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Effects of AR-L115 BS and dobutamine on myocardial metabolism and high energy phosphate stores (1 figure).

AR-L115 BS [2 – ((2 – methoxy – 4 – methysylfinyl)phenyl) – 1H – imidazo (4,5-b) pyridine] is a non sympathomimetic, non-glycoside positive inotrope. Various mechanisms such as changes in calcium sensitivity of the contractile proteins, caffeine-like effects on the sarcoplasmic reticulum or a phosphodiesterase inhibition have been advocated to explain the positive inotropic effects of this agent.

The aim of this study was to determine the effects of AR-L115 BS on the high energy phosphate stores of the normal as well as of the hypertrophied myocardium. Six normal anaesthetized open-chest dogs and seven dogs with left ventricular (LV) hypertrophy were studied. LV hypertrophy resulted from a 6-10 weeks volume overload (aortocaval fistula) which increased LV mass from 4.8 $\pm$ 1.2 g/kg (SD) in normal dogs to 6.5 $\pm$ 0.7 g/kg ($P < 0.01$). LV and aortic pressures were recorded by means of micromanometers; coronary blood flow and oxygen content of arterial and coronary sinus blood were also determined. Epicardial biopsies, sampled by means of a bone-forceps precooled with liquid nitrogen, were obtained under basal conditions, during a dobutamine infusion (0.1-0.8 mg/min) and during AR-L115 BS infusion (2-6 mg/min). Dobutamine, a full β_1 adrenoreceptor agonist with limited β_2 activity, was used to produce a reference positive inotropic stimulation; the doses were adapted to increase peak (+) dP/dt or dP/dt/DP40 to the same extent with both drugs.

Thus, in normal dogs, positive inotropic stimulation with either dobutamine or AR-L115 BS resulted in significant decreases in ADP without significant changes in ATP. Accordingly, the ATP/ADP ratio increased significantly with both drugs (Fig. 1) and the adenylate charge rose slightly from 0.861 $\pm$ 0.025 in control to 0.887 $\pm$ 0.036 (NS) with dobutamine and to 0.912 $\pm$ 0.009 ($P < 0.05$) with AR-L115 BS. In dogs with chronic LV overload, the changes in high energy phosphate stores

	ATP μmol/g	ADP μmol/g	AMP μmol/g	P. creat. / Total creat. %	Lactic Acid μmol/g
Normal dogs					
Control	4.9 ± 1.0	0.76 ± 0.24	0.44 ± 0.11	42 ± 7	2.6 ± 0.8
Dobutamine	4.7 ± 0.9	0.61 ± 0.19*	0.31 ± 0.05	40 ± 9	2.0 ± 0.9
AR-L115 BS	5.0 ± 0.7	0.56 ± 0.15*	0.21 ± 0.06*	36 ± 8	1.8 ± 0.6
Hypertrophy					
Control	4.8 ± 0.5	0.74 ± 0.19	0.31 ± 0.11	42 ± 10	4.1 ± 1.8
Dobutamine	4.6 ± 0.5	0.73 ± 0.22	0.29 ± 0.11	40 ± 11	3.6 ± 1.4
AR-L115 BS	4.3 ± 1.0	0.62 ± 0.14	0.19 ± 0.08*	36 ± 15	3.4 ± 2.0

* $P < 0.05$ *vs.* control.

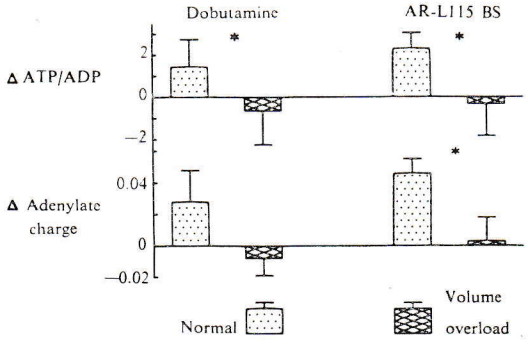

FIG. 1. *Absolute changes in high energy phosphate stores ATP/ADP ratio : ΔATP/ADP or adenylate charge : Δadenylate charge during inotropic stimulation.*

Mean ± SEM.

P value refer to the comparison between normal and volume overload (Mann-Withney Ranking test).

* $P < 0.05$.

induced by AR-L115 or dobutamine were again similar. In this setting however, ATP tended to be lower during the inotropic stimulation and no significant drop in ADP was noted. Consequently, the ATP/ADP ratio tended to decrease with both drugs (Fig. 1) while adenylate charge slightly declined with dobutamine and was almost unchanged with AR-L115 BS (Fig. 1).

In both group of dogs, the heart rate and myocardial oxygen consumption were comparable during AR-L115 BS or dobutamine but the mean aortic pressures were lower during AR-L115 BS than during dobutamine (118 *vs.* 155 mmHg in normal, 98 *vs.* 121 mmHg in volume overload, $P < 0.05$); the LV end-diastolic pressures were also significantly reduced by AR-L115 BS.

In conclusion, no deleterious effects of AR-L115 BS on the high energy phosphate stores were evidenced when these effects were compared to the changes induced by a beta agonist. In addition, the observation that both drugs induced less favorable changes in energy stores in chronic volume overload than in normal suggests an impaired adaptability of the myocardial metabolism in this type of LV hypertrophy.