MECHANISM OF LOW OUTPUT IN EXPERIMENTAL RIGHT VENTRICULAR INFARCTION. James A. Goldstein, MD, Gus J. Vlahakes, MD, Edward D. Verrier, MD, Nelson Schiller, MD, FACC, John V. Tyberg, MD, PhD, FACC, Kanu Chatterjee, MD, FRCP, FACC. Cardiovascular Res. Inst., Univ. of Calif., San Francisco.

RV infarction (RVI) can result in decreased CO. To elucidate the mechanism involved, selective RVI was produced in 15 dogs with the pericardium intact. CO, intrapericardial pressure (IPP) and RV and LV pressures were measured; stroke work (SW) and end-diastolic transmural pressures (TM) were calculated. Data were obtained before (Control) and after RVI and after subsequent pericardiotomy.

mean ± SEM	Control	RVI	Pericardiotomy
CO ($L \cdot min^{-1}$)	2.0±0.6	† 1.3±0.5	‡ 1.8±0.5
RV SW ($g \cdot m \cdot m^{-2}$)	5.3±2.7	† 2.1±1.5	3.3±1.1
RV TM (mm Hg)	1.0±1.3	* 1.7±1.8	†† 6.2±1.6
LV SW ($g \cdot m \cdot m^{-2}$)	25.9±10.1	† 11.8±6.8	** 21.2±6.0
LV TM (mm Hg)	4.6±1.8	† 2.0±1.9	†† 9.2±2.8
IPP (mm Hg)	4.7±1.5	† 7.6±1.8	†† 0±0

Analysis of variance: Control vs RVI: *P<0.05, †P<0.001; Pericardiotomy vs RVI: ‡P<0.05, **P<0.005, ††P<0.001.

RVI resulted in RV failure as evidenced by decreased RV SW despite increased RV TM; LV SW decreased concomitantly with reduced LV TM, suggesting that low CO resulted from reduced LV preload. Two-dimensional echocardiography demonstrated marked RV dilatation and decreased LV size. IPP increased and equalization of ventricular diastolic pressures was noted. Subsequent pericardiotomy increased LV SW, LV TM, CO, and RV TM, with resolution of ventricular diastolic pressure equalization.

Low CO in RVI is due primarily to reduced LV preload resulting, in part, from depressed RV function. Elevated IPP, resulting from RV dilatation, further reduced LV preload and produced diastolic pressure equalization. Pericardiotomy improved LV filling and hence increased CO. The pericardium may thus play an important role in the pathophysiology of low CO in RVI.

TUESDAY, MARCH 17, 1981
PM
PHARMACOLOGY: CONCEPTS IN THERAPY OF VENTRICULAR ARRHYTHMIAS
4:00-5:30

CHRONIC INTRAVENOUS INFUSION OF ANTIARRHYTHMIC DRUGS USING A TOTALLY IMPLANTED DRUG DELIVERY SYSTEM
Jeffrey L. Anderson, MD, FACC; Richard P. Donahue, BS; Marilyn E. Conlon, MA; Stanislaw Pasyk, MD; Phillip L. Stetson, PhD, MD; Arthur B. Simon, MD; William E. Burmeister, PhD; Elton M. Tucker, BS; Bertram Pitt,MD, FACC. University of Michigan, Ann Arbor, MI.

The success of antiarrhythmic therapy is in part limited by an inability to maintain therapeutic steady state plasma concentrations (Css) over time. A totally implantable, self-powered drug delivery system ("Infusaid", Metal Bellows Co., Sharon, MA) has recently become available. In order to establish the feasibility of this system to chronically deliver therapeutic doses of selected antiarrhythmic agents, we subjected it to both in vitro and in vivo testing. The Infusaid pump consists of a hollow titanium disk separated into 2 chambers by a bellows and powered by pressure of fluorocarbon vapor at 37°C. Pressure on the bellows forces infusate from the reservoir (35 or 50ml) at a constant rate through a filter and fine-bore silastic catheter positioned in the vena cava. During 3 months in vitro testing, procainamide (P), and bretylium (B), were found suitable for chronic delivery. Delivery of lidocaine (35%,70%) was limited by high viscosity and corrosion of steel elements. In vivo feasibility studies in dogs lasting 2 weeks were carried out with P and B. The pump was placed in a subcutaneous abdominal pocket in 4 animals. P (0.5 g/ml), delivered at 4 ml/d (70 mg/kg/d), provided mean Css of 5.3 mcg/ml. Css was attained by 8-24 hr. B (50 mg/ml), delivered at 8 ml/d (13 mg/kg/d), provided Css of 0.80 mcg/ml (range 0.41-1.49 mcg/ml). Css was attained by 24-48 hr. In contrast, oral B resulted in mean Css of only 0.19 mcg/ml in patients. In conclusion, chronic intravenous delivery of therapeutic B and P is feasible and suggests further study in man.

EARLY AND LATE PROTEOLYSIS IN ACUTE MYOCARDIAL INFARCTION
Roberto Bolli, MD, Richard O. Cannon, MD, Robert E. Goldstein, MD, FACC, Stephen E. Epstein, MD, FACC, NHLBI, Bethesda, Md.

Lysosomal proteases have been thought to play an important role both in the production and in the healing of acute myocardial infarction (AMI). However, the changes in proteolysis (PR) occurring in the evolution of AMI are unknown. Thus, control (C) rats underwent coronary artery occlusion (O); 2,6,24,48 and 72 hrs after O, slices were obtained from ischemic (IZ), normal (NZ) or border zone (BZ) myocardium and incubated for 1 hr in oxygenated or in anoxic Krebs-Ringer-HCO_3^- buffer. Cycloheximide was added (.5mM) to block protein synthesis. PR was measured by net tyrosine production (pmol/mg tissue, mean ±SE):

	2hrs(n=17)	6hrs(n=7)	24hrs(n=9)	48hrs(n=8)	72hrs(n=21)
NZ	92±13	-	86±11	102±16	114±8
BZ	-	-	192±31	401±46*	394±27*
IZ	77±7	33±11**	98±11***	262±23***	249±23***

(*=p<.02 vs 24hrs;**=p<.01 vs 2hrs;***=p<.001 vs 6 hrs) Thus, in AMI, PR follows a biphasic pattern: it decreases early, when irreversible damage develops, and later increases markedly both in the BZ and in the IZ, concomitant with the infiltration of inflammatory cells. To test the concept that this late rise in PR could be important in the healing of AMI, we gave methylprednisolone 50 mg/kg i.v. to 6 rats at 5 min after O and 50 mg/kg i.m. at 3,6,24 and 48 hrs after O: at 72 hrs PR both in BZ (225±56) and IZ (170±17) was significantly decreased ($p < .02$) relative to C. This inhibition of late PR may contribute to impaired healing of AMI reported when this steroid dose is given to rats. Our data suggest that lysosomal and, more generally, cellular proteases do not contribute to ischemic cell death but may play an important role in the healing phase of AMI.

EFFECT OF PROSTACYCLIN ON VENTRICULAR ARRHYTHMIAS AND INTRACARDIAC CONDUCTION IN MYOCARDIAL ISCHEMIA
Thomas L. DeBauche, M.D., Tedd A. Brandon, B.S., Lair G.T. Ribeiro, M.D., Kevin Holyfield, Richard R. Miller, M.D., FACC, Baylor College of Medicine, Houston, Texas

Several of the prostaglandins have been shown to possess antiarrhythmic properties. To elucidate the effects of prostacyclin (PGI_2) on ventricular (V) ectopy in acute ischemia, 29 dogs undergoing proximal left anterior descending coronary artery occlusion (CAO) were randomized to PGI_2 (n=12) or control (C) (n=17). Occlusion site was equal (p=ns) in both groups. All had continuous ECG recordings and 11, His bundle electrography. PGI_2, .5-2.0 µg/kg/min began 15 min pre-CAO and continued 30 min post-CAO. Post-CAO, V ectopic beats per 1000 beats were reduced by PGI_2: C, 160±49; PGI_2, 63±27, (-60%; p<.02). V tachycardia (tach) episodes were similar: C, 24 in 17 dogs; PGI_2, 14 in 12 dogs (p=ns). However, in C, V tach resulted in V fibrillation in nine animals (53%) vs one (8%) in PGI_2 (p<.02). V tach features were examined: duration, C, 14±14 (SD) beats vs PGI_2, 6±10 (p=ns); cycle length, C, 203±49 msec vs PGI_2, 317±75 (p<.02). PGI_2 did not alter sinus rate (153±8 to 149±9 bpm) or HV intervals (36±2 to 35±2 msec) (both p=ns); AH was shortened 79±5 to 70±6 msec (p<.05). In eight dogs given a nitrate to lower BP equal to PGI_2, AH was unchanged. Thus, PGI_2 reduces total ventricular ectopy and tends to shorten AH conduction in acute myocardial ischemia. Of particular interest, PGI_2, while not preventing the occurrence of ventricular tachycardia, increases the V tach cycle length and attenuates the progression to ventricular fibrillation. Thus, PGI_2, in acute myocardial ischemia, markedly reduces the occurrence of ventricular fibrillation and mortality during the first 30 minutes following coronary artery occlusion.