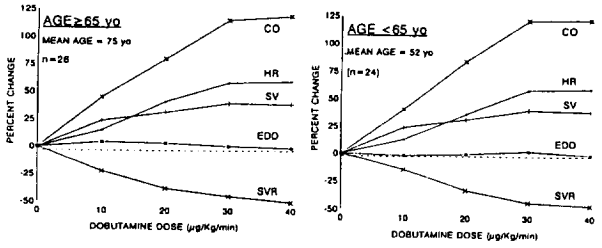
2 gender-matched groups of subjects widely separated in age by 2 decades: an older group (age 73 ± 4, n = 42) and a younger group (age 53 ± 7, n = 41), during graded 3 minute infusions of DOB at 5, 10, and 20 μg/kg/min. We excluded subjects who were on cardioactive medications or who had abnormal LV function or conduction defects. *Results:* HR responses of the two groups were nearly identical at all doses. In contrast, SBP responses differed markedly (see figure). With increasing DOB dose, the young had an increase in SBP while the old had a progressive decrease in SBP ($p < 0.01$ by ANOVA), even after adjusting for higher resting SBP in the old. The SBP response was not affected by wall motion or LV function. *Conclusion:* Aging markedly alters the blood pressure but not the heart rate response to DOB. These data may help explain the frequency of hypotension during DSE.

4:45

807-4 Normal Hemodynamic Responses to Dobutamine Infusion in the Elderly

Craig Lampert, Herman D. Movsowitz, Larry E. Jacobs, Alfred Ioli, Morris N. Kotler
Albert Einstein Medical Center, Philadelphia, PA

Elderly patients undergoing conventional exercise stress testing (CST) rely predominantly on an increased preload (Starling mechanism) to augment cardiac output (CO). In contrast, younger patients rely predominantly on an increased heart rate (HR) and decreased systemic vascular resistance (SVR) to augment CO. To determine normal physiologic hemodynamic responses to incremental dobutamine infusion in young (<65 yo) as compared to elderly (≥65 yo) patients, we analyzed the results of 50 consecutive patients with normal regional wall motion and normal ejection fraction at rest. All patients underwent 2-D echocardiography and continuous wave Doppler evaluation of the left ventricular outflow tract (LVOT) during each stage of the dobutamine infusion protocol. No patients developed regional wall motion abnormalities during dobutamine infusion. HR, velocity time integral (VTI) across the LVOT and end diastolic dimensions (EDD) were recorded. Stroke volume (SV = VTI × cross sectional area of LVOT), CO (HR × SV) and SVR (80 × mean arterial pressure ÷ CO) were calculated. The mean % change from baseline of HR, SV, EDD, SVR and CO are shown:



Conclusion: 1) There is no statistical difference in the hemodynamic response to dobutamine in young versus elderly patients. 2) Elderly patients undergoing dobutamine stress testing augment their CO by increasing HR and SV, decreasing SVR and with no change in EDD. 3) This is in contrast to that observed during CST. 4) Adequate heart rate response in the elderly might be more important during dobutamine infusion than during CST.

808 Electrophysiology — Basic Ventricular Arrhythmias

Wednesday, March 22, 1995, 4:00 p.m.–5:00 p.m.
Ernest N. Morial Convention Center, Room 14

4:00

808-1 Focal Mechanisms Underlying Sustained Ventricular Tachycardia in Ischemic Cardiomyopathy

Carolyn M. Johnson, Steven Pogwizd *Washington University, St. Louis, MO*

To define the mechanism of ventricular tachycardia (VT) induced by programmed electrical stimulation in the setting of congestive heart failure, 3-dimensional cardiac mapping was performed in six dogs with ischemic cardiomyopathy induced by multiple intracoronary embolizations with microspheres. Ejection fraction (EF) progressively decreased from 54 ± 2 to 30 ± 5% ($p < 0.005$) after an average of 6 weekly embolizations. Four months later (EF = 28 ± 5%), each dog underwent a thoracotomy with insertion of plunge-needle electrodes into the heart under pentobarbital anesthesia. Continuous recording from 232 intramural sites throughout the left and right ventricles and the interventricular septum was performed during spontaneous rhythm and during programmed stimulation in both the absence and presence of isoproterenol (Iso) (0.1 mg/kg/min). Three dogs (1 at baseline, 2 during Iso) developed sustained VT (SuVT) during programmed stimulation with up to 3 extrastimuli. After the last extrastimulus, the first beat of SuVT (T_1) initiated in the subendocardium by a focal mechanism, based on the absence of electrical activity from the termination of the last extrastimulus to the initiation of T_1 despite the presence of multiple intermediate electrode sites. Maintenance of SuVT was also due to a focal mechanism arising in the subendocardium, with a total activation time (TAT) of subsequent SuVT beats (99 ± 14 msec, n = 6) that was comparable to that of initiating beats (85 ± 8 msec, n = 6, p = 0.08). There was no evidence of macroreentry. Episodes of SuVT (n = 3) exhibited TATs of the last extrastimulus before SuVT (106 ± 11 msec) and coupling intervals of T_1 (196 ± 70 msec) that were comparable to those observed in nonsustained VT (n = 3) (138 ± 26 msec, p = 0.19; 166 ± 26 msec, p = 0.59). Conduction delay during sinus rhythm in dogs with SuVT (TAT 47 ± 5 msec, n = 10) was comparable to that in dogs without SuVT (TAT 47 ± 4 msec, n = 10, p = 0.96) and was unchanged by Iso (TAT 50 ± 4 msec, n = 7, p = 0.40). In the 2 dogs with inducible SuVT on Iso only, TATs of the last extrastimulus (124 ± 22 msec) and of T_1 (110 ± 36 msec) at baseline were unchanged by infusion of Iso (108 ± 13 msec, p = 0.59; 79 ± 1 msec, p = 0.49). Thus, inducible sustained VT in a model of ischemic cardiomyopathy is due to a focal mechanism, as opposed to macroreentry, and this focal mechanism is enhanced by β-adrenergic stimulation.

4:15

808-2 Sudden Heart Rate Speeding and Slowing Facilitates the Inducibility of Ventricular Tachycardia in Dogs

Tadashi Satoh, Harold P. Pride, Douglas P. Zipes. *Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, IN*

Clinically, torsades de pointes (TdP) often occurs when the heart rate suddenly slows (eg. atrial fibrillation to sinus rhythm). We investigated whether the dose of cesium chloride (CsCl) required to induce early afterdepolarizations (EADs), the putative mechanism of TdP, and ventricular tachycardia (VT) was different in dogs with a paced left ventricular cycle length (PCL) of 1,000 msec for a 1 week versus dogs with a PCL of 1,000 msec for 1 week and 500 msec for 1 hour prior to a PCL of 1,000 msec. All dogs had atrioventricular (AV) block induced by radiofrequency ablation and were studied closed chest. While recording surface ECG leads I,II,III and LV endocardial monophasic action potential (MAP), CsCl was injected incrementally (0.25, 0.5, 0.625, 0.75, 1.0 mM/kg) until sustained VT was induced. In group 1 (n = 6), CsCl was injected during PCL = 1,000 msec. In group 2 (n = 7), CsCl was injected during PCL = 1,000 msec after PCL = 500 msec for 1 hour. In group 1, VT was induced at 0.75 mM/kg in 3 dogs and at 1.0 mM/kg in 3 dogs. VT was induced at 0.75 mM/kg in all 7 dogs in group 2 ($p < 0.05$). The area of EAD as a percentage of LV MAP area (%EAD) in group 2 dogs exceeded that of group 1 at 0.5, 0.625, 0.75 mM/kg.

CsCl (mM/kg)	0.25	0.5	0.625	0.75
Group 1 (%EAD)	108 ± 2.4	115 ± 3.9	119 ± 5.4	129 ± 5.1
Group 2 (%EAD)	108 ± 3.6	118 ± 2.1	127 ± 3.9	135 ± 5.4
p	ns	<0.05	<0.01	<0.05

We conclude that only 1 hour of rapid pacing after 1 week of bradycardia is sufficient to produce a change in myocardial responsiveness to the K^+ channel blocker, CsCl, and increases the susceptibility of VT induction, possibly via an increase in EAD amplitude.

4:30

808-3 Reentrant Wavefronts During Wiggers' Stage II Ventricular Fibrillation in Dogs

John J. Lee, Dustan Hough, Chun Hwang, Wei Fan, Michael C. Fishbein, Claudio Bonometti, Hrayr S. Karaguezian, Peng-Sheng Chen *Cedars-Sinai Medical Center, and UCLA School of Medicine, Los Angeles, CA*

The mechanisms of ventricular fibrillation (VF) are unknown. Reentrant wavefronts have been shown to underlie the onset (Wiggers' stage I) of electrically induced VF in intact canine ventricles. These reentrant wavefronts, however, have a limited lifespan (1–2 s) while VF persists. Using computerized mapping techniques, we studied the mechanism by which VF is maintained beyond the initial few seconds (Wiggers' stage II), both in normal and subendocardium-ablated canine ventricles. Eleven open-chest dogs were studied. In 6 of the dogs, the RV subendocardium was ablated with Lugol's solution. A plaque electrode array with 317–509 bipolar recording electrodes was sutured on the RV epicardium. VF was induced by a strong premature stimulus (S_2). Starting 2.5 s after the onset of VF, 2–5 s of data were analyzed. The activation patterns were visualized via dynamic display. Conventional isochronal maps were also constructed. Of the 15 runs of VF in dogs with intact ventricles, 3 episodes of reentrant wavefronts were detected. The mean lifespan was 4.5 ± 2.1 rotations. The mean cycle length was 102.5 ±

5.5 msec. The incidence of reentry was 0.018 ± 0.048 rotations/sec-cm^2. Of the 18 runs of VF in dogs with ablated ventricles, 8 episodes of reentry were detected. The mean lifespan was 3.6 ± 1.1 rotations ($p = 0.39$ compared with intact ventricles). The mean cycle length was 107.2 ± 9.6 msec ($p = 0.16$). The incidence of reentry was 0.075 ± 0.097 rotations/sec-cm^2 ($p = 0.048$). In both groups of dogs, dynamic displays of the activation patterns demonstrate that the reentrant wavefronts spiral rather than follow a simple circular pathway. *Conclusions:* (a) reentrant wavefronts are consistently present during Wiggers' stage II VF, (b) ablation of the subendocardium and Purkinje fibers results in an increased incidence of reentrant wavefronts on the epicardium, and (c) the reentrant wavefronts are compatible with spiral waves of excitation.

4:45

808-4 The Presence and Duration of an Excitable Gap During Ventricular Fibrillation in a Canine Model of Myocardial Infarction

George Horvath, Nikhil Patel, Roger S. Damle, Sandeep Jain, Nikki S. Robinson, Jeffrey J. Goldberger, Alan H. Kadish. *Northwestern University Medical School, Chicago, IL*

An excitable gap (EG) occupying 50% of the cycle length has been reported in a non-infarcted canine model of ventricular fibrillation (VF). To evaluate the presence and duration of an EG in VF post infarction, we studied 9 mongrel dogs at 5 days (n = 5) and 8 weeks (n = 4) post LAD ligation. VF induced by programmed stimulation was recorded using an 8 by 14 electrode array (2.5 mm interelectrode distance) over the infarcted area. The mean VF cycle length (VFCL) was determined at each site. EG was determined by a wavefront analysis propagation method. Sites at which both conduction and block occurred on different cycles were analyzed. At each, the interval from each activation to the subsequent blocked (R-B) or conducted (R-C) impulse was recorded, along with the R-C interval immediately preceding. The recovery period at each site was estimated as the range bounded by the maximal R-B and minimal R-C. The EG was determined by the difference of the recovery period and the mean R-C at each site. *Results:* Fifty eight sites were suitable for analysis.

Results of analysis (Mean or mean ± standard deviation):

Group	Mean R–C	Max R–B	Min R–C	EG	Mean EG as %CL
5 Day	154 ± 29 ms	104 ± 31 ms	124 ± 35 ms	29–49 ms	22–31%
8 Week	132 ± 23 ms	97 ± 21 ms	101 ± 25 ms	30–35 ms	23–30%
	$p = 0.002$	$p = 0.28$	$p = 0.008$		

The mean R-C at these sites was longer than the mean VFCL for all sites in the 5 day group (mean VFCL 133 ± 22 ms at 5 days, 130 ± 15 ms at 8 weeks). A trend toward a longer upper limit of EG was seen in the 5 day group ($p = 0.08$). In 29% of all sites (36% at 5 days, 20% at 8 weeks) a significant EG (≥10 ms) was not present.

Conclusions: An excitable gap exists at most sites during VF in a canine model of myocardial infarction, but is absent in a minority of sites. The gap may be shorter in absolute duration in chronic infarction (8 weeks) than in subacute infarction (5 days), although the proportion of cycle length occupied by the EG is similar in both groups. The site to site heterogeneity in the magnitude and presence of EG in infarcted myocardium has implications for the use of pacing techniques to modulate VF.

809 Autonomic Nervous System Adaptation in Heart Failure

Wednesday, March 22, 1995, 4:00 p.m.–5:00 p.m.
Ernest N. Morial Convention Center, Room 6

4:00

809-1 Different Respiratory Rates Affect the Measurement of Autonomic Tone by Power Spectral Analysis of Heart Rate Variability in Patients with Heart Failure

John E. Sanderson, Dickens T.K. Yeung, Leata Y.C. Yeung, Richard L.C. Kay, Brian Tomlinson, Luciano Bernardi [1], Kam S. Woo. *Chinese University of Hong Kong;* [1] *University of Pavia, Italy*

Power spectral analysis of heart rate variability is frequently used as an easy non invasive method for assessing autonomic tone. However changes in respiratory rate are frequently ignored and these may have an important effect on the measurements of spectral components, especially in heart failure. We have assessed the effect of different respiratory rates (10, 15, 20 min^{-1} and spontaneous) on low frequency (LF) and high frequency (HF) components of HR variability in 11 heart failure pts (CCF) (EF = 40 ± 4%; 9 males) and 9 normal subjects (5 males).

Results: LF & HF spectral power in normalized units (%); S = spontaneous (mean ± SEM)

	LF10	HF10	LF15	HF15	LF20	HF20	LFS	HFS
Supine								
CCF	19 ± 8	63 ± 9*	18 ± 5	54 ± 7	13 ± 4	47 ± 8*	16 ± 6	49 ± 8
Normal	14 ± 6	68 ± 8	18 ± 6	58 ± 10	15 ± 6	70 ± 5	22 ± 9	55 ± 10
Stand								
CCF	15 ± 7	66 ± 6	19 ± 7	46 ± 8	30 ± 10	51 ± 9	7 ± 5	31 ± 10
Normal	28 ± 9	55 ± 8	30 ± 9	42 ± 9	58 ± 10	27 ± 5	50 ± 12	17 ± 5

*$p < 0.05$

Supine HF power falls with increasing respiratory rate in most CCF pts and this effect is similar to that seen in normals on standing (i.e. at increased sympathetic levels). An improvement in clinical state of CCF pts will lower respiratory rate and this effect alone will increase HF power rather than any therapy.

4:15

809-2 Effect of Digoxin on Cardiac Sympathetic Activity in Congestive Heart Failure

Gary E. Newton, Jeffrey H. Tong, Anne M. Schofield, Andrew D. Baines, John S. Floras, John D. Parker *Mount Sinai Hospital, Toronto, Canada*

The effect of cardiac glycosides on cardiac sympathetic activity in congestive heart failure (CHF) remains uncertain.

Methods: We measured total body and cardiac norepinephrine spillover (NESP) using the norepinephrine isotope-dilution technique at baseline and 30 minutes after digoxin (0.25 mg iv). LV pressure, its first derivative (Millar), and systemic BP were also measured before and after digoxin. We studied 15 patients with CHF; 5 with normal LV filling pressures (LVEDP ≤ 14, mean 9 ± 2 mmHg), and 10 with high LV filling pressures (LVEDP > 14, mean 26 ± 3 mmHg).

Results: The groups had similar baseline HR, BP, and LV +dP/dt. The high LVEDP group had a lower EF (20 ± 2 vs 34 ± 2%, $p < 0.05$), a lower CI (1.7 ± 0.2 vs 2.8 ± 0.3 L/min/m^2, $p < 0.05$), and higher mean PA pressures (31 ± 4 vs 14 ± 2 mmHg, $p < 0.05$) at baseline, as compared to the normal LVEDP group. HR, BP, LVEDP, LV +dp/dt, coronary sinus blood flow, and total body NESP did not change in either group following digoxin. Cardiac NESP was unchanged in response to digoxin in the normal LVEDP group. Importantly, digoxin caused a consistent reduction in cardiac NESP in the high LVEDP group:

LVEDP	Cardiac NESP (pmol/min)	
	Baseline	Digoxin
≤14 mmHg	91 ± 28	111 ± 36
>14 mmHg	189 ± 63	159 ± 57*

All data expressed as mean ± SEM. *$p = 0.016$, by paired t test

Conclusion: This study demonstrates that the acute administration of digoxin reduces cardiac NESP in patients with CHF and high LV filling pressures. This reduction in cardiac sympathetic activity appears to be mediated by a non-hemodynamic mechanism, since digoxin in the dose used in this study did not cause changes in either the loading conditions or the contractile state of the LV.

4:30

809-3 Desipramine Attenuates the Cardiac Sympathetic Nerve Terminal Abnormalities in Congestive Heart Failure

Akito Yatani, Suzanne Y. Felten, Yoshihiro Himura, Michihiro Kashiki, Chang-seng Liang *University of Rochester Med. Ctr., Rochester, NY*

We have shown that cardiac norepinephrine (NE) reuptake activity and tyrosine hydroxylase (TH), a rate-limiting enzyme for NE synthesis, are reduced in congestive heart failure (CHF). To determine whether the changes of TH are caused by neurotoxic effects of NE, we administered the neuronal uptake inhibitor desipramine (DMI, 225 mg/day) to pacing-induced CHF and sham-operated (SHAM) dogs for 6 weeks. CHF was characterized by tachycardia, low aortic pressure, elevated left atrial pressure, decreased left ventricular dP/dt and reduced cardiac output. DMI produced no hemodynamic effects. The effects of DMI on left ventricular NE uptake activity (fmol/mg/15 min) and immunocytochemical TH profiles were:

Group	NE uptake	TH
SHAM (n = 12)	133 ± 9	813 ± 43
SHAM + DMI (n = 6)	49 ± 11*	769 ± 14
CHF (n = 12)	64 ± 8*	409 ± 42*
CHF + DMI (n = 7)	40 ± 9*†	642 ± 49*†

Values are mean ± SE. *$p < 0.05$ vs. SHAM; †$p < 0.05$ vs. CHF