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Myocardial Force–Velocity Relations during Ketamine Anesthesia at Constant Heart Rate

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To elucidate the mechanism of cardiac stimulation during ketamine anesthesia, myocardial force–velocity relationships were determined in six subjects whose heart rates were controlled by atrial pacing. Contractility changes were seen in three patients and preloading effects in the other three. It is not possible to predict which effect will predominate in the surgical population. However, marked preloading would be detrimental to the patient already utilizing that mechanism to maintain cardiac compensation. (Key words: Anesthetics, intravenous: ketamine; Heart: ketamine.)

HEMODYNAMIC studies indicate that cardiac stimulation occurs during ketamine anesthesia.[1,2,3] Cardiac stimulation may result from preloading (the Frank-Starling mechanism) or from enhancement of myocardial contractility (positive inotropism). We have reported[3] increases in cardiac index (CI) and stroke work index (SWI) after intravenous administration of ketamine, and found that the relationship between left ventricular end-diastolic pressure (LVEDP) and CI suggested an overall positive inotropic mechanism. Some subjects, however, had increased LVEDP, evidence of preloading or a mixed mechanism. Increase in heart rate (HR) was not alone responsible for the cardiac effects, since CI and SWI increased to similar extents in unpaced and in paced subjects.[3] Increasing HR is, however, known to affect contractility.[4] We have, therefore, attempted to clarify the mechanism of cardiac stimulation by examination of the myocardial force–velocity relations in the six subjects previously reported who were paced at a constant rate before and after administration of ketamine (Subjects 7–12).[3]

Method

The experimental protocol has been described.[3] Briefly, subjects were six patients undergoing routine diagnostic heart catheterization and coronary angiography. All were in functional classes I or II (AHA) and were accepted for study on the basis of normal or near-normal left ventricular (LV) function as assessed by LV cineangiography. Three patients with cardiac disease were included on this basis: one with an atrial septal defect and two with coronary disease. Informed consent was obtained prior to the study.

Each subject was fasting and was premedicated with diazepam, 5–20 mg, im, two to three hours prior to study. Diazepam has been shown by Dalen *et al.*[5] to have little effect on the circulatory system.

Approximately half an hour *after* the diagnostic information had been obtained, two catheters were positioned, a pacing catheter in the coronary sinus and a LV catheter with a catheter tip micromanometer. Control data were then obtained in the unpaced (state A) and paced (state B) states, followed immediately by administration of 2 mg/kg ketamine, iv, over a period of 1 minute. During the 15 minutes after ketamine injection, serial paced data were obtained (states C_1, C_2 . . C_5). The pacing rate was approximately 1.5 times the resting rate, maintaining pacing control after ketamine in all cases. The mean of all measurements of

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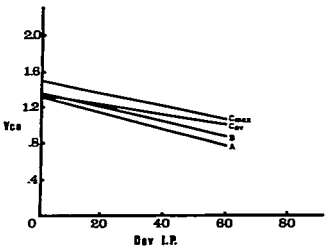

FIG. 1. Mean force–velocity plots, effects of pacing and ketamine. A, unpaced control; B, paced control; C_{av}, mean response after ketamine; C_{max}, peak response after ketamine. Dev. I.P. is developed isovolumic ventricular pressure (torr) and V_{CE} is contractile element velocity (muscle lengths/sec) calculated as $V_{CE} = \frac{dp/dt}{32 \times \text{Dev. I.P.}}$. The V_{CE} plots have been extrapolated to theoretical V_{max}.

each variable after ketamine administration was designated C_{av} and the peak response C_{max}.

Force–velocity relations were based on the three-component model of muscle mechanics[6,7] by relating calculated contractile element velocity of shortening (V_{CE}) to instantaneous developed isovolumic ventricular pressure (Dev. I.P.). Dev. I.P. is the intraventricular pressure developed during isovolumic systole, designating the onset of systole as zero pressure. Dev. I.P. and its simultaneous first derivative (dp/dt) were recorded with a catheter-tip micromanometer (Statham p 866), a high-fidelity recording system, and an electronic differentiating circuit (Hewlett-Packard 760 Series). The frequency response of the recording system was flat to 200 Hz. The phase lag of the differentiating circuit was 90 degrees at 32 Hz. The micromanometer was calibrated at room temperature in a saline-filled closed chamber connected to a pressure bottle and a mercury manometer. Because of the problem of thermal baseline drift, it was again aligned *in vivo* with an equisensitive conventional catheter system connected to an external transducer. However, the use of Dev. I.P. in the calculations, that is, pressure developed after the onset of systole, removes the dependency on a stable baseline.

Using a semiautomatic A to D plotter, simultaneous points were measured on both Dev. I.P. and dp/dt curves at 5-msec intervals during isovolumic systole above 15 torr, setting the onset of systole as zero pressure. V_{CE} corresponding to each point was calculated by the formula:

$$V_{CE} = \frac{dp/dt}{32 \times \text{Dev. I.P.}}$$

(32 is the series' elastic constant)[8]

Points from at least three consecutive heart cycles in each state were used to construct linear best-fit force–velocity plots for each subject by a standard computer-programmed regression analysis.

Mean force–velocity plots for states A, B, C_{av} and C_{max} were also calculated.

Respiration was spontaneous, and arterial P_{O_2} and P_{CO_2} were not changed after ketamine.

Results

The hemodynamic data for these subjects have been reported.[3] The mean force–velocity plots for states A, B, C_{max}, and C_{av}, extrapolated from 15 torr to zero, are depicted in figure 1.

Symmetrical elevation is interpreted as enhancement of contractility, asymmetric elevation with decreased slope as preloading. Pacing (state B *vs.* state A) had only a small effect on contractility. The peak effect of ketamine, C_{max}, is of the pattern ascribed to enhancement of contractility, whereas the average effect over the observation period, C_{av}, resembles preloading. Thus, both mechanisms are seen, though not necessarily simultaneously.

Individual force–velocity plots are depicted in figure 2. Subjects 1, 3, and 5 showed contractility changes, whereas Subjects 2, 4, and 6 showed only preloading effects. No correlation between the mechanism involved and the disease state of the subject was demonstrable.

Discussion

Isovolumic force–velocity relations based on high-fidelity recording of ventricular pressure and its first derivative are currently

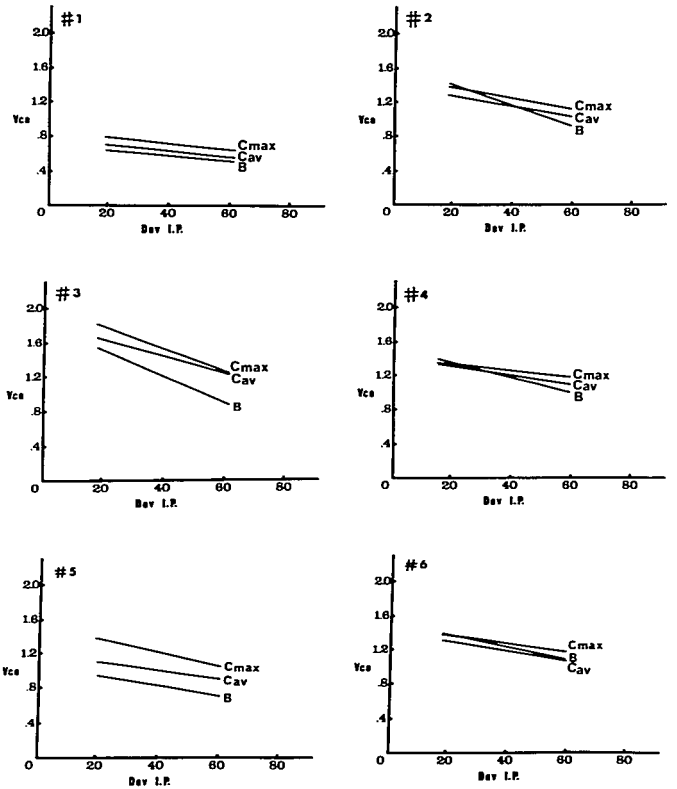

FIG 2. Individual force–velocity plots, effects of ketamine. B, paced control: C_{av}, mean response after ketamine; C_{max}, peak response after ketamine. Dev. I.P. is developed isovolumic ventricular pressure (torr), and V_{CE} is contractile element velocity (muscle lengths/sec) calculated as $V_{CE} = \frac{dp/dt}{32 \times \text{Dev. I.P.}}$. Subjects 1, 3, and 5 show contractility changes, while 2, 4, and 6 show only preloading effects.

the most acceptable method of describing myocardial contractility.[9,10,11,12] The most frequent index for comparison is V_{max}, the theoretical velocity of the contractile element in the unloaded state, obtained by extrapolating the force–velocity relation to zero load. However, at low pressures the force–velocity relation of isolated papillary muscle strips is hyperbolic, not a straight line.[13] To avoid large errors of measurement at the

lower pressures, we calculated V_{CE} only down to 15 torr. By our method, a long linear extrapolation of V_{CE} from 15 torr to zero pressure reduces the validity of V_{max} as an indicator of contractility. We believe, therefore, that the straight portions of the plots, between V_{20} and V_{60}, more accurately describe myocardial function in these subjects. Symmetrical elevation then indicates enhancement of contractility.

Similarly, pure preloading is defined as an increase in P_o without a change in V_{max}. P_o is the intercept of the force–velocity plot with the pressure axis and indicates maximum isometric pressure development.[11] This is equivalent to asymmetric elevation and decrease in slope of the linear portion of the plot. Estimation of preloading based on LVEDP in the same subjects did not yield conclusive results,[3] but correlation of LVEDP with CI suggested an overall inotropic effect. Small drifts in the baseline introduce considerable error in measurement of LVEDP, and changes in LVEDP may be distorted by concomitant changes in myocardial contractility or compliance. Therefore, we believe the force–velocity plot is a more sensitive indicator of preloading than LVEDP measurement.

An integral feature of this study was rate control, which eliminated the effects of rate changes on contractility. Though the observed change in contractility with pacing (state A to B) was small, we expect the effect on contractility after ketamine in unpaced patients would be somewhat greater than that which we measured during pacing.

In summary, analysis of force–velocity relations in a small group of subjects after administration of ketamine indicates that both preloading and contractility effects occur. Preloading implies increased end-diastolic ventricular volume, and may occur either in response to outflow impedance or because of increased venous return. Although the small sample size does not allow us to predict which mechanism predominates in the surgical population, we advise caution in the use of this agent for patients with severe myocardial disease or cardiac decompensation, that is, in patients who may already be maximally utilizing preloading (the Frank-Starling mechanism) to maintain cardiac output.

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