DEVELOPMENTAL CHANGES IN THE EFFECTS OF AMRINONE ON CARDIAC CONTRACTION. Ofer Binah PhD; Peter Danilo Jr, PhD; Michael R. Rosen MD, FACC, Columbia University, New York, NY

Previously we have shown that in isolated cardiac muscle from newborn canine hearts, amrinone (A) has a slight negative inotropic effect, whereas in hearts from 3 month and older dogs A is positively inotropic. To test whether there is an age-related differential effect of A on contractility in the in situ heart, we infused A (0.3, 1, 3 and 10 mg/kg IV) into pentobarbital anesthetized dogs aged 0-2 days (Grp I); 3 months (Grp II); and 5 yrs (Grp III). For all animals we recorded a lead II ECG, aortic pressure and left ventricular dP/dt. Maximum effects of A occurred at 10 mg/kg. In the following table they are presented as % change from control. (*) indicates $P<.05$ compared to control.

	Grp I (n=6)	Grp II (n=4)	Grp III (n=4)
Syst BP	-30±5*	-18±4*	-21±5*
Diast BP	-40±5*	-48±2*	-62±2*
Pulse pres.	-20±6*	+32±11*	+136±17*
dP/dt	+11±9	+95±30*	+172±20*
ECG			
R-R	-20±4*	-7±2	-21±1*
P-R	-2±3	-14±4	-11±2*
Q-T_C	+0.3±5	-7±2	-4±2
QRS	-2±4	+4±2	+4±2

We conclude that in the intact dog, as in isolated muscle, A has a positive inotropic effect at age ≥ 3 months. This is seen as an increased dP/dt and pulse pressure. In the newborn, however, A is not positively inotropic. Our results in intact dogs are consistent with those in isolated muscle and suggest that the positive inotropic effect of A is age-related, and that greater benefit from this drug may accrue in older than in very young patients.

ALTERED PLATELET ALPHA$_2$ ADRENORECEPTORS IN CONGESTIVE HEART FAILURE

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The alpha$_2$ adrenoreceptor located upon noradrenergic neurons regulates the release of neurotransmitter. This receptor is also present upon human blood platelets. Drugs and procedures which increase neuronal norepinephrine (NE) release recently have been shown to decrease the number of alpha$_2$ receptors on platelet membranes. It is not known whether such changes are the result of increases in circulating NE levels. Patients with chronic congestive heart failure (CHF) are known to have increased levels of circulating NE. The purpose of the present study was to determine the status of platelet alpha$_2$ adrenoreceptors in these patients. Twenty subjects (10 normal volunteers and 10 patients with CHF as diagnosed by clinical and invasive monitoring) were studied. Specific, high-affinity binding of the alpha$_2$ receptor antagonist ^{3}H-yohimbine to isolated platelet membranes was used to determine the number (B_{max}) and dissociation constant (K_D) of alpha$_2$ receptors. In the control population the B_{max} was 188 ± 12 (SEM) fmole/mg protein and the K_D was 3.0 ± 0.1 nM. There was about a 32% decrease in the B_{max} in patients with CHF ($P<.0025$) but no change in K_D (3.2 ± 1.0 nM). This study supports the hypothesis that increased levels of circulating catecholamines in CHF leads to decreases in platelet alpha$_2$ adrenoreceptors. If similar changes occur on noradrenergic nerve terminals, the use of alpha$_2$ agonists to decrease circulating NE levels in this disease might be affected adversely. It also raises the possibility that there is decreased platelet aggregation in response to epinephrine in CHF.

SEROTONIN BLOCKADE IN THE TREATMENT OF CARDIAC FAILURE.

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Serotonin, which is released by platelets, is a potent vasoconstrictor ; it also enhances the vascular effects of catecholamines and angiotensin as well as the platelet aggregation induced by adrenaline. Since heart failure is attended by high catecholamine blood levels and enhanced platelet aggregation, serotonin might play a role in this condition. Ketanserin (K) selectively blocks 5-HT$_2$ (serotonin) receptors. K was administered IV (10 mg/in 3 min) to 8 patients with cardiac failure already treated with digitalis, frusemide, and, in 4 cases, vasodilators (cardiac index < 2.5 l/min/m2 and/or pulmonary wedge pressure > 18 mm Hg). K induced a short- lived (15-30 min), but significant ($p < 0.05$) fall in right atrial (-40 %), pulmonary artery (-25 %), pulmonary wedge (-30 %) and mean systemic arterial (-17 %) pressures. Systemic dynamic (-18 %) and total pulmonary vascular (-28 %) resistances were also reduced. Heart rate was unchanged. Cardiac index increased (+ 15 %). The platelet aggregate ratio, measured in 2 patients, was initially low indicating enhanced aggregation (0.47 and 0.53 ; normal values : 0.88 + 0.07) ; it was partially or totally corrected 15 min after K administration. In 4 additional cases, K did not decrease the blood pressure response to phenylephrine perfusion (50, 100 and 200 µg/min consecutively, each during 4 min), thus confirming the absence of α -lytic effect.
Conc. : 1) The role of serotonin in cardiac failure and 2) the possible beneficial effects of K in this condition deserve further attention.

ACUTE EFFECTS OF ADRIAMYCIN ON CONTRACTION OF CULTURED HEART CELLS.

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To quantify the acute effects of adriamycin on the function of isolated cardiac myocytes we have monitored electrooptically the contraction of cultured chick embryo ventricular cells. Cultures were exposed to adriamycin concentrations varying from 10^{-7} to 10^{-4} M and observed continuously for 6 hours. Individual cell wall motion, velocity, and frequency of contraction were analyzed from strip chart recordings. At high doses (10^{-4} and 10^{-5} M) cell function deteriorated by 3 hours to <25% of baseline values. At low doses (10^{-6} and 10^{-7} M) frequency of contraction increased slightly but approached baseline values by 6 hours. Cell wall motion in 10^{-6} M decreased significantly ($p<0.001$) at 2.5 hours, but returned to baseline by 6 hours. Velocity of contraction in 10^{-6} M decreased significantly ($p<0.05$) to 75% of baseline and did not recover by 6 hours. Motion and velocity were not affected significantly by exposure to 10^{-7} M adriamycin over the 6-hour observation period. Dose-response curves for all 3 functional parameters showed a threshold effect between 10^{-6} and 10^{-5} M, with decreasing function for increasing doses. We conclude that the acute effects of adriamycin on cultured heart cell wall motion are: a) direct, b) quantifiable, c) dose-dependent, and d) observable at concentrations as low as 10^{-6} M.