TITLE: THE COMBINED CARDIOVASCULAR EFFECTS OF AMRINONE AND DOBUTAMINE

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Introduction. For management of patients with severe heart failure, the choice of the appropriate intoropic agent is dependent upon the patient's clinical condition. Therefore, the different mechanisms of action of Amrinone (Am) and Dobutamine (Db) on the myocardial cell (selective phosphodiesterase fraction III inhibition vs. direct myocardial β_1 receptor stimulation) and recent reports that amrinone potentiates the effects of adrenergic drugs suggest that synergism may occur.[1,2]

Methods. To test this hypothesis 12 dogs were anesthetized with fentanyl, monitored for arrhythmias, ventilated via endotracheal tube with positive pressure ventilation, and instrumented to provide hemodynamic data. Cardiac output, stroke volume, left ventricular stroke work, pulmonary vascular resistance, and systemic vascular resistance were indexed according to the body surface area: CI, SVI, LVSWI, PVRI, and SVRI, respectively. In Group 1 (6 dogs), control hemodynamics values were obtained, then Db was added via a volumetric infusion pump in increments of 2.5 mcg/mg/min to a total of 10 mcg/mg/min. Then, Am with an initial 0.75 mg/kg bolus, and an incremental infusion of 2.5 mcg/mg/min to a total of 10 mcg/mg/min was added to the dobutamine infusion, noting the hemodynamic parameters at each increment. In Group 2 (6 dogs), a similar protocol was performed, except Am was initially infused followed by similar incremental concentrations of Db.

Statistical analysis was with 2-way ANOVA and 1-way ANOVA, with Duncan's a posteriori multiple range test. Significance was $p < 0.05$.

Results. The prime objective of this study was to determine if combination therapy was synergistic. By using equi-potent concentrations of Am and Db, 2-way ANOVA demonstrated no drug interaction at any drug level or with any hemodynamic parameters.

Group I (Dobutamine)

As shown in the table, with increasing inotropic support, HR and MAP increased by 39%* and 16%*, respectively. While the CVP, MPAP, and SVI were essentially unchanged. Prominent vasodilatation was evident, with a decrease of PCWP, PVRI, and SVRI by 24%*, 20%*, and 25%*, respectively. Hemodynamic parameters indicating increasing inotropy were also elevated. CI, LVSWI, and peak positive LV dP/dt were increased by 42%*, 30%*, and 48%*, respectively.

Group 2 (Amrinone)

Also, as shown in the table, with increasing inotropic support, the HP and CVP remained essentially unchanged, while the MAP increased by 38%*. There was prominent pulmonary vascular constriction. The MPAP, PCWP, and PVRI were increased by 33%*, 43%*, and 38%*, respectively. In addition, significant systemic vasoconstriction was evident with a 57%* increase in SVRI. While, hemodynamic parameters indicating increasing inotropy show a 25%* increase in peak positive LV dP/dt and a 44%* increase in LVSWI. CI and SVI showed an initial increase, but declined 7% and 4% with maximal support.

Discussion. The quest for the optimal timing and choice of combination inotropic support is controversial. Previous investigators have described Am and Db hemodynamic properties but this research design elucidated interesting results associated with an agent when added to another inotropic agent.[1,2] As shown in Group 1, when Am is added to Db, there was significant preload and afterload reduction with an increase in CI as the SVI remained unchanged. In Group 2, when Db is added to Am, there was significant preload and afterload constriction with a diminished CI and SVI. In both groups it appears that the change in CI is based on the state of vascular tone rather than SVI. Also, in each group, LVSWI and peak positive LV dP/dt were elevated, but less so in the amrinone group. The mode of action of elevated vascular tone is not clear. Therefore, according to the 2-way ANOVA test, the lack of interaction between these two agents implies two different mechanisms of action independent of each other, additive, but not interactive.

* $p < 0.05$.

References

1. Mancini D, LeJemtel T, and Sonnenblick E: American Journal of Cardiology 56:8B-15B, 1985.
2. Gage J, Rutman H, Lucido D, LeJemtel T: Circulation 74:2:367-373, 1986.

SUMMARY OF HEMODYNAMIC DATA FOR ALL DOGS

	Dose (mcg/kg/min) 0.0	2.5	5.0	7.5	10.0
Group 1 Dobutamine(n=6)					
HR(beats/min)	92.3±21.5	99.9±25.6	117.5±30.0	118.6±29.8	128.5±34.3
MAP(mm Hg)	114.9±25.1	125.3±25.2	130.5±29.8	132.0±27.2	133.5±30.0
CVP(cm H_2O)	8.5±3.3	7.8±3.6	7.2±3.6	7.4±3.9	6.9±4.4
MPAP(mm Hg)	16.7±3.4	17.0±4.0	17.5±4.3	18.5±4.8	18.6±5.0
PCWP(mm Hg)	10.3±3.8	8.9±3.3	8.9±3.2	8.7±3.5	8.3±3.2
PVRI(dynes·sec·cm^{-5}/M^2)	141.9±48.0	118.5±46.5	110.4±39.4	122.9±56.9	118.8±45.2
SVRI(dynes·sec·cm^{-5}/M^2)	1942±752	1784±849	1634±666	1538±613	1471±556
SVI(ml/min/M^2)	57.3±15.6	63.1±19.5	63.2±15.8	61.3±16.4	59.9±15.9
CI(liters/min/M^2)	5.2±1.9	6.2±2.4	6.6±2.2	7.1±2.0	7.4±2.0
LVSWI(gm·m/M^2)	79.2±26.3	95.0±31.8	102.7±30.1	102.0±33.9	101.6±35.7
dP/dt(mm Hg/sec)	3175±800	3974±861	4301±845	4551±650	4707±808
Group 2 Amrinone(n=6)					
HR(beats/min)	107.8±37.9	117.0±36.9	109.6±28.4	102.6±23.4	104.4±35.2
MAP(mm Hg)	97.4±19.0	115.5±20.3	133.6±26.9	140.1±28.8	134.1±25.1
CVP(cm H_2O)	7.1±3.8	7.7±3.4	7.6±2.3	7.2±3.5	8.2±4.2
MPAP(mm Hg)	15.2±3.9	16.0±3.6	18.4±3.2	18.4±3.5	20.6±4.2
PCWP(mm Hg)	7.3±3.2	9.0±2.8	9.6±2.9	9.2±3.4	10.5±3.7
PVRI(dynes·sec·cm^{-5}/M^2)	106.9±39.4	94.8±42.0	107.4±36.8	137.7±46.3	148±50.5
SVRI(dynes·sec·cm^{-5}/M^2)	1218±426	1205±269	1615±593	2039±686	1912±765
SVI(ml/min/M^2)	61.9±14.6	67.6±15.7	63.9±18.6	55.1±16.6	59.3±18.5
CI(liters/min/M^2)	6.4±2.2	7.7±2.5	6.8±2.0	5.7±1.8	6.0±2.3
LVSWI(gm·m/M^2)	74.5±19.6	100.3±35.0	107.3±37.7	97.9±29.1	98.0±32.0
dP/dt(mm Hg/sec)	3228±833	3940±919	4359±974	4527±1021	4109±985

[a] $p<0.05$ vs. 0.0 mcg/kg/min dose
[b] $p<0.05$ vs. 2.5 mcg/kg/min dose
[c] $p<0.05$ vs. 5.0 mcg/kg/min dose

HR = heart rate; MAP = Mean arterial pressure; CVP = central venous pressure MPAP mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure PVRI = pulmonary vascular resistance index; SVRI systemic vascular resistance index; SVI = stroke volume index; CI = cardiac index; LVSWI left ventricular stroke work index; dP/dt = peak positive LV force of contraction