HYPOTENSIVE RESPONSE TO VASOPRESSIN INHIBITION IN CONGESTIVE HEART FAILURE DOGS AFTER AREA POSTREMA ABLATION

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Acute administration of arginine vasopressin has been shown to decrease sympathetic nervous system tone through the area postrema (AP) of the hindbrain. However, the effect of chronic elevation of vasopressin through the AP upon the sympathetic nervous system in the intact animal is unknown. Therefore, we used a vasopressin V1 inhibitor (VPI) to determine the physiologic effect of chronically elevated vasopressin in AP-ablated (N=8) and sham-ablated (N=5) congestive heart failure (CHF) dogs. CHF was produced by tricuspid avulsion and pulmonary artery constriction. Mean AO pressure (mmHg), LV dP/dt (x10^{3}mmHg/sec), and CO (L/min) at baseline and for 30 min after VPI were (mean±SE):

Ablation		Mean AO	LV dP/dt	CO
Sham	Baseline	102±6	25±2	3.5±0.5
	VPI	106±7	27±3*	4.0±0.4*
AP	Baseline	100±6	23±2	3.1±0.4
	VPI	94±3**	24±2	3.0±0.3

*p<0.05 versus sham baseline, **p<0.05 versus AP baseline

Thus, VPI caused an increase in LV dP/dt and CO in CHF dogs without a decrease in AO pressure. AP ablation abolished the increase in CO and LV dP/dt and produced a depressor response to VPI. The results are consistent with the increase in LV function after VPI being mediated through the AP and further suggest that chronic elevations of vasopressin may decrease LV function in CHF through an interaction with the AP of the hindbrain.

POSITIVE INOTROPIC THERAPY: MECHANICS AND ENERGETICS IN SEVERE HEART FAILURE. A ^{31}P MRS STUDY.

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The aim of the study was to assess the effect of dobutamine (DOB), amrinone (AMR), dibutyryl-cyclic AMP (AMP) and digoxin (DIG) on mechanical performance, high energy phosphate metabolism assessed by ^{31}P MRS, phosphorylation potential (PP) and myocardial oxygen consumption (MVO_2) in cardiomyopathic hamster hearts with advanced heart failure. Using a Langendorff preparation, rate-pressure product (RPP), inorganic phosphorus (Pi), phosphocreatine (PCr), ß-adenosine triphosphate (ATP) and MVO_2 were monitored during control conditions and positive inotropic therapy.

	RPP	ATP	PP	MVO_2
	[bpmxmmHgx10^3]	[mM]		[µM/g/min]
Control (n=9)	13.3±1.9	6.5±0.4	3.65±0.09	20.3±2.8
DOB (n=7)	18.2±4.4	5.8±0.7	3.38±0.09	26.6±2.2
AMR (n=6)	47.7±5.2**	9.5±0.6*	4.17±0.04*	30.0±2.0*
AMP (n=6)	59.6±6.1**	6.6±0.3	3.82±0.09	29.4±2.2*
DIG (n=6)	8.0±1.1*	7.4±0.2	4.04±0.16	29.6±2.3*

* = p<0.05, ** = p<0.005

Despite an increase of mechanical performance and MVO_2, high energy phosphate metabolites improved during administration of AMR in this cardiomyopathic hamster model. Correlation between RPP and MVO_2 was r=0.85. Correlation between RPP and PP was moderate in normal hearts (r=0.48) and poor in cardiomyopathic hearts (r=0.31). Therefore, agents which increased cAMP, but not necessarily high energy phosphate metabolites, improved RPP and MVO_2 in failing hearts. Positive inotropic agents such as dobutamine and digoxin did not cause an increase in RPP or MVO_2 and thus, had an adverse effect on the failing heart. Amrinone improved the over-all state of the failing heart.

DOPPLER DIASTOLIC FLOW IN COMPENSATED AND FAILING CANINE HEARTS WITH PRESSURE-OVERLOAD HYPERTROPHY.

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To evaluate the changes in LV size and diastolic function during the gradual development of LV hypertrophy and to identify early markers of LV failure we placed an aortic band on 4 puppies 8-weeks-old (B) and compared with 3 normal age-matched puppies (N); serial M-mode, 2-D echo and Doppler studies were performed during the following 30 weeks.

Results: Starting from week 10 after banding all B significantly increased LV mass (vs N p<.05). 2 B significantly (vs N p<.05) increased LV internal diameter, LV weight/body weight, isovolumic relaxation time and E wave slope, decreased E wave deceleration time and developed signs of failure. No differences were found in Doppler E and A wave velocities, E/A ratio, or in the atrial contribution to total filling between B and N.

In conclusion: the development of LV hypertrophy is not related to alterations in Doppler filling parameters, however, development of cardiac failure and LV dilation is associated with significant changes in E wave deceleration time and slope.

IMPROVED HEMODYNAMIC FUNCTION IN CONGESTIVE HEART FAILURE WITH THE METABOLIC AGENT SODIUM DICHLOROACETATE (DCA)

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Sodium dichloroacetate (DCA) is an investigational agent which stimulates pyruvate dehydrogenase (PDH) activity and thereby enhances glucose and lactate utilization by cardiac muscle. To determine whether enhanced substrate utilization with DCA improves mechanical performance in patients with heart failure (CHF), we administered DCA (50 mg/kg) to seven patients with Class IV CHF and measured net myocardial lactate utilization, oxygen consumption and indices of myocardial mechanical performance. At baseline, the HR, RA, PA, PCW, and SVR were elevated and the cardiac index was low (2.0 L/min/M2). With DCA, the HR, RA, PA and PCW did not change, but the cardiac index rose (from 2.01 to 2.21, p=.034) and SVR fell (from 1364 to 1249, p=.016). Myocardial oxygen consumption was elevated at baseline (15.5 ml O2/min) and fell with DCA to 12.0 (p=.01) as the LV stroke work index increased (from 16.1 to 17.0, p=.02). LV mechanical efficiency thus increased (from 39.5 to 50.5, p=.012). The peak effects of DCA at 60 min were then compared to those of dobutamine at clinically optimal doses (5-10 µg/kg/min IV) in the same patients:

	DCA	Net Δ	Dobut	Net Δ	DCA v Dobut
% lactate extraction	41.4	+18.7	7.3	-17.8	p=.041
cardiac index	2.21	+0.20	2.25	+0.49	NS
stroke volume index	24.1	+2.3	24.1	+3.2	NS
LVSWI	17.0	+1.6	16.1	+2.0	NS
MVO2	12.0	-3.5	16.2	+0.6	p=.037
LV Mech Efficiency	50.5	+11.0	25.6	+3.7	p=.051

Thus, DCA augments LV systolic performance to the same degree as dobutamine but with the advantage of a much lower energy cost (MVO2). The improvement in mechanical performance and efficiency with DCA appears to be related to enhanced substrate utilization.