IC-SP-IV-Dob caused an additional fall in LVPSP ($\Delta = -17 \pm 6$ mmHg; $p < 0.01$).

Conclusions: 1) Receptor-mediated Cor Endo stimulation modulates LV function in Tx recipients; 2) Arg augments Cor Endo influence on LV function after Tx probably by providing more substrate for Cor Endo production of NO; 3) β-adrenergic stimulation with Dob augments Cor Endo influence on LV function probably by potentiating the myocardial cardiodepressant action of NO.

941-5 Abnormal Magnitude and Orientation of Deformation and Reduced Rigid Body Motion Throughout the Left Ventricle in Healed Reperfused First Anterior Infarction

Charles J. McCreery, Lori Semonik, Walter J. Rogers, Thomas P. Power, Therese M. Theobold, Nathaniel Reichek, Christopher M. Kramer. *MCP/Hahnemann University, Pittsburgh, PA*

To determine intramyocardial deformation and rigid body motion after healed reperfused first anterior myocardial infarction (MI), we used magnetic resonance tagging (MRI) in 11 patients (9 M, aged 54 ± 14), 8 ± 1 weeks post MI. Peak CK was 3949 ± 2061 and all had single vessel disease. Results were compared to 9 normal subjects (NL) (7 M, aged 30 ± 3). Breathhold, segmented k-space tagged images were obtained with 7 mm thick short axis slices (n = 11 ± 1) spanning the left ventricle (LV). Mean EF by MRI was 44 ± 6%. Stripe intersections were used to create triangular finite elements that were tracked from the undeformed state to end systole to measure the orthogonal principal strains, λ_1 (1 + greatest systolic stretch), λ_2 (1 – greatest systolic shortening), β (angular deviation of λ_1 from the radial direction) and displacement D. Data from 3 slices (apex, mid & base) were averaged by region. Results ± SD as shown:

	λ_1	λ_2	β (degrees)	D (mm)
Septum MI	1.05 ± 0.05*	0.89 ± 0.06*	35 ± 21*	3.7 ± 1.7
NI	1.17 ± 0.07	0.82 ± 0.04	8 ± 5	3.8 ± 1.0
Anterior MI	1.04 ± 0.05*	0.83 ± 0.08*	37 ± 24*	4.6 ± 2.1*
NI	1.09 ± 0.05	0.77 ± 0.08	15 ± 6	6.9 ± 1.7
Lateral MI	1.09 ± 0.05*	0.84 ± 0.06*	27 ± 21*	4.5 ± 2.1*
NI	1.15 ± 0.07	0.75 ± 0.05	7 ± 4	6.6 ± 1.8
Inferior MI	1.03 ± 0.05*	0.85 ± 0.08#	23 ± 16#	4.4 ± 2.5#
NI	1.09 ± 0.06	0.81 ± 0.07	16 ± 11	5.7 ± 1.9

*$p < 0.01$ versus normal. #$p < 0.05$ versus normal.

Following healed reperfused first anterior MI the magnitude *and* orientation of deformation are abnormal and displacement is reduced throughout the LV. This may reflect global changes in mechanical load or regional reorganization of myocardial architecture after infarct healing.

941-6 The Severity of Functional Mitral Regurgitation in Acute Myocardial Infarction Is Related to Left Ventricular Shape

Mohsin Alam, Omar Nass, Sidney Goldstein, Fareed Khaja, George Divine, Lois Graham, Steven Borzak, Howard Rosman, Hani N. Sabbah. *Henry Ford Heart and Vascular Institute, Detroit, MI*

The aim of the study was to examine the relationship between functional mitral regurgitation (MR) and left ventricular (LV) shape and function in the setting of acute myocardial infarction (MI). Two-dimensional echocardiogram with color flow Doppler studies were prospectively performed in 103 patients with first Q or non-Q wave MI within 48 hours of admission. The maximum mitral regurgitant jet by color flow was graded mild if the jet area < 20% of left atrial (LA) area, moderate if 20–40% of LA area, and severe if > 40% LA area. The left ventricular sphericity index was assessed based on the ratio of LV major-to-minor axis during end-systole (ESR) and end-diastole (EDR).

MR	No	EDR	ESR	EF (%)
None or Mild	81	1.9 ± 0.3	2.1 ± 0.5	52.3 ± 12.3
Moderate	18	1.6 ± 0.2	1.7 ± 0.3	53.6 ± 9.6
Severe	4	1.5 ± 0.2	1.3 ± 0.1	40 ± 12.5
Anova P-value		P = 0.01	P = 0.002	P = 0.116

In conclusion, This data indicates that in patients with acute myocardial infarction the degree of MR is related to sphericity of the left ventricle and not to ejection fraction.

941-7 Cardioprotection During Chemo- and Radiotherapy for Neoplastic Disease

Beat C. Aeschbacher, Philipp Wagdi, Martin Fluri, Anton Fikrle, Bernhard Meier. *Cardiology, University Hospital, Bern, Switzerland*

Objectives: To assess the cardioprotective value of an antioxidant regimen (AO), including N-acetylcysteine, vitamins E and C, in patients receiving high dose chemo- (CT) and/or radiotherapy (RT) for malignant disease.

Methods: Prospective, placebo (PL) controlled, randomized and double blinded pilot study involving 14 patients receiving CT and 12 patients receiving RT.

Results: The main results are shown (mean ± SD):

	All (n = 26)		CT (n = 14)		RT (n = 12)	
	AO	PL	AO	PL	AO	PL
Before	63 ± 4%	67 ± 6%	62 ± 2%	63 ± 5%	64 ± 6%	70 ± 8%
After	63 ± 4%	61 ± 6%	63 ± 2%	61 ± 5%	64 ± 5%	60 ± 4%
Diff	n.s.	$p < 0.05$	n.s.	n.s.	n.s.	$p < 0.05$
$\Delta > 10\%$	0% (0/13)	46% (6/13)	0% (0/6)	25% (2/8)	0% (0/6)	66% (4/6)

Before: Ejection fraction before chemo-/radiotherapy. After: Ejection fraction after chemo-/readiotherapy. Diff.: Difference between Before and After. $\Delta > 10\%$: Ejection fraction decreased more than 10%

No patient in the AO group showed deterioration of ejection fraction of more then 10%. The ejection fraction of the whole study population and all subgroups receiving AO did not decrease significantly.

Conclusion: Our results suggest efficient cardioprotection by this non-toxic, inexpensive, and well tolerated antioxidant drug combination of N-acetylcysteine, and vitamins E and C. Initiation of larger confirmatory studies is strongly encouraged by these promising results. The small number of patients in this pilot study precludes a definitive statement.

942 Autonomic Function in Heart Failure

Tuesday, March 26, 1996, 9:00 a.m.–11:00 a.m.
Orange County Convention Center, Hall E
Presentation Hour: 10:00 a.m.–11:00 a.m.

942-61 MIBG Assessment of Sympathetic Nervous System Activation in Congestive Heart Failure

Michael W. Dae, Dong-Wei Gao, Carole Stillson, J. William O'Connell, Elias H. Botvinick, Philip C. Ursell. *University of California, San Francisco, CA*

Whether reduced myocardial norepinephrine (NE) and elevated plasma NE in CHF are due to activation of the SNS or abnormal neuronal uptake remains controversial. To address this problem, we studied the uptake and washout kinetics of I-125 MIBG in rabbit hearts with moderate CHF (echo fractional shortening 27% vs 47% in controls, $p < 0.02$). Nonneuronal uptake of MIBG is absent in rabbit hearts, as in humans. Hence, early uptake of MIBG reflects neuronal localization. CHF was induced by the injection of 1 mg/kg of adriamycin (ADR) twice a week for 8 weeks. ADR treated rabbits (n = 12), and control rabbits (n = 8) were anesthetized, ventilated, and the heart was imaged for three hours using a pinhole collimator, following the injection of 770 ± 90 uCi I-125 MIBG. The hearts were then excised and biopsied for tissue NE, tissue MIBG, and sympathetic nerve histology. Image data was analyzed for heart to mediastinal ratio (Ht/Med) at 15 minutes (early), 3 hours (late), and MIBG washout (W/O). Arterial blood was sampled for plasma NE. ADR treated hearts showed the following results relative to control hearts:

Ht/Med (early)	Ht/Med (late)	MIBG W/O	MIBG Tissue	NE Tissue	NE Plasma
−0.2%*	−30%**	+28%**	−50%#	−47%#	+129%#

*p = ns, **$p < 0.01$, #$p < 0.05$

Sympathetic nerve morphology was normal. Initial MIBG uptake was normal in CHF, suggesting preserved neuronal uptake, while MIBG washout was enhanced, consistent with activation of the SNS. Activation of the SNS results in decreased MIBG over time, which correlates with decreased tissue NE and elevated plasma NE. MIBG imaging allows noninvasive assessment of dynamic changes in SNS activity in CHF, and may help to monitor the effects of therapy.

942-62 Differential Effects of Captopril and Hydralazine on Autonomic Function in Cardiac Failure

Nicholas E.R. Goodfield, Susanna J. Leiper, Keith A.A. Fox, Andrew D. Flapan. *Royal Infirmary, Edinburgh, UK*

ACE inhibitors and hydralazine (H) improve prognosis in patients with cardiac failure by slowing disease progression. In the VHEFT II and HY-C trials, ACE inhibition exhibited an advantage over H by reducing the incidence of sudden death. One possible mechanism to explain this would be differing effects on autonomic tone.

We examined autonomic function following an oral dose of captopril 6.25

mg (C) or H 25 mg. In a randomised cross-over study, nineteen patients with cardiac failure (NYHA II–III, LVEF < 40%) underwent standard autonomic function tests (AFT) before and one hour after drug administration. This was repeated the following day with the alternate drug.

Results:

	Pre H	Post H	Pre C	Post C
Valsalva Ratio	1.23	1.25	1.26	1.23
Postural ΔHR (30/15 ratio)	1.09	1.19	1.17	1.09
Respiration ΔHR (bpm)	8.26	10.9**	9.06	12.06***
Posture ΔBP (mmHg)	−3.1	−6.3	−6.7	−6.5
Handgrip ΔBP (mmHg)	14.9	15.1	13.5	16.9*
AFT Score§	4.6	4.4	4.7	3.7**

*P < 0.05, **p < 0.02, ***p < 0.01. § each test is scored, normal = 0, borderline = 1, abnormal = 2. AFT score = sum of scores for patient

H and C have differing effects on the autonomic nervous system. C improves both sympathetic and parasympathetic function, in contrast to H which exhibits no effect on the sympathetic component and a less marked effect on the parasympathetic component. This may contribute to the reduction in sudden death seen with ACE inhibition in the VHEFT II and HY-C studies.

942-63 Effects of Digitalis and Angiotensin Converting Enzyme Inhibitors on Postexercise Vagal Reactivation in Patients With Chronic Heart Failure

Katsuji Imai, Masashi Naka, Naokazu Kinoshita, Hideyuki Sato, Yukihiro Koretsune. *Osaka Minami National Hosp., The First Dept. of Med., Osaka Univ., Osaka, Japan*

We have reported that the rapid heart rate (HR) recovery within 30 sec after exercise is mediated by vagal reactivation, and that this mechanism is impaired in patients with chronic heart failure (CHF). The blunted vagal reactivation may exert harmful effects on the failing heart by slowing HR recovery and by increasing myocardial oxygen consumption. Digitalis and converting enzyme inhibitors have vagomimetic actions. To investigate the effects of these drugs on postexercise vagal reactivation, we obtained the time constant of the HR decay for 30 sec after exercise (T30) under following three conditions in 10 patients with CHF and in 8 normal subjects: 1) baseline exercise at the anaerobic threshold (AT) level, 2) exercise at AT with a single intravenous administration of 0.25 mg of digoxin, and 3) exercise at AT with a single oral administration of 12.5 mg of captopril. The exercise tests were randomly performed at 1-week intervals. When compared with baseline data, T30 was significantly shortened by digoxin (182 ± 62 to 124 ± 30 sec, $p < 0.05$), but it was unaffected by captopril (170 ± 53 sec) in normal subjects. In patients with CHF, T30 was significantly shortened by both digoxin and captopril (285 ± 176 to 190 ± 52 and to 171 ± 114 sec, respectively, $p < 0.05$). Thus, digoxin accelerated postexercise vagal reactivation probably via a direct action on the central nerve system, independent of the presence of CHF. In contrast, captopril accelerated vagal reactivation solely in patients with CHF probably via an indirect action such as inhibition of neurohumoral activation. The beneficial effects of digitalis and converting enzyme inhibitors on chronic heart failure may be attributed partly to acceleration of postexercise vagal reactivation.

942-64 Cardiac Sympathetic Neuronal Activity and Function in the Early Phase of Left Ventricular Volume and Pressure Overload

G. Aernout Somsen, Eric A. Dubois, Kor Brandsma, Jan de Jong, Poll A. van der Wouw, Harry D. Batink, Eric A. van Royen, Kong I. Lie, Pieter A. van Zwieten. *Dept. of Cardiology and Pharmacotherapy, Academic Medical Centre, Amsterdam, the Netherlands*

Chronic cardiac overload gives rise to increased cardiac sympathetic activity and depressed neuronal function. In this study we evaluated the short term effects of cardiac overload on cardiac sympathetic neuronal activity (β-adrenoceptor density (Bmax)/myocardial noradrenaline concentration (NA)) and function ([123I]-metaiodobenzyl-guanidine (MIBG) uptake) in a rabbit model.

In nine rabbits (group 1) volume overload (aortic valve perforation) and pressure overload (banding of the abdominal aorta) was induced in a two stage surgical procedure. Five animals were sham operated (group 2). Echocardiography was performed at baseline and two weeks after the second operation. Three weeks after the last operation, 90 minutes after injection of 50 μCi [123I]-MIBG, the animals were killed.

Conclusion: Although cardiac sympathetic activity is increased, neuronal function is preserved in early cardiac overload. Therefore, pharmacological reduction of this increased cardiac sympathetic drive may be beneficial in early phase of cardiac overload, even when heart failure is not overt.

	Group 1	Group 2	p
LV/body weight ratio (× 10^{-3})	2.75 ± 0.29	1.89 ± 0.13	<0.003
LV-enddiastolic diameter	1.57 ± 0.15	1.35 ± 0.17	<0.05
LV-fractional shortening	38.2 ± 5.7	36.9 ± 8.2	n.s.
Bmax (fmol/mg protein)	167 ± 36	224 ± 38	<0.03
Myocardial NA (ng/g)	1004 ± 394	1643 ± 109	<0.02
[123I]-MIBG (% ID/g × kg)	2.2 ± 0.58	1.8 ± 0.44	n.s.

LV = left ventricular, ID = Injected Dose

942-65 Role of Nitric Oxide in Parasympathetic Modulation of β-Adrenergic Inotropic Responses in Humans With Heart Failure

Joshua M. Hare, Michael M. Givertz, Mark A. Creager, Wilson S. Colucci. *Brigham & Women's Hospital, Harvard Medical School, Boston, MA11*

Nitric oxide synthase (NOS) activity, which is increased in failing human myocardium, influences parasympathetic regulation of myocardial contractility and chronotropy in cardiac myocytes and in normal dogs. The effect of NOS activity on parasympathetic antagonism of β-adrenergic contractility has not been studied in patients. Accordingly, we assessed the effect of the muscarinic agonist acetylcholine on the positive inotropic response (+dP/dt) to the β-adrenergic receptor agonist dobutamine (DOB), before and after inhibition of NOS in 8 patients with heart failure (HF) and 7 normals (NLS). DOB was infused intravenously before and during intracoronary infusion of acetylcholine (10^{-6} M). This was repeated during intracoronary infusion of the NOS inhibitor N^G-monomethyl-L-arginine (L-NMMA, 20 μmol/min for 10 min). DOB alone increased +dP/dt by 40 ± 6 and 73 ± 14% in HF and NLS, respectively ($p < 0.02$, HF vs. NLS). Intracoronary acetylcholine inhibited the response to DOB by 39 ± 8 and 31 ± 4% in HF and NLS, respectively ($p < 0.001$ for each). With coinfusion of L-NMMA, the cholinergic inhibitory effect was reduced by 50 ± 16% ($p < 0.02$) to 21 ± 8% in HF, but was not affected in NLS (32 ± 5%). Thus, NO plays a role in modulating the inotropic effects of acetylcholine in HF, but not NLS. This may reflect increased expression of NOS in failing myocardium.

942-66 Heart Rate Variability in Chronic Heart Failure. Is it an Index of Autonomic Tone or a Marker of Respiratory Rhythm Disorders?

Andrea Mortara, GianDomenico Pinna, Roberto Maestri, Alexander Prpa, Franco Cobelli, Luigi Tavazzi. *Division of Cardiology, "S.Maugeri" Foundation, IRCCS, Montescano, Pavia, Italy*

Cheyne-Stokes respiration (CS) and periodic breathing (PB) have been described as frequent events in pts with chronic heart failure (CHF) both during day- and night-time. To address the relationship between breathing disorders and modulation of heart rate, 40 pts with mild to moderate CHF (mean age 51 ± 9 yrs, LVEF 27 ± 8, NYHA cl. I-III, stable therapy within two weeks) underwent simultaneous 20' recordings of RR intervals, instantaneous lung volume (ILV), beat-to-beat arterial oxygen saturation (SaO2, ear probe) at baseline (B) and during controlled breathing (CB, 12 breaths/min). Fourteen pts showed a normal respiratory pattern (NB), while 26 pts had a persistent alteration of breathing with a typical CS in 8 (20%) and PB in 18 pts (45%). At baseline PB and CS, but not NB, exhibit a dominant oscillation in the very low frequency band (VLF, 0.01–0.03 Hz) in ILV and SaO2 which were highly coherent with VLF oscillation in RR. Controlled breathing eliminated PB and CS in all pts with a significant increase in SaO2 (PB = +1.1%, $p < 0.01$, CS = +2.5%, $p < 0.001$). Changes in RR interval (RR), Total Power (TP) and VLF Power (VLF) from B to CB are reported in the table. No differences were observed in LF and HF power.

	RR (B) (ms)	RR (CB) (ms)	TP (B) (ms^2)	TP (CB) (ms^2)	VLF (B) (ms^2)	VLF (CB) (ms^2)
NB	885 ± 194	887 ± 196	515 ± 361	589 ± 654	306 ± 224	339 ± 217
PB	820 ± 126	818 ± 112	744 ± 680*	489 ± 654	576 ± 709*	324 ± 480
CS	841 ± 147	837 ± 185	841 ± 897*	291 ± 251	766 ± 860*	207 ± 189

*p < 0.01

In conclusion abnormalities of breathing activity are very frequent in CHF and produce wide oscillations in the VLF band both in SaO2 and RR interval signals. The voluntary control of ventilation abolishes Cheyne-Stokes and periodic breathing thus causing a dramatic reduction of VLF power and total heart rate variability. These data support the hypothesis that a strong cardiorespiratory rhythm exists in CHF and suggest caution to relate the amount of HRV directly to autonomic tone.

TUESDAY POSTER