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Effects of Dobutamine and Sulmazol (AR-L115 BS) on Myocardial Metabolism and Coronary, Femoral, and Renal Blood Flows: A Comparative Study in Normal Dogs and in Dogs with Chronic Volume Overload

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Summary: We compared the hemodynamic and metabolic effects of dobutamine and sulmazol (AR-L115 BS) in normal dogs and in dogs with chronic volume overload. In both cases, the doses of dobutamine and sulmazol were adapted to produce comparable increases in two indices of inotropic state, peak (+) left ventricular dP/dt and dP/dt normalized by a developed pressure of 40 mm Hg. In normal dogs, both drugs had similar effects on myocardial oxygen consumption, myocardial high-energy phosphate stores, and renal or femoral blood flows; in addition, mean aortic pressure (129 ± 8 to 114 ± 10 mm Hg; $p < 0.002$), the renal vascular resistance (−18%; $p < 0.005$), and the coronary vascular resistance (−30%; $p < 0.05$) were all decreased significantly during sulmazol administration. In chronic volume overload, the changes in renal and femoral blood flows and in myocardial high-energy phosphate stores induced by dobutamine or sulmazol were again similar. However, sulmazol still decreased mean aortic pressure (−20 ± 5 mm Hg; $p < 0.002$) and markedly reduced the left ventricular filling pressure (−40%; $p < 0.006$), while these parameters were not significantly modified after dobutamine. Myocardial oxygen consumption was unchanged after sulmazol but increased slightly with dobutamine. Finally, the frequency of ventricular premature beat was unchanged by sulmazol but increased after dobutamine. In conclusion, sulmazol is likely to be superior to dobutamine to stimulate a failing left ventricle when clinical status is characterized by markedly elevated filling pressures. It might also be superior when the coronary vascular reserve is reduced or in the presence of ventricular arrhythmias. **Key Words:** Dobutamine—Sulmazol—Myocardial metabolism—Chronic volume overload—Inotropic drugs.

Sulmazol, AR-L115 BS; 2-[(2-methoxy-4-methylsulfinyl)phenyl]-1*H*-imidazo(4,5-b)pyridine, is a new phenyl-imidazo-pyridine derivative combining positive inotropic effects with strong vasodilator properties (1,2). This agent is presently proposed for the treatment of patients with severe congestive heart failure (3–5). However, despite preliminary reports suggesting that sulmazol is still active in patients fully medicated with digitalis or β-stimulants (4), the superiority of sulmazol over alternative inotropes such as the β_1-stimulants has not been established. More particularly, it is not yet clear whether the improvement induced by sulmazol is due to its inotropic properties, its vasodilator effects, or both. Furthermore, the effects of sulmazol on the metabolism of the myocardial cell are still unknown.

The purpose of the present study was therefore to compare the changes in myocardial metabolism as well as in coronary, renal, and femoral blood flows during the administration of equipotent doses of sulmazol and of a cardioselective β_1-stimulant, dobutamine (6–9).

Furthermore, since the hemodynamic and cardiac responses to inotropes may be different in the presence of myocardial hypertrophy or failure (10–12), this comparison was performed not only in normal dogs but also in animals in which a syndrome of congestive heart failure had been induced by an aortocaval fistula.

MATERIALS AND METHODS

Twenty-one mongrel dogs weighing (19–34 kg) were used in this study; 11 had normal cardiovascular function

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(normal dogs), and in 10 other dogs a chronic volume overload had been induced by an infrarenal aortocaval fistula as described by Taylor et al. (13). In brief, after anesthesia with 20 mg/kg pentobarbital, the abdominal aorta and vena cava were exposed, and a side-to-side anastomosis, 10–15 mm in length, was constructed. The animals were returned to the kennels and studied after 6 to 10 weeks when signs of heart failure were present (evidenced by dyspnea, limb edema, or ascites and by a rapid weight gain of 10% above the control weight).

Instrumentation

The study was performed with the animals under general anesthesia (25 mg/kg pentobarbital); ventilation was maintained by a Harvard respirator, adapted to maintain arterial pH between 7.35 and 7.50. Animal temperature was controlled by a heating pad (average rectal temperature, 38.0°C; range, 36.5–38.5°C).

First, electromagnetic flow probes (In Vivo Metrics) were placed around the right femoral artery and around the left renal artery; umbilical tape was loosely placed downstream of the flow probe to obtain zero flow base line during brief arterial occlusions. Care was taken not to kink the renal artery and to ensure stability of the flow signals throughout the experiments. Then, a left thoracotomy was performed through the fifth intercostal space, and the heart was suspended in a pericardial cradle. The left circumflex artery was dissected free near its origin and was also fitted with an electromagnetic flow probe (In Vivo Metrics). A 3-F multihole-tip Teflon catheter was introduced by the Seldinger technique in the great cardiac vein and advanced into the coronary sinus. A triple Millar micromanometer (model PC772) was introduced in the left ventricle (LV) through a stab incision at the apex and its tip advanced into the aortic root. A 7-F fluid-filled catheter, connected to a Statham P23dB strain gauge, was similarly introduced in the LV to provide pressure reference for the micromanometers. After completion of this procedure, the animal was allowed to stabilize during 15 min before the experimental protocol was started.

Experimental protocol

Hemodynamic parameters were first recorded under basal conditions. Thereafter, arterial and coronary sinus blood samples were drawn simultaneously in heparinized syringes; for biochemical studies, an epicardial biopsy specimen (average weight, 100 mg) was obtained according to the technique of Pool et al. (14,15), using a bone rongeur precooled with liquid nitrogen. This biopsy specimen was immediately stored in liquid nitrogen. At the end of the control period, brief arterial occlusions (± 10 s) were performed to record zero flow levels.

Dobutamine was infused (Harvard infusion pump) starting at a rate of 1.15 μg/kg/min, and the rate of infusion was increased every 5 min until a stable increase in peak (+) *dP/dt* of approximately 30% above control was observed. This was achieved by an average infusion rate of 4.6 ± 2.0 μg/kg/min in normal dogs (range, 2.8 to 11.5) and of 10.1 ± 0.4 μg/kg/min (range, 2.8 to 28) in those with volume overload. This infusion rate was maintained at a constant level, and at the 10th min, hemodynamic data, blood samples, biopsy specimens, and zero flows were obtained as in the control state. When hemodynamic data and LV *dP/dt* had returned to basal values, 15 to 20 min after cessation of dobutamine, a bolus of sulmazol (0.5 mg/kg) was administered intravenously and an infusion was started at 28 μg/kg/min and increased until peak (+) *dP/dt* rose to approximately the same level as during dobutamine. This was obtained by an average infusion rate of 130 ± 25 μg/kg/min (range, 58 to 285) in normal dogs and of 170 ± 35 μg/kg/min (range, 115 to 285) in volume overload. These infusion rates produced comparable sulmazol plasma levels in both groups (2.38 ± 0.48 μg/ml plasma in normal dogs and 2.36 ± 0.51 μg/ml in those with volume overload). When hemodynamics had been stable during 10 min of sulmazol administration, hemodynamic data and a myocardial biopsy specimen were obtained as described above.

This entire protocol was performed in seven normal dogs and in seven with volume overload. Further, to establish that the sequence dobutamine–sulmazol did not modify the effects of the latter drug, six additional dogs received only sulmazol (three normal and three with overload) and one normal dog received dobutamine only. It was indeed impossible to infuse these agents randomly because of the long duration of action of sulmazol.

At the end of the experiments, the heart was arrested with KCl given intravenously and was removed for postmortem examination.

Measurements and computations

All data were simultaneously recorded on analog magnetic tape (Honeywell model 101) and on paper (Devices type M 8). The Millar transducers had stable electrical zero (drift, <0.7 mm Hg/h), linear gain up to 200 mm Hg, and a flat frequency response up to 2,000 Hz. The hydrostatic zero reference point was at the level of the right atrium, and the systolic pressure recorded by the Millar manometers was adjusted to match the systolic pressure recorded by means of the fluid-filled catheter.

The femoral and renal flow probes were connected to synchronized SEM 275 electromagnetic flow meters and the coronary probe was connected to a Biotronex BL-610 pulsed logic flow meter. Flow probes were calibrated with saline before the study and had a linear gain up to 500 ml/min for probes of 2–3 mm diameter and up to 750 ml/min for probes of 4–5 mm diameter.

Analog data filtered at 100 Hz were digitized every 2 ms and processed off-line by means of a Hewlett-Packard 2113E computer. The first derivative of the LV pressure, LV *dP/dt*, was computed after digital filtering with a recursive method implementing a 6th order Butterworth type low-pass filter with a bandwith of 50 Hz (−3 dB). Specific points on the signals [e.g., the peak (+) *dP/dt*] were automatically detected by a set of subroutines (16). The value of LV *dP/dt* at a developed pressure of 40 mm Hg and normalized by this developed pressure, i.e., $(dP/dt)/DP_{40}$, was computed and used as an index of inotropic state (17). As an index of isovolumic LV relaxation, we used the time constant T_1 of the exponential LV pressure fall during the first 40 ms after peak (−) *dP/dt* (18). For that purpose, pressure-versus-time data were fitted into a single exponential relationship by the method of least squares (r ranging from 0.980 to 0.999). Blood flow signals were averaged throughout each cardiac cycle, and the actual flow values were derived, taking into account the calibration factor and the zero flow level. The number of ventricular premature beats occurring spontaneously during control or during the 10-min drug infusions was also determined.

The myocardial biopsy specimens while still frozen were pulverized in steel cartridges cooled with liquid nitrogen and extracted in 1 ml of 0.5 N perchloric acid at 0°C. The extracts were neutralized with 2 N NaOH diluted to 10 ml with water. Creatine was measured by its reaction with diacetyl-α-naphtol (19); after acid hydrolysis (10 min at 65°C in 0.4 N HCl followed by neutralization with NaOH), the total creatine (C_T = creatine + phosphorylcreatine) was measured by the same reaction. Phosphorylcreatine was computed as the difference between creatine and C_T. The analyses of ATP, ADP, AMP, and lactic acid were performed in duplicate as described in Bergmeyer (20). The concentrations of these metabolites are expressed in μmol/g wet weight. The high-energy phosphate contents were estimated, as described previously, by the quotients [(ATP + phosphorylcreatine)/C_T] and [(ATP + ADP + phosphorylcreatine)/C_T], with total creatine serving as an index of tissue extraction (14,21). The adenylate charge, another index of the energy charge potential of the cell was calculated, as (ATP + 0.5 ADP)/(ATP + ADP + AMP) (22); the ATP/ADP ratio, which is thought to regulate several metabolic pathways, was also determined (23).

The oxygen content of arterial and venous blood samples was determined using a Lex-O_2-CON analyzer. Statistical comparisons between groups of dogs or between drugs were performed using a Mann-Whitney test. The effects of each drug were compared with the corresponding control data using a paired *t* test.

RESULTS

Hemodynamic changes during dobutamine and sulmazol infusion

Since the hemodynamic and metabolic changes produced by sulmazol were identical when it was given either after dobutamine or alone, all sulmazol data were pooled for statistical analysis.

Normal dogs. The relevant hemodynamic data before and after dobutamine or sulmazol are summarized in Table 1.

In normal dogs, both drugs increased significantly peak (+) *dP/dt* (+36% with dobutamine, +39% with sulmazol) and (*dP/dt*)/DP_{40} and improved LV relaxation without significant change in LV end-diastolic pressure (LVEDP). Myocardial oxygen consumption increased with both drugs, but this change was not statistically significant. Similarly, neither with dobutamine nor with sulmazol was a change in renal or femoral blood flow noted.

Several differences between the hemodynamic responses were, however, present. Sulmazol indeed slightly increased heart rate and reduced LV systolic pressure from 139 ± 8 to 126 ± 8 mm Hg ($p < 0.005$) and mean aortic pressure from 129 ± 8 to 114 ± 10 mm Hg ($p < 0.002$). In addition, despite similar changes in myocardial oxygen consumption, a significant decrease in coronary vascular resistance (−30%; $p < 0.05$), attended by a decrease in oxygen extraction, was observed only after sulmazol administration.

Dogs with chronic volume overload. At the time of the study, all dogs with an aortocaval fistula had significant LV hypertrophy (6.44 ± 0.19 versus 4.77 ± 0.45 g/kg body weight in normal dogs; $p < 0.01$), increased LVEDP (18.5 ± 1.9 versus 9.1 ± 2.2 mm Hg; $p < 0.01$), and decreased renal blood flow (218 ± 41 versus 436 ± 60 ml/min/100 g kidney weight; $p < 0.01$).

In this setting, sulmazol and dobutamine still produced comparable inotropic stimulation, as evidenced by the changes in peak (+) *dP/dt* (+1,073 ± 371 mm Hg/s with dobutamine and +718 ± 210 mm Hg/s with sulmazol; difference not significant), by the changes in (*dP/dt*)/DP_{40} (+45% with dobutamine and +50% with sulmazol; difference not significant), and by the relaxation index T_1 (which decreased to 29 ± 2 and 28 ± 4 ms, respectively).

The changes in LV systolic pressure, LVEDP, mean aortic pressure, and coronary blood flow were, however, markedly different. Sulmazol indeed significantly decreased LVEDP (from 18.5 ± 1.9 to 11.0 ± 2.2 mm Hg; $p < 0.006$), LV systolic pressure (−15 ± 6 mm Hg; $p < 0.03$), and mean aortic pressure (−20 ± 5 mm Hg; $p < 0.002$), while these parameters remained unchanged during dobutamine administration. Myocardial oxygen consumption tended to be less during sulmazol than during dobutamine administration (5.5 ± 0.8 versus 6.8 ± 0.8 ml/min; $p < 0.1$); this might explain why coronary blood flow increased more after dobutamine than after sulmazol (+36% versus −2%; $p < 0.05$, dobutamine versus sulmazol). In addition, although the renal and femoral blood flow responses were identical, the renal vascular resistance was decreased after sulmazol. Another difference was also noted: the femoral vascular resistance decreased significantly by 12% with sulmazol but increased with dobutamine (Table 1; $p < 0.01$, dobutamine versus sulmazol).

Metabolic changes

The average changes in high-energy phosphate stores are summarized in Table 2 for both groups of animals.

Normal dogs. As can be seen in Table 2, the global metabolic response observed in normal dogs after dobutamine or sulmazol was identical. Both drugs produced significant decreases in ADP (−25 and −26%) and in AMP (−29 and −36%) without altering ATP levels or lactate concentrations. The total energy store, estimated either from the sum (ATP + phosphorylcreatine) or from (ATP + ADP + phosphorylcreatine), was unchanged while the adenylate charge and the ATP/ADP ratio increased. The changes in adenylate charge and ATP/ADP ratio were statistically significant in the case of sulmazol only, but examination of individual data (Fig. 1) indicates that the response was basically similar with both drugs.

Dogs with chronic volume overload. No differ-

TABLE 1. *Hemodynamic effects of dobutamine and AR-L115 BS (sulmazol)*

	Heart rate (beats/min)	LV pressure (mm Hg)		Peak (+) dP/dt (mm Hg/s)	$(dP/dt)/DP_{40}$ (s^{-1})	Mean AoP (mm Hg)	$M\dot{V}O_2$ (ml/min)
		Systolic	End-diastolic				
Normal dogs							
Control (n = 8)	149 ± 7	152 ± 3	10.1 ± 2.6	2,393 ± 230	33.3 ± 4.7	142 ± 4	6.3 ± 0.6
Dobutamine	157 ± 8	164 ± 10	13.1 ± 4.3	3,257 ± 378	43.5 ± 5.4	149 ± 9	8.0 ± 1.4
p				<0.025	<0.035		<0.1
Control (n = 10)	143 ± 7	139 ± 8	9.1 ± 2.2	2,090 ± 189	30.5 ± 3.8	129 ± 8	6.5 ± 0.9
AR-L115 BS	159 ± 9	126 ± 8	5.8 ± 1.8	2,907 ± 251	47.3 ± 5.8	114 ± 10	7.5 ± 1.5
p	<0.004	<0.005		<0.003	<0.002	<0.002	
Chronic volume overload							
Control (n = 7)	155 ± 8	138 ± 11	18.1 ± 2.3	2,490 ± 267	28.6 ± 3.3	116 ± 10	5.7 ± 0.4
Dobutamine	161 ± 6	137 ± 9	16.4 ± 1.8	3,563 ± 342	41.6 ± 3.4	117 ± 8	6.8 ± 0.8
p				<0.03	<0.02		
Control (n = 10)	148 ± 7	141 ± 8	18.5 ± 1.9	2,531 ± 212	33.0 ± 3.9	120 ± 8	5.9 ± 0.3
AR-L115 BS	154 ± 6	126 ± 6	11.0 ± 2.2	3,249 ± 242	49.5 ± 7.1	100 ± 5	5.5 ± 0.8
p	<0.04	<0.03	<0.006	<0.006	<0.003	<0.002	

	d A–V (vol %)	Q̇ Cor (ml/min)	Cor. resist. (mm Hg/ml/min)	Q̇ Ren (ml/min/ 100 g kw)	Ren. resist. (%)	Q̇ Fem (ml/min/ kg bw)	Fem. resist. (%)	T_1 (ms)
Normal dogs								
Control (n = 8)	16.1 ± 0.8	40 ± 5	4.0 ± 0.6	488 ± 78	100	1.8 ± 0.6	100	35 ± 5
Dobutamine	16.9 ± 1.2	48 ± 8	3.7 ± 0.6	531 ± 84	98 ± 14	1.7 ± 0.3	99 ± 26	29 ± 3
p								<0.06
Control (n = 10)	16.0 ± 0.6	42 ± 7	3.7 ± 0.5	436 ± 60	100	1.6 ± 0.4	100	35 ± 3
AR-L115 BS	13.9 ± 1.3	52 ± 8	2.6 ± 0.4	471 ± 59	82 ± 6	1.6 ± 0.5	123 ± 28	25 ± 2
p	<0.1	<0.015	<0.05		<0.005			<0.006
Chronic volume overload								
Control (n = 7)	14.9 ± 0.8	39 ± 2	2.9 ± 0.2	210 ± 61	100	1.4 ± 0.4	100	36 ± 3
Dobutamine	13.7 ± 1.0	53 ± 6	2.5 ± 0.4	260 ± 49	80 ± 20	1.3 ± 0.4	121 ± 13	29 ± 2
p	<0.025	<0.05					<0.1	<0.01
Control (n = 10)	13.9 ± 0.9	46 ± 5	2.8 ± 0.2	218 ± 47	100	1.5 ± 0.4	100	37 ± 3
AR-L115 BS	12.4 ± 1.0	45 ± 5	2.4 ± 0.4	276 ± 37	65 ± 14	1.3 ± 0.3	88 ± 6	28 ± 4
p	<0.006				<0.02		<0.05	<0.006

$M\dot{V}O_2$, myocardial oxygen consumption; d A–V, arterio-venous difference (aorta-coronary sinus); Q̇ Cor, coronary flow; Cor. resist., coronary resistance; T_1, time constant of isovolumic left ventricular (LV) pressure fall; Q̇ Ren, renal flow; Ren. resist., renal resistance; Q̇ Fem, femoral flow; Fem. resist., femoral resistance; kg bw, kg body weight; g kw, g kidney weight; AoP, aortic pressure.

Values are means ± SEM.

The p values refer to the comparison with the corresponding control (paired *t* test).

ence was noted between normal and chronically overloaded myocardium with respect to their ATP, ADP, AMP, or phosphorylcreatine contents under basal conditions. Myocardial lactate concentration was higher in chronic overload but was definitely outside the normal range in four dogs only (these dogs had lactate concentrations of, respectively, 4.12, 4.32, 5.38, and 6.85 μmol/g).

As can be seen in Table 2, the metabolic response to inotropic stimuli slightly differed from normal, mainly by the lack of significant ADP decreases and by the fact that ATP stores were poorly preserved (Fig. 2). Accordingly, the changes in adenylate charge (Fig. 1) and in ATP/ADP ratio (+1.78 ± 0.58 in normal dogs versus −0.82 ± 0.81 in those with volume overload; $p < 0.02$) were significantly reduced when compared with the normal response. Nevertheless, the indices of total energy stores did not change significantly, because phosphorylcreatine stores compensated for the ATP decline. Such a compensation was particularly evident during sulmazol administration: in normal dogs, ATP increased slightly during sulmazol administration and phosphorylcreatine showed an opposite drop, while in those with chronic overload, an inverse pattern of response was observed.

The normal AMP decline was still observed in chronic overload during sulmazol but not during dobutamine administration, and the AMP levels were lower with the former drug than with the latter drug (0.18 ± 0.02 versus 0.29 ± 0.05 μmol/g; $p < 0.05$). Finally, it may be noteworthy that after sulmazol, myocardial lactate levels returned toward normal values in all four dogs in which this parameter was clearly elevated (from an average of 5.17 to 2.99 μmol/g; $p < 0.05$).

TABLE 2. *Effects of dobutamine and AR-L115 BS (sulmazol) on high-energy phosphate stores and myocardial lactic acid*

	ATP (μmol/g)	ADP (μmol/g)	AMP (μmol/g)	Lactic acid (μmol/g)	Adenylate charge	(ATP + CP)/C_T	(ATP + ADP + CP)/C_T	ATP/ADP
Normal dogs								
Control (n = 7)	4.92 ± 0.39	0.80 ± 0.10	0.45 ± 0.04	2.74 ± 0.32	0.859 ± 0.009	0.65 ± 0.02	0.69 ± 0.02	6.60 ± 1.05
Dobutamine	4.69 ± 0.33	0.60 ± 0.07	0.32 ± 0.02	2.24 ± 0.39	0.888 ± 0.013	0.63 ± 0.03	0.66 ± 0.03	8.52 ± 1.11
p		<0.025	<0.025					
Control (n = 10)	4.38 ± 0.37	0.86 ± 0.11	0.47 ± 0.06	2.77 ± 0.30	0.837 ± 0.020	0.66 ± 0.01	0.70 ± 0.01	5.86 ± 0.99
AR-L115 BS	4.47 ± 0.33	0.64 ± 0.07	0.30 ± 0.05	2.17 ± 0.27	0.881 ± 0.016	0.67 ± 0.03	0.71 ± 0.03	7.48 ± 0.90
p		<0.02	<0.005		<0.002			<0.04
Chronic volume overload								
Control (n = 7)	4.87 ± 0.19	0.73 ± 0.09	0.33 ± 0.05	4.00 ± 0.95	0.877 ± 0.010	0.68 ± 0.03	0.72 ± 0.03	7.03 ± 0.69
Dobutamine	4.28 ± 0.37	0.71 ± 0.09	0.29 ± 0.05	3.64 ± 0.61	0.874 ± 0.007	0.65 ± 0.03	0.69 ± 0.03	6.37 ± 1.04
Control (n = 10)	4.39 ± 0.28	0.66 ± 0.08	0.29 ± 0.03	3.50 ± 0.62	0.882 ± 0.007	0.67 ± 0.03	0.71 ± 0.03	7.05 ± 0.52
AR-L115 BS	3.44 ± 0.45	0.58 ± 0.08	0.18 ± 0.02	2.96 ± 0.59	0.877 ± 0.013	0.63 ± 0.03	0.67 ± 0.03	6.34 ± 0.81
p	<0.02		<0.02					

CP, phosporylcreatine; C_T, total creatine.
Values are mean ± SEM.
The p values refer to the comparison with the corresponding control (paired *t* test).
Metabolite concentrations are expressed in μmol/g tissue wet weight.

In summary, myocardium with chronic overload did not exhibit an entirely normal metabolic response to the inotropic stimuli but, in this setting also, the metabolic effects of sulmazol and dobutamine appeared identical (Figs. 1 and 2).

Frequency of ventricular premature beats

After instrumentation had been completed, spontaneous ventricular premature beats were observed in 11 dogs. During the 10-min steady-state infusion of dobutamine, ventricular premature beats occurred at an average rate of 10 ± 5/10 min, a value significantly greater than during control or than during the steady-state sulmazol administration (4 ± 2/10 min; $p < 0.05$). In the remaining dogs, no premature beats were observed except during the biopsy procedure, which was excluded from this analysis.

DISCUSSION

The study was designed to discriminate the beneficial effects of sulmazol related to its inotropic properties from those linked to its vasodilator effects. Special attention was also directed toward the effects of this agent on the myocardial energy stores to detect potentially detrimental alterations.

For these purposes, we compared the effects of sulmazol and dobutamine. Dobutamine is a β_1-agonist with little α- or β_2-agonist effects (24,25). Previous studies in normal anesthetized dogs have shown that dobutamine increased myocardial contractile force and cardiac output with minimal increases in mean aortic pressure (25). Robie et al. (25) explained these results by a greater net effect of β-adrenergic vasodilation than of α-adrenergic vasoconstriction. These effects of dobutamine on the mean aortic pressure appear similar in our study, since neither in normal dogs nor in those with

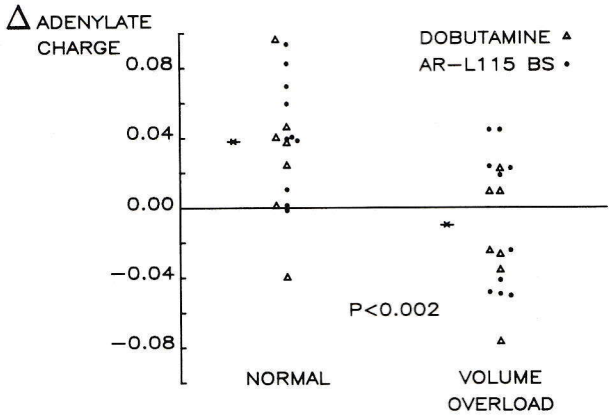

FIG. 1. Individual changes in adenylate charge (Δ adenylate charge), during dobutamine or sulmazol (AR-L115 BS) infusion. The p value refers to the comparison between normal dogs and dogs with chronic volume overload (Mann-Whitney rank test).

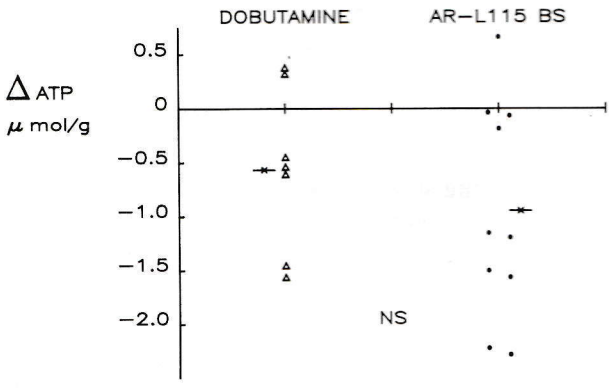

FIG. 2. Individual changes in myocardial ATP during dobutamine or sulmazol (AR-L115 BS) infusion in dogs with chronic volume overload. Both drugs tended to decrease myocardial ATP concentration, but no significant difference was present between dobutamine and sulmazol.

volume overload was a significant increase in this parameter observed. Thus, at the doses used in the present study, dobutamine was close to the ideal tool in evidencing the hemodynamic and metabolic effects of a pure increase in inotropic state, although we cannot entirely exclude the possibility that some adrenergic vasoconstriction may have limited the hemodynamic benefit.

The mode of action of sulmazol, on the other hand, is different from catecholamines and cardiac glycosides; changes in calcium sensitivity of the contractile proteins, phosphodiesterase inhibition, or alteration of the calcium handling by the cell are among the hypotheses proposed to explain its inotropic action (1,26).

The inotropic effects of both agents were assessed by means of the peak (+) dP/dt and of the $(dP/dt)/DP_{40}$ value (17). These indices are indeed very sensitive to acute changes in inotropic state, although it is recognized that a quantitative evaluation of the inotropic state, based on these parameters only, may be subject to error in intact hearts. However, $(dP/dt)/DP_{40}$ is little affected by preload and afterload changes (17); in addition, the absolute changes in peak (+) dP/dt as well as in $(dP/dt)/DP_{40}$ were not significantly different during dobutamine or sulmazol administration. This suggests that the inotropic stimulation produced by dobutamine and sulmazol was roughly identical both in normal dogs and in dogs with volume overload. Such a conclusion is further supported by the analysis of the changes in LV relaxation. The accelerations in LV relaxation, an active process which is also affected by inotropic stimuli (18), were indeed also of the same magnitude during dobutamine and sulmazol.

Normal dogs

When these comparable inotropic stimuli were imposed in normal dogs, few hemodynamic differences were observed between the two inotropes, aside from the expected decreases in mean aortic and in LV systolic pressures during sulmazol. Renal blood flow was unchanged during sulmazol administration, indicating that renal vasodilation compensated for the drop in perfusion pressure.

An increase in coronary blood flow in excess of the metabolic demand, as reflected by the increase in coronary venous blood saturation, was also present during sulmazol administration; thus, in the coronary bed, the sulmazol vasodilator effect largely compensated for the decrease in driving pressure. Another finding in normal animals is the similarity of the changes in high-energy phosphate stores during drug administration. Since the mechanism of action of sulmazol at the cellular level is still unknown, one could not exclude *a priori* that sulmazol could adversely affect several metabolic pathways. The fact that the changes in energy stores were identical to those induced by a physiologic stimulation of the β_1-receptors indicates that the energy-yielding pathways remain normal in the presence of sulmazol.

Dogs with chronic volume overload

In dogs with chronic volume overload, the sulmazol effects differed from those of dobutamine in several aspects, and these differences may help in clarifying the benefits of sulmazol when compared with pure inotropes or pure vasodilators.

One difference, which might be of major clinical relevance, is the fact that only sulmazol was able to reduce LV filling pressure significantly. This suggests that the vasodilation in addition to enhanced contractility is an important determinant of the decline in cardiac filling pressures.

Second, sulmazol did not increase the frequency of premature ventricular depolarizations occurring in these instrumented hearts; dobutamine, on the other hand, exacerbated these arrhythmias. This side effect of the catecholamines is well established and appears to be related mainly to an increased automaticity (27). Our data suggest that sulmazol could be safer in this respect; this conclusion is also supported by the fact that sulmazol at therapeutic concentrations does not modify the action potential (28).

Third, myocardial oxygen consumption of the overloaded ventricles was not augmented during sulmazol administration, probably because of a larger decrease in cardiac size and filling pressure than during dobutamine administration (29). Thus, this effect is more likely to be entirely related to the hemodynamic effects of sulmazol rather than to a specific metabolic property of this drug. Nevertheless, the total high-energy phosphate stores were preserved at a lower oxygen cost during sulmazol than during dobutamine administration. In our experimental conditions, where some coronary vascular reserve was likely to persist, this might not be relevant. In ischemic heart disease, however, when oxygen supply and demand are out of balance, dobutamine has been shown to promote ischemia (6,9), and the effects of sulmazol might be worth investigating in this setting.

On the other hand, several effects of sulmazol and dobutamine were very similar. Negligible changes in femoral flow were present during the interventions, despite opposite responses in femoral resistance. In addition, neither dobutamine nor sulmazol was able to normalize the depressed renal blood flow in dogs with chronic overload. A fall in renal resistance large enough to compensate for a 20 mm Hg decrease in mean aortic pressure was observed after sulmazol, but our setup did not allow us to determine if this renal vasodilation was caused by renal autoregulation or by sulmazol itself.

Finally, a potentially important observation is the fact that the metabolic adaptation to an inotropic stimulation is abnormal in ventricles with chronic volume overload. It is clear that a global analysis like the one performed in this study does not allow

one to conclude that the impaired response of the adenylate charge (Fig. 1) or of the ATP/ADP ratio is detrimental or that such a response is present in other forms of myocardial failure. Furthermore, the drop in myocardial lactic acid observed in four dogs with overload during sulmazol administration could be interpreted as an improvement in the aerobic metabolism. The decline in ATP (Fig. 2), perhaps related to an adenine loss, nevertheless emphasizes the need for studies in various types of myocardial disease to clarify the metabolic changes induced by long-term inotropic stimulation and to rule out deleterious effects of such therapy.

In conclusion, sulmazol is a positive inotrope which appears superior to cardioselective β_1-agonists by its more pronounced effects on the cardiac filling pressure and by its lack of arrhythmogenic effects; the vasodilation induced by this agent also appears beneficial in preventing a rise in myocardial oxygen consumption.

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