the sustained outward current remained unchanged at this concentration. Using 3, 10, 50 and 100 μM chrom, IC_{50} for I_{to1} blockade was calculated as 29 μM. In summary, the effects of chrom on action potentials of human atrial myocytes can be due to blockade of I_{Ks} and I_{to1}.

Conclusion: Although I_{Ks} is difficult to detect and small in amplitude, our data point out to a significant role of I_{Ks} in the repolarization of the human atrium, since the frequency-independent action potential prolongation in phase 3 is unlikely to be exclusively an I_{to1} effect.

1200-170 Impared Effect of Dofetilide on the Delayed Rectifier Potassium Current During Acidosis

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Background: Acidosis is an important factor in the setting of myocardial ischemia. In the present work, we investigated the effect of the new class III antiarrhythmic agent dofetilide on the delayed rectifier K^+ current (I_K) under different extracellular H^+ concentrations.

Methods: Isolated guinea pig cardiomyocytes were used for the whole cell patch-clamp experiments. Depolarizing pulses of 200 ms were applied to different test potentials ranging from −20 to +60 mV from a holding potential of −40 mV; tail currents were measured upon repolarization to −40 mV.

Results: At physiological pH, dofetilide decreased both the time-dependent current and the tail currents in a dose-dependent manner at concentrations $\geq 10^{-8}$M. However, at an extracellular pH of 6.8, time-dependent currents were only significantly decreased at concentrations $\geq 10^{-6}$M (−34 ± 4% for 10^{-6}M at +40 mV, $p < 0.05$). Tail currents were already significantly decreased by the administration of 10^{-7}M dofetilide, though only by −20 ± 6% (pH = 6.8) compared to −51 ± 3% at a pH of 7.4 ($p < 0.05$).

Conclusions: Inhibition of I_K by dofetilide was decreased during acidosis. Since increasing the extracellular H^+ concentration should increase the protonized form of dofetilide, it is suggested that the nonionized form of dofetilide is the one responsible for its class III drug action. This may imply a loss of antiarrhythmic efficacy of dofetilide during acidosis.

1200-171 A Novel Inwardly-Rectifying Transient Outward Potassium Current Plays an Important Role in Maintaining Cell Excitability of Canine Myocardium

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Background: We have previously described a novel inwardly-rectifying transient outward K_+ current ($I_{to,ir}$) in canine ventricular myocytes. $I_{to,ir}$ is sensitive to the application of Ba^{2+}, and activates upon depolarization over a time course comparable to I_{Na}, pointing to possible action of it in cell excitability. The present study determined the role of $I_{to,ir}$ in maintaining cardiac excitability.

Methods: We used whole-cell patch configuration (at 36°C) to record action potentials (APs) and current. Cell excitability was determined with variable rectangular current steps by measuring minimum current intensity for triggering APs, and the intensity-duration curve was plotted in the absence and presence of Ba^{2+}.

Results: The intensity-duration curve was substantially shifted to left-down direction by the addition of Ba^{2+} (1 and 5 μM), indicating an increase in cell excitability. The minimum current intensity (3-ms duration) for triggering APs was decreased from 142 ± 21 pA (control) to 116 ± 19 and 82 ± 15 pA ($P < 0.01$, $n = 8$) in the presence of 1 and 5 μM Ba^{2+}. At voltage step (300-ms) to −20 mV from a holding potential of −80 mV, $I_{to,ir}$ was 1.8 ± 0.5 nA in control, and reduced respectively to 1.3 ± 0.1 and 0.9 ± 0.2 nA after the addition of 1 and 5 μM Ba^{2+} ($P < 0.01$, $n = 7$).

Conclusion: Ba^{2+}-induced increase in cell excitability is corresponding to the reduction of $I_{to,ir}$, and therefore, $I_{to,ir}$ plays an important role in maintaining cardiac excitability, particularly in increased $[K^+]_o$ as in acute myocardial ischemia.

1200-172 Direct Comparison of Flecainide and Propafenone Binding Indices From *in vivo* Conduction Delay in Intact Canine Myocardium

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To identify potential variability within the IC anti-arrhythmic drug class, apparent rate constants describing propafenone (PR) and flecainide (FL) binding were derived from use-dependent conduction delay (CD) in the intact canine heart. Following drug loading by rapid pacing at an interstimulus interval (ISI) = 0.3 sec, changes in PR- and FL-induced CD with slower pacing at 0.45 to 1.0 sec ISIs were measured with a 56-electrode epicardial sock. Both PR- and FL-induced CD declined monoexponentially with an overall rate, $R\lambda^*$. As predicted by a two-state model of drug-myocardial interaction, $R\lambda^*$ for both agents was a linear function of the diastolic recovery interval, tr, (tr = ISI − APD_{90}) where $R\lambda^* = \lambda ata + \lambda rtr$ (λr = resting state uptake rate, λa = activated state uptake rate for FL and inactivated state uptake rate for PR, and ta = 1 ms). Use-dependent PR and FL effects *in vivo* were quantitatively described by apparent active state binding and unbinding rates of ka and 1a, and resting state kr and 1 r as follows:

	ka (× $10^6 M^{-1}s^{-1}$)	1a (s^{-1})	kr (× $10^3 M^{-1}s^{-1}$)	1r (s^{-1})
PR	5.8 ± 2.3	47 ± 12	4.2 ± 3.3	0.12 ± 0.02
FL	2.8 ± 1.9	0.08 ± 0.03	0.51 ± 0.58	0.36 ± 0.09

Activated state uptake and unbinding were substantially greater for FL than PR. The time constant for recovery from FL block ($\tau r = 1/\lambda r$) of 7.8 ± 1.7 sec was also longer than the PR τr of (2.9 ± 0.7 sec.) ($P < 0.005$). These characterizations show marked differences in drug binding and unbinding within the IC class. These predict superior use-dependent CD with FL, but a lesser proarrhythmic propensity with PR as expressed by its shorter τr.

1201 Supraventricular Arrhythmias: Mechanism and Treatment

Wednesday, April 1, 1998, Noon–2:00 p.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: 1:00 p.m.–2:00 p.m.

1201-161 Anatomical Geometry at the Atrioventricular Junction Determines the Occurrence of Atrioventricular Nodal Reentrant Tachycardia in Human

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Background: Despite a clear delineation of atrioventricular (AV) node and perinodal inputs within the Koch's triangle, the anatomical mechanism underlying the occurrence of AV nodal reentrant tachycardia (AVNRT) in human remains unknown.

Methods: We hypothesized that the geometrical interaction between the AV junctional structures including the Koch's triangle, coronary sinus (CS) and AV node (indicated by AV nodal artery ending) determines the occurrence of AVNRT in human. Anatomy assessment via orthogonal selective coronary arteriography and simultaneous CS venography plus right ventriculography were performed and compared between 57 patients (pts) with AVNRT (group A, 20 men, 37 women, age 54 ± 11 years) and 28 pts without (group B, 13 men, 15 women, age 48 ± 7 years).

Results: Anatomical characteristics of the Koch's triangle (Δ), the CS orifice (CSO) and the location of the AV node in group A and B pts were listed as follows.

Group	A:TA	TT	Base	CSO	CSD/CSO%	H-AVN	AVN-CSO
A	21 ± 6	24 ± 5	15 ± 3	12 ± 3	36 ± 11	9 ± 5	6 ± 6
B	18 ± 5	22 ± 5	16 ± 4	8 ± 3	60 ± 22	6 ± 3	10 ± 5
P	0.02	0.09	NS	<0.01	<0.01	<0.01	<0.01

All numbers in mm, and in mean ± SD TA, TT, Base, lengths of tricuspid annulus (TA), tendon of Todaro (TT), base borders of Koch's triangle; CSO, CSD, diameter of orifice & distal CS. H-AVN, AVN-CSO, distance between AV nodal artery ending and His bundle (H) site o: CSO roof. Compared to group B, group A pts had a larger CSO size with a swifter tapering of the CS lumen and a more low-setting of the AV node, but had similar dimensions of the Koch's triangle.

Conclusions: Pts with clinical AVNRT had a lower AV node position within the Koch's triangle and a closer proximity to a larger CSO, which may create an electrophysiologic milieu for the development of AVNRT.

1201-162 Fluoroscopic Dimensions of the Triangle of Koch and Feasibility of Radiofrequency Ablation of the Slow Nodal Pathway

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The dimensions of the Triangle of Koch (TK) may influence the ease for slow nodal pathway (SP) ablation. In 65 consecutive patients (Pts) (45 ± 16 years, 71% female) subjected to radiofrequency catheter ablation (RFCA) of the SP, manual injection of contrast into the right atrium was made to visualize the septal leaflet of the tricuspid valve (TVS). Angiographic references in RAO projection were: a) tip of the His catheter (Hc); b) point of inflection of the cateter entering the coronary sinus (CSos) c) anterior limit of the TVS; d) inferior limit of the TVS. Reference for measurements: electrodes of the Hc. Dimensions obtained (Figure): 1) Hc-CSos (fluoroscopic Todaro; FT); 2) horizontal distance from the mid point of the FT to the anterior limit of the TVS (mid Koch); 3) horizontal distance from the CSos to the anterior limit of the TVs (TK base); 4) vertical distance from the CSos to the inferior limit of the TVS [Eustachian-tricuspideal pouch (ETP)]). RF applications (app) for ablation 4 ± 4.6 (median 2). Pts were divided into two groups: A. ≤2 app (38), B. >2 app (27). There were no differences in age or sex. An ETP was more frequent in group B than in group A (39% vs 59% p < 0.01).

	≤2 App	>2 App	p
Ft Todaro	39 ± 7 (40)	37 ± 8 (34)	NS
mid Koch	14 ± 6 (15)	16 ± 7 (15)	NS
TK base	21 ± 9 (22)	25 ± 10 (25)	<0.001
ET Pouch	2 ± 5 (0)	11 ± 15 (11)	<0.001

Conclusions: RFCA of the SP may be more difficult, requiring a greater number of RF applications, in Pts with a wide TK base, and specially in those with a well developed ETP.

1201-163 Effect of Radiofrequency Catheter Ablation of Accessory Pathways on Autonomic Tone in Children

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Background: Radiofrequency catheter ablation (RFCA) of supraventricular tachycardia (SVT) is increasingly being used as a curative approach in the pediatric population. Inadvertent effects of RFCA on cardiac autonomic function have been described in adults, but have never been evaluated in children.

Methods: We determined the effects of RFCA on invasive and noninvasive parameters of cardiac autonomic function in eight children (5–16 y.o, 6 male, 2 female) with inducible AV reciprocating tachycardia (AVRT) before and within 24 hours after successful RFCA of accessory pathways (7/8 concealed; 2 right-, 6 left-sided).

Results: (mean ± standard deviation)

Parameter	Before RFCA	After RFCA	P
Sinus cycle length (SCL)	838 ± 157	679 ± 47	0.039
AH interval (at 500 msec)	121 ± 13	94 ± 17	0.017
Atrial ERP (at 500 msec)	238 ± 55	235 ± 36	NS
Wenkebach cycle length (WCL)	370 ± 39	285 ± 24	0.020
Ventricular ERP (at 500 msec)	235 ± 14	222 ± 16	0.043
Baroreceptor sensitivity	3.83 ± 1.97	4.52 ± 2.88	NS
Valsalva (RR ratio)	1.66 ± 0.38	1.61 ± 0.17	NS
Deep breathing (RR % change)	53 ± 21%	45 ± 26%	NS
Response to tilt (% Change in heart rate at 2 min)	20 ± 18%	26 ± 11%	NS

Standard time- and frequency domain parameters of 24 hour heart rate variability analysis did not change significantly following RFCA. The changes in SCL, WCL and ERPs were abolished by pharmacologic autonomic blockade with atropine and esmolol.

Conclusion: In pediatric patients, RFCA of accessory pathways is associated with changes in electrophysiologic parameters consistent with increased sympathetic and/or decreased parasympathetic tone.

1201-164 Intravenous Dofetilide for Termination of Paroxysmal Supraventricular Tachycardia

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Abstract: Dofetilide (DOF), a new, highly selective potassium channel blocker, was tested IV for acute termination of sustained stable re-entrant paroxysmal supraventricular tachycardia (PSVT).

In a multicenter, double blind trial, 96 patients were randomized equally to either placebo (PLA) or IV infusion of DOF at 6 mcg/kg for 15 mins. The patient population included 51 males and 45 females between ages 18 and 85. PSVT occurred spontaneously in 6 patients and was induced in the lab in 90.

DOF and PLA groups were matched for age, gender, structural heart disease, and mechanism of PSVT. Patients were observed for 30 mins. after the start of infusion. The rate of conversion and the time to conversion were compared: 39 of 48 patients (81%) in the DOF group converted to sinus rhythm, vs 18 of 48 patients (38%) in the PLA group ($p < 0.001$). The time to conversion was also significantly shorter (median = 9.5 mins.) for DOF vs PLA ($p < 0.0001$).

There were no serious adverse events and no proarrhythmias. The incidence of treatment emergent adverse events of all causalities was slightly smaller on DOF (25%) than on PLA (31%).

Conclusion: IV DOF was more efficacious than PLA in terminating PSVT. It was well tolerated and no proarrhythmic events were observed.

1201-165 Efficacy and Safety of Intravenous Dofetilide in Acute Conversion of Supraventricular Arrhythmias in Wolff Parkinson White Syndrome

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Background: Intravenous dofetilide is a class III antiarrhythmic agent and selective potassium channel blocker for I_{Kr}, which may be useful in the acute management of supraventricular tachycardias.

Methods: Fifteen male patients (age 34 ± 13 yrs, range 18–63 yrs) with preexcitation on ECG underwent electrophysiologic (EP) testing and induction of sustained AV reentrant tachycardia (n = 4) or atrial fibrillation (n = 12). Patients were randomized to receive an infusion of either placebo (n = 5), dofetilide 2.5 mcg/min (n = 5) or dofetilide 4 mcg/min (n = 5) over 15 minutes. Non-responders received a second infusion of higher dose dofetilide (2.5–6 mcg/min) for 15 minutes and underwent repeat EP testing.

Results: Two of five patients responded to 2.5 mcg/min dofetilide and 4/5 patients responded to 4.0 mcg/min dofetilide, compared to 1/5 patients with placebo. After a second infusion of higher dose dofetilide (including placebo crossover), 11/15 patients responded to dofetilide (73%). One patient experienced mild pain at the infusion site. There were no study discontinuations, proarrhythmias or serious adverse events.

Conclusion: Intravenous dofetilide is a safe and promising agent for acute termination of supraventricular arrhythmias in the Wolff Parkinson White Syndrome.

1202 Ventricular Arrhythmias: Mechanism and Ablation

Wednesday, April 1, 1998, Noon–2:00 p.m.
Georgia World Congress Center, West Exhibit Hall Level
Presentation Hour: Noon–1:00 p.m.

1202-173 Systolic Potentials During Ventricular Tachycardia Are Indicative of Critical Sites Within the Reentry Circuit in Patients With Coronary Artery Disease

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Background: Isolated diastolic potentials (IDP) have been found to be helpful to locate critical sites within the reentry circuit in patients (pts) with ventricular tachycardia (VT) and coronary artery disease (CAD). Isolated potentials