TITLE : INOTROPIC EFFECTS OF KETAMINE ON RAT CARDIAC PAPILLARY MUSCLE

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INTRODUCTION : Ketamine has been shown to produce marked increase in arterial blood pressure, heart rate, and cardiac output (1). These effects are thought to be due to : 1) sympathomimetic effects mediated within the central nervous system structures ; 2) inhibition of intraneuronal and extraneuronal catecholamines uptake. The myocardial effects of ketamine remains controversial since ketamine has been reported to be either a negative (2) or a positive inotropic agent (3). Critically ill patients may respond to ketamine with an unexpected fall in blood pressure which was thought to result from the inability of sympatomimetic actions of ketamine to counterbalance its direct vasodilatory and myocardial depressant effects (1). It would be of interest to know if ketamine is a myocardial depressant agent or not. We have therefore undertaken an in vitro study of the effects of ketamine on rat cardiac papillary muscle.

METHODS : Hearts were quickly removed from adult male Wistar rats after brief anesthesia with ether. Left ventricular papillary muscles were excised and suspended vertically in a Krebs-Henseleit solution (bubbled with 95% O2 - 5% CO2, pH 7.40, 29°C), and field stimulated (0.12Hz). After 1 hr stabilization period at Lmax (i.e., the initial muscle length at the apex of the length-active isometric tension curve), ketamine hydrochloride was added to the bathing solution. Muscles were divided into 3 groups : Group 1 (n=8) ketamine (10-4 M), Group 2 (n=8) ketamine (10-5 M) ; in Groupe 3 (n=6) extracellular calcium $[Ca^{++}]_o$ was lowered from 2.5 to 0.5 mM, and then ketamine (10-5 M) was added. The electromagnetic lever system has been previously described (4). Mechanical parameters were calculated from 4 twitches : the first twitch was isotonic and was loaded with only the preload at Lmax ; the second was abruptly clamped to zero-load just after the electrical stimulus ; the third was isometric at Lmax ; the fourth twitch was isotonic and was afterloaded to half-value of the isometric active force at Lmax. The following mechanical parameters were recorded before and 1 hr after ketamine : the maximum unloaded shortening velocity (Vmax) by means of the zero-load clamp technique ; maximum shortening (maxVc) and lengthening (maxVr) velocities of the twitch with preload only ; isometric active force at Lmax normalized per cross-sectional area (AF/s) ; time-to-peak force (TPF) ; time-to-peak shortening (TPS) ; coefficient R1=maxVc/maxVr, tests the coupling between contraction and relaxation under low loading conditions ; coefficient R2 = +dF.dt-lmax/-dF.dt-lmax (ratio of peak positive and negative derivative forces of the isometric twitch) tests the coupling between contraction and relaxation under heavy loading conditions ; an index of load sensitivity of relaxation (ILS) which ranges from about 0.75 in a typical load-sensitive relaxation, to 1 in a typical load-insensitive relaxation. Data were expressed as mean percent of control values ± SD. Comparisons were performed using paired Student's t test. $P < 0.05$ was considered significant.

RESULTS : Both ketamine (10-4 M) and (10-5 M) lowered duration of the twitch (TPS, TPF), impaired isotonic relaxation (maxVr) and the load sensitivity of relaxation (ILS), impaired the contraction-relaxation coupling at low loading conditions (R1), while they did not modify the coupling at heavy loading conditions (R2) (Table). Ketamine (10-5 M) had a positive inotropic effect as shown by the increase in Vmax. This positive inotropic effect was confirmed at low $[Ca^{++}]_o$: in Group 3, both Vmax (138±25%) and AF/s (119±17%) increased significantly. Ketamine (10-4 M) did not modify Vmax (Table).

DISCUSSION : The positive inotropic effect of ketamine (10-5 M) was associated with an increase in R1 and no modification of R2, as shown with ouabaine, but not with β-sympathomimetic drugs that decrease R1 and R2. Moreover, ketamine slightly impaired the load sensitivity of relaxation and reduced the duration of the twitch. Therefore, the positive inotropic effect of ketamine (10-5 M) mimics the mechanical effects of digitalis. Our study demonstrated that low concentrations of ketamine have a positive inotropic effect, whereas high concentrations of ketamine, that are consistent with peak plasma concentrations after intravenous bolus, have not. Higher concentrations were not tested but might have negative inotropic action (2). The unexpected fall in blood pressure observed with ketamine in critically ill patients may be due to : 1) a too high plasma concentration of ketamine resulting in a negative inotropic effect ; 2) the effect of ketamine on vascular tone and not on myocardium if ketamine dosage is adequate.

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TABLE : Effects of ketamine on main mechanical parameters of rat cardiac papillary muscle

	KETAMINE (10-5 M) % CV	P	KETAMINE (10-4 M) % CV	P
Vmax	120 ± 14	0.01	93 ± 11	NS
AF/s	103 ± 8	NS	93 ± 26	NS
maxVr	79 ± 10	0.001	69 ± 19	0.01
R1	141 ± 13	0.001	151 ± 29	0.01
R2	100 ± 10	NS	98 ± 14	NS
TPS	91 ± 3	0.001	93 ± 8	0.05
TPF	88 ± 5	0.001	89 ± 5	0.001
ILS	106 ± 3	0.001	107 ± 4	0.01

Data are mean % of control values (CV) ± SD