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USE OF FLUNARIZINE TO IDENTIFY TRIGGERED ACTIVITY AS A MECHANISM OF CLINICAL ARRHYTHMIAS

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We have previously shown that in the canine heart Flunarizine (F) slows and terminates tachycardias (T) based on triggered activity caused by delayed afterdepolarizations (DAD's), while it accelerates T and/or rhythms based on normal and abnormal automaticity. To investigate the clinical relevance of DAD's, F was given iv (0.5 - 1 mg/kg in 5-10 min) to 20 patients. Mean age was 44 ± 22 years. Fifteen patients had supraventricular (SVT) and 5 patients ventricular T (VT). Blood pressure, cycle length of T, and/or number of ectopic beats/min were measured 10 min before and up to 40 min after F.

SVT	n	F	VT	n	F
atrial T	10	3+	idiopathic VT	3	1*
atrial flutter	2	0	accelerated ven-		
accessory pathway	2	0	tricular rhythm	1	1*
sinus T	1	0	digitalis VT	1	1*

Results (table) : F decreased 1) cycle length of 5 T from 490 ± 85 to 590 ± 115 ms ($p \leq 0.01$) and 2) ectopic beats from 110 to 30 beats/min in 1 T (+). Termination occurred in 3 T (*). Blood pressure decreased from 125 ± 22 / 82 ± 14 to 110 ± 22 / 74 ± 10 mm Hg ($p \leq 0.01$).
In conclusion, F identified 6 of 20 T (30%) as possibly based on triggered activity resulting from DAD's. These data suggest that F can be of help to identify a specific arrhythmogenic mechanism allowing more specific antiarrhythmic drug therapy.

Thursday, March 22, 1990
8:30AM–10:00AM, Room 23
Mechanisms of Diastolic Dysfunction

Effect of Chronic Mitral Regurgitation on Diastolic Function in Conscious Dogs: Mechanisms Causing Augmented Early Diastolic Filling.

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We hypothesized that the LV's ability to increase total stroke volume in chronic mitral regurgitation (MR) is dependent, in part, upon a compensatory change in diastolic function producing augmented diastolic filling. Diastolic function was examined in 5 normal dogs (NML) and 7 with chronic (3 months) MR using simultaneous echo and cath. Chronic MR caused LV dilation (end diastolic dimension increased from 47±1 to 57±1 mm*), increased stroke volume (stroke dimension increased from 17±1 to 23±1 mm*) and LV hypertrophy (LV/body weight increased from 3.4±1 to 4.5±1 g/kg*). * = $p<0.05$ vs NML. Early diastolic filling rate increased from 3.0±0.2 to 4.0±0.1 sec^{-1}*, and filling fraction during the first 40% of diastole increased from 54±3 to 79±3%*. Determinants of filling were measured: time constant (ms) of ventricular (τp) and myocardial ($\tau\sigma$) relaxation, transmitral LA/LV pressure gradient, end systolic circumferential stress (σes, g/cm^2), chamber stiffness normalized for LV mass (Kc) and muscle stiffness (Km). Data = mean ± SEM.

	σes	LA/LV	τp	$\tau\sigma$	Kc	Km
NML	56±4	7±1	28±2	30±3	4.1±0.7	5.4±1.1
MR	56±4	17±2*	29±2	35±4	1.7±0.2*	4.3±0.6

In chronic MR, increased rate and extent of early diastolic filling were not associated with accelerated myocardial inactivation (τp or $\tau\sigma$) or decreased afterload (σes). Rather, augmented filling was produced by a compensatory increase in passive chamber compliance (decreased Kc) and increased left atrial driving force (increased LA/LV). Thus, unlike most cardiac diseases, chronic MR results in improved diastolic function.

COMBINATION ETHACIZIN AND ETHMOZIN TREATMENT OF RESISTANT VENTRICULAR ECTOPY - EXPERIMENTAL, THEORETICAL, AND CLINICAL STUDY.

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Ethacizin (EC) has a slower unbinding rate from the Na channel than ethmozin (EM). Can this difference in use-dependence be exploited by combination treatment for ventricular ectopy (VE)? In canine hearts conduction delay in response to 50-pulse pacing trains at a rate of 100/min with EC (1.5 mg/kg) and EM (3 mg/kg) combined was greater than EC alone, but the delay at 60/min was less than EC alone. Use-dependent block of Na channels was simulated by the guarded receptor model using rate constants for EC and EM measured from voltage clamp experiments. At rapid rates the combination was additive. At slower rates use-dependent block was less than with EC alone because EM protected the binding site from EC during the binding phase and unbound before the next beat. Thus the combination showed additive use-dependent effects at rapid rates and competitive antagonism at slow rates in both the experimental model and the simulation. Combination therapy was tested in 6 patients (age 35±8) with idiopathic symptomatic VE. EC alone (200 mg/d) showed PR (.22±.01 s) and QRS (.10±.05 s) prolongation, and 3 patients remained symptomatic with VE on either EC or EM (800 mg/d) alone. Combination treatment (EC 100 mg/d and EM 400 mg/d) resolved symptoms in all patients and reduced VE 78±4% on quantitative Holter monitoring without side effects or PR or QRS prolongation. These data provide a theoretical and experimental rationale for the efficacy and safety of combining two Class I antiarrhythmic drugs.

DOPPLER FINDINGS OF MITRAL REGURGITATION AND IMPAIRED LEFT VENTRICULAR FILLING PROPERTIES IN SYSTEMIC SCLEROSIS

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In systemic sclerosis (Sscl) cardiac involvement (not previously evaluated by Doppler) is prognostically important. To study left ventricular (LV) filling characteristics in Sscl, we applied pulsed wave Doppler (PWD) in consecutive Sscl patients (pts) (n=30) and a matched control group (n=48). Mitral regurgitation was evaluated by pulsed and continuous wave Doppler. Atrial emptying index was calculated from M-mode echocardiography, and a/H ratio from apexcardiogram.

We found the PWD velocity of the A wave to be high in Sscl pts compared to controls (0.74±0.07 vs 0.54±0.02 m/s, $p<0.002$), while the E-wave did not differ. The A/E ratio was increased in Sscl (1.09±0.08 vs 0.80±0.04, $p=0.0002$). The high A/E ratio indicating reduced distensibility, correlated to interventricular septal thickness ($r=0.53$, $p<0.001$), apexcardiographic a/H ratio ($r=0.49$, $p<0.001$), and atrial emptying index ($r=-0.55$, $p<0.001$). Early filling was impaired, with a prolonged pressure half time (99±6 vs 84±4 ms, $p=0.02$), and a reduced first third filling fraction (0.41±0.02 vs 0.48±0.01, $p<0.001$). The latter was related to atrial emptying index ($r=0.56$, $p<0.001$), and to some extent to septal thickness ($r=-0.29$, $p<0.05$). Mitral regurgitation (MR) was found in 40% of Sscl pts and in 4% of controls ($p<0.001$). PWD measures of LV filling properties were not related to the degree of MR or to systolic blood pressure.

We conclude that LV distensibility and early filling properties are impaired in Sscl but not related to blood pressure, thus probably secondary to the myocardial fibrosis. Particularly distensibility seems to be related to LV wall thickness. MR is a common finding in Sscl.