

The Effects of Methoxyflurane and Sympathetic-nerve Stimulation on Myocardial Mechanics

Shiro Shimosato, M.D.,* Carolyn Shanks, B.A.,
Benjamin E. Etsten, M.D.†

The effect of methoxyflurane on the contractile state of the intact canine left ventricle was studied by determining the instantaneous relations between myocardial force (F_c) and contractile element velocity (V_{ce}) during the course of single, isovolumic beats. Responses of the heart during anesthesia with methoxyflurane were also tested by imposing cardiac sympathetic nerve stimulation. In eight experiments, methoxyflurane (arterial blood concentration: 17.0 ± 1.4 mg./100 ml.) caused a decrease in the maximum force (-45.1 ± 13.1 per cent) with relatively unchanged maximum velocity of shortening (-2.6 ± 1.3 per cent). Frequency-graded superimposed cardiac sympathetic nerve stimulation produced increased maximum force towards the control levels. These findings are related to a direct negative inotropic effect of methoxyflurane upon the intrinsic contractile state of the myocardium.

THE ALTERED CARDIAC PERFORMANCE that occurs during methoxyflurane (Penthane) anesthesia has been described in terms of decreased slopes of "ventricular function curves," i.e., reduction of ventricular stroke work at any given ventricular end-diastolic volume or pressure.¹ However, our recent studies¹⁻³ of the differential effects of diethyl ether upon left and right ventricular function curves in the intact dog indicate that ventricular stroke work is not only a function of end-diastolic

pressure (preload) but also a function of the resistance to ejection or mean aortic pressure (afterload). Recently, it has been shown that the contractile state of isolated cardiac muscle, like that of skeletal muscle,⁴ can be characterized best in terms of the relation between force of contraction and velocity of shortening.⁵⁻⁷ Subsequently, it has been demonstrated that an inverse relationship between force and velocity also applies to the intact canine left ventricle^{8,9} and that a change in the position of the force-velocity curve reflects a change in the contractile state.⁸⁻¹¹

The present investigation was designed, therefore, to determine the effect of methoxyflurane upon the inotropic state of the left ventricle as characterized by the relation between the force of contraction and the velocity of shortening in the intact canine heart. In addition, the effect of cardiac sympathetic nerve stimulation on the force-velocity relation during methoxyflurane anesthesia was studied.

Methods

Studies were performed on eight mongrel dogs (average weight, 16.5 kg.), each serving as its own control. Each dog was anesthetized with either chloralose alone (average dose: 124 mg./kg.) or a 1:10 chloralose-urethane solution (chloralose 45.7 mg./kg., urethane 457.2 mg./kg.) injected intravenously. The trachea was intubated with a cuffed endotracheal tube after intravenous administration of gallamine triethiodide (40 mg., i.v.). Respiration was controlled by means of a volume-limited ventilator¹² using a nonbreathing system. The tidal volume and respiratory frequency were kept constant to maintain arterial blood gases within a normal range (pH 7.35-7.40; P_{CO_2} , 35-40 mm. Hg).

* Assistant Professor of Anesthesiology.

† Professor of Anesthesiology.

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The root of the aorta and the left stellate ganglion were exposed via a sternal-splitting thoracotomy. The descending sympathetic chain and associated ganglion were separated from the stellate ganglion to the level of the sixth thoracic vertebral body. A bipolar electrode was applied to the caudal pole of the left stellate ganglion stimulated with square-wave impulses of 5-msec. duration and 7 volts' intensity for 30 seconds. Frequency of stimulation was varied from 0.5/sec. to 10/sec. using a Grass stimulator (Model S4) with a stimulus isolation unit. Both vagi were sectioned in the neck.

Left ventricular pressure was measured through a teflon needle (B.D. #15-T) inserted through the ventricular apex and connected directly to a Statham P23Db transducer. Testing of this pressure-recording system revealed a uniform (± 5 per cent) amplitude response to 50 cycles per second. The first derivative of the ventricular pressure pulse was continuously computed electrically by an R-C differentiating circuit,[†] the amplitude of which was a linear function of frequency to 40 cycles/second.

A noncannulating probe was placed in the aortic root, and ejection rate was measured with a sine-wave electromagnetic flowmeter (Multi-flu, Model M-4000, Statham, Calif.). The flowmeter was calibrated by the method of Case et al.¹³ using cellulose dialysis tubing. The average value of the probe factor readings was 48.1 ± 1.14 (\pm SE) ml./min./mm. paper deflection, giving a flow reading error of less than 2 per cent. Cardiac output was determined by the indocyanine dye-dilution technique.¹⁴ A thermistor was inserted into the descending aorta through a femoral artery, and the left ventricular ejection fraction was determined by the thermal dilution technique as described previously.¹⁵⁻¹⁸ All determinations were recorded together with the electrocardiogram on a multichannel oscillograph (Sanborn, Model 560) at a paper speed of 200 mm./sec.

[†] Sanborn Model 350-1500A plus a differentiator plug-in; the latter was made by Mr. J. Brown, Hewlett-Packard Co., Sanborn Division, Waltham, Mass.

MEASUREMENTS

Control measurements of cardiac output and thermal dilution curves were made in duplicate. An isovolumic contraction, systole without ejection of blood, was produced in order to determine force-velocity relations; sudden occlusion of the aorta distal to the flowmeter probe was accomplished by rapid application of a Rumel tourniquet, for one systole only, and in each case zero flow was recorded in the flow-rate recording. Measurements of force-velocity relations were repeated during cardiac sympathetic nerve stimulation at various frequencies.

After determination of force-velocity relations, cardiac output and end-diastolic volume during the control state, a Pentec vaporizer was inserted into the nonbreathing ventilation system, and methoxyflurane administered. Determinations of force-velocity relations were repeated during a specific level of methoxyflurane anesthesia. The concentration of methoxyflurane in arterial blood was determined by a gas chromatographic method as described previously.¹⁷ Arterial blood samples, taken immediately before and after measurement of the force-velocity relationships, were analyzed for pH and P_{CO_2} .

CALCULATIONS

Analyses of force-velocity relations were made at 10-msec. intervals throughout systole in the manner described by Levine and Britman (see appendix).⁹ In all computations it was assumed that the left ventricle may be represented as a homogeneous thin-walled spherical configuration, and that all portions of the ventricle contract simultaneously and equally. It has been demonstrated that the variation of difference in calculated force for varying axis ratios in spheroids and ellipsoids in the physiologic range is less than 10 per cent.¹⁸ Left ventricular end-diastolic volume (EDV) was measured by the thermal dilution technique^{15, 16, 19} using the formula:

$$EDV = \frac{SV}{\left(1 - \frac{\Delta T_n + 1}{\Delta T_n}\right)}$$

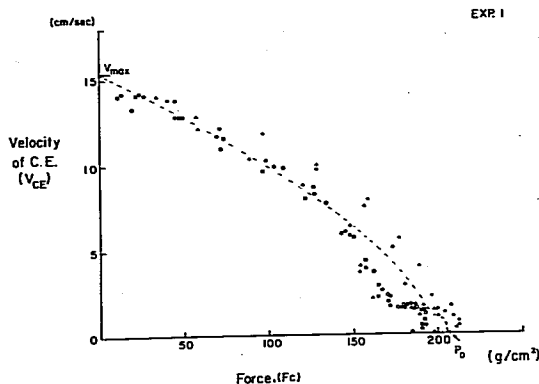


FIG. 1. Velocity of shortening of the contractile element in cm./sec. (V_{CE}) plotted against myocardial wall force per unit of circumference in $Gm./cm.^2$ (F_c) during isovolumic beats. Each of the different marks indicates points derived from average values of duplicate measurements which were made repeatedly during the control period in one dog.

where, SV = stroke volume; EDV = end-diastolic volume; ΔT_n and ΔT_{n+1} are differences between baseline aortic temperature and those at beats n and $n+1$, respectively, measured at end-diastole from the exponential step function of the aortic thermodilution curve (see appendix and fig. 6). Stroke volume was determined by integrating the area under the flow-rate curve using Simpson's rule²⁰ and correlated with the value obtained by dividing cardiac output (dye dilution) by heart rate. Comparisons between stroke volume determined by dye-dilution method and stroke volume directly by the magnetic flowmeter revealed a maximum deviation of ± 2.0 per cent. Therefore, the stroke volume derived from the flow-rate curve was used for the calculation of end-diastolic volume. Left ventricular radius (R) was calculated from the volume equation of a sphere, $V = 4/3 (\pi R^3)$, by solving for R . The force per unit length of circumference (F_c) in $Gm./cm.^2$ was calculated using the formula²¹:

$$F_c = \frac{PR}{2},$$

where P = intraventricular pressure in $Gm./cm.^2$

The shortening velocity of the contractile element (dl/dt) may be calculated by dividing the rate of force development (dF/dt),

calculated from changes in the intraventricular pressure, by the stiffness of the series elastic element (dF/dl); thus,

$$dl/dt = \frac{dF/dt}{dF/dl}$$

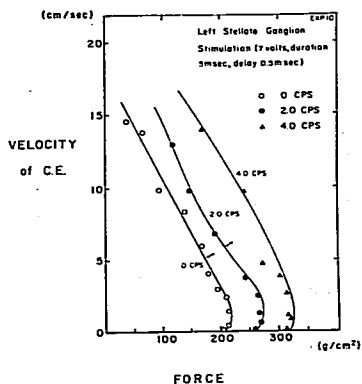


FIG. 2. Force-velocity relations obtained prior to (open circles) and during (dots and triangles) the frequency-graded left stellate ganglion stimulation during the control state. Both maximum shortening velocity of the contractile element and maximum force increased during the cardiac sympathetic nerve stimulation as a function of the frequency of stimulation.

TABLE 1. Values of Hemodynamics, End-diastolic Ventricular Volume, Peak Force and Maximum Velocity of Shortening of the Contractile Elements before and during Methoxyflurane Anesthesia in Eight Dogs*

Exp. No.	Methoxyflurane Conc. (mg./100 ml)	HR (beats/min.)	MAP (mm. Hg)	Max. dp/dt (mm. Hg/sec.)	EDV ml.	Po (Gm./cm. ²)	V _{max} (cm./sec.)
1	0	149	104	1,283	30.1	193	15.6
	24.1	124	65	683	36.4	127	15.2
2	0	141	99	2,355	44.6	319	20.6
	20.0	127	58	723	41.9	136	20.7
	22.8	123	57	679	34.6	118	20.0
3	0	181	123	2,246	95.9	378	31.0
	12.6	135	93	1,531	117.3	307	29.5
6	0	173	103	3,041	34.6	379	20.0
	16.9	141	63	7,441	21.6	122	18.5
7	0	202	126	3,412	25.0	301	22.0
	11.6	170	85	1,610	34.9	245	23.0
	13.0	158	67	1,575	35.6	202	22.0
9	0	158	93	1,986	37.8	323	23.0
	13.0	133	83	986	30.8	174	22.5
10	0	173	107	1,794	18.8	202	19.7
	14.5	144	76	1,024	22.8	149	20.0
11	0	172	126	1,890	29.4	355	14.6
	15.5	139	101	1,225	10.5	138	13.0
	23.0	120	53	569	21.9	106	14.0
Mean ± SE	17.0 mg./100 ml. ± 1.4	-18.5% ± 1.7	-34.7% ± 4.0	-51.1% ± 4.3	-2.5% ± 10.3	-45.1% ± 13.1	-2.6 ± 1.3
P		<0.01	<0.01	<0.01	>0.5	>0.01	>0.05

Methoxyflurane conc. = arterial blood methoxyflurane concentration; HR = heart rate; MAP = mean arterial pressure; Max dp/dt = maximum values of the first derivative of the left ventricular pressure; EDV = end-diastolic volume of left ventricle; Po = peak myocardial wall force; V_{max} = maximum velocity of shortening of the contractile element.

The stiffness of the series elastic element has been shown to be a linear function of force in cardiac muscle: $dF/dl = kF$.^{22, 23} In the intact dog heart, $k = 17.7$ (corrected for a muscle of 1 cm.³ dimension).²⁴ Calculation of dF/dt was done by differentiation of the equation,

$$F = \frac{PR}{2};$$

$dF/dt = 1/2 (R \cdot dP/dt - P \cdot dR/dt)$. Since dR/dt equals zero in the isovolumic contractions, $dF/dt = 1/2 R (dP/dt)$. Having calculated dF/dl and dF/dt , it was then possible to calculate dl/dt (per cm. of circumference).

The rate of shortening of contractile elements, V_{CE} , was expressed for the entire circumference by multiplying $2\pi R$:

$$V_{CE} = \frac{2\pi R (1/2 R dP/dt)}{17.7 PR/2} = \frac{\pi R dP/dt}{8.9 P}$$

Direct measurements of intraventricular pressure (P), and left ventricular dp/dt were made on the original tracing and all derived computations were performed by means of an IBM system 360 model 30 digital computer* (see appendix).

* System Computer Application Department, Tufts-New England Medical Center Hospitals.

Results

REPRODUCIBILITY OF THE FORCE-VELOCITY RELATIONS

Each of force-velocity curves was constructed by plotting average values of the myocardial force per unit of length of circumference (F_0) in Gm./cm.² against those of shortening velocity of the contractile element (V_{CE}) in cm./sec. obtained from two single isovolumic contractions. The mean values of peak force (P_0) and maximum velocity of shortening (V_{max}) obtained by extrapolation of the value of V_{CE} to a zero force, in seven determinations were 15.6 ± 0.1 (\pm SE) cm./sec. for V_{max} and 193 ± 3.6 (\pm SE) Gm./cm.² for P_0 , respectively.

EFFECT OF LEFT-STELLATE-GANGLION STIMULATION

During the control state, stimulation of the left stellate ganglion caused increases in both maximum velocity of shortening (V_{max}) and peak force (P_0) (fig. 2).

The average increase in peak force (P_0) in four experiments with stimulus frequencies of 0.5, 1.0, 2.0, 4.0 and 6.0 per second, were 12 per cent, 24 per cent, 32 per cent, 38 per cent and 22 per cent, respectively. The increases in the maximum velocity of shortening (V_{max}) with the frequency-graded stimulation to the left stellate ganglion were, on the average, 2 per cent for 0.5 c.p.s., 14 per cent for 1.0 c.p.s., 20 per cent for 2 c.p.s., 29 per cent for 4 c.p.s., and 26 per cent for 6 c.p.s., respectively.

EFFECT OF METHOXYFLURANE

Changes in peak force (P_0) and maximum velocity of shortening (V_{max}) during the administration of methoxyflurane are summarized in table 1. In all experiments, methoxyflurane (average arterial blood concentration: 17.0 ± 1.4 mg./100 ml.) caused a reduction in peak force (P_0) (fig. 3). The average reduction in P_0 during anesthesia from control values in eight experiments was -45.1 ± 13.1 per cent ($P < 0.01$), ranging from -18.6 per cent to

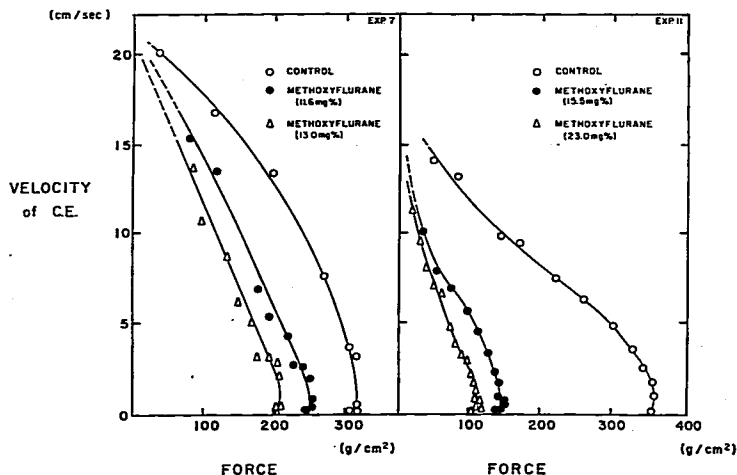
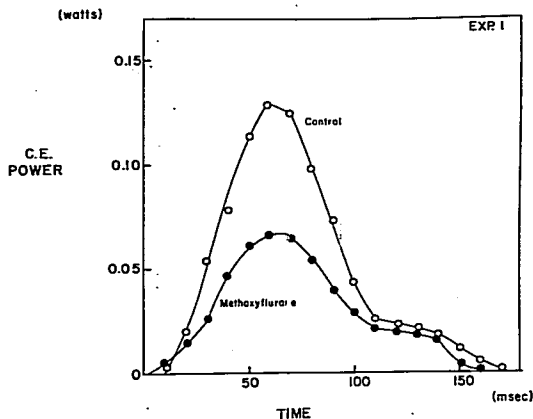


FIG. 3. Force-velocity relations from two experiments prior to (open circles) and during the administration of methoxyflurane (dots and triangles). In both experiments there is a decrease in the maximum force (P_0) during anesthesia.

FIG. 4. Power-time plots obtained in one dog (exp. 1) prior to (open circles) and during methoxyflurane anesthesia (dots). There is a decrease in the contractile element power during the administration of methoxyflurane.



— 70.2 per cent. The average change in maximum velocity of shortening (V_{max}) during anesthesia was -2.6 ± 1.3 per cent ($P > 0.05$). Contractile element power, calculated as a product of the shortening velocity of the contractile element (V_{CE}) and myocardial force per unit of circumference (F_C), also decreased during anesthesia (fig. 4).

EFFECT OF CARDIAC SYMPATHETIC NERVE STIMULATION DURING ANESTHESIA

The left-stellate-ganglion stimulation resulted in increases in peak force (P_0) but not in maximum velocity (V_{max}) during a specific level of methoxyflurane anesthesia (fig. 5). Table 2 shows values of P_0 and V_{max} and percentage changes in these parameters before and during methoxyflurane anesthesia with and without sympathetic nerve stimulation in four dogs. The percentage increases in P_0 during anesthesia in response to sympathetic stimulation differed significantly ($P < 0.01$) from those of the control state at any given frequency of stimulation. The mean percentage changes in P_0 in four dogs, during anesthesia with stimulation frequencies of 2, 4 and 6 per second, were 63 per cent, 67 per cent and 59 per cent. During anesthesia the values of V_{max} were unchanged with sympathetic

stimulation in contrast to significant increases in V_{max} values during the control state. Statistical analysis revealed that changes in V_{max} during anesthesia with sympathetic stimulation differed from those of the control state ($P < 0.01$).

EFFECT OF METHOXYFLURANE ON HEMODYNAMICS

During anesthesia the average change in heart rate was -18.5 ± 1.7 per cent ($P < 0.01$). Mean arterial blood pressure and left ventricular dP/dt decreased significantly on an average of -34.7 ± 4.0 per cent ($P < 0.01$), and -51.1 ± 4.3 per cent ($P < 0.01$), respectively. The change in left ventricular end-diastolic volume was -2.5 ± 10.3 per cent ($P > 0.5$).

Discussion

There have been contradictory definitions in the descriptions of changes in myocardial contractility during anesthesia.¹ The application of the force-velocity relation, a fundamental property of skeletal muscle, to analyses of myocardial contraction has been shown to be important in determining the intrinsic contractile state of isolated cardiac muscle, *i.e.*, myocardial contractility.⁵⁻⁷ Recently it has been

demonstrated that at a given left ventricular end-diastolic pressure, the force-velocity relation also reflects the contractile state of the intact canine ventricle.⁸⁻¹¹ In a previous publication,² we suggested that the effect of an anesthetic agent upon myocardial contractility is a complex and integrated function of the action upon several important parameters, which include preload (end-diastolic ventricular pressure), afterload (mean arterial pressure), and inotropic state of the myocardium (force-velocity relations). The findings of the present study show that the instantaneous reciprocal relation between the myocardial wall force (F_c) and the shortening velocity of the contractile elements (V_{CE}) obtained during

the course of single isovolumic contractions is a useful and sensitive method to determine the changes in the contractile state of the heart.

The present study indicates that methoxyflurane exerts a direct negative inotropic effect upon the contractile state of the intact dog heart. At any given myocardial force, there were reductions of the shortening velocity of the contractile element. The product of force and velocity of shortening is the contractile element power.³ This decreased at any given myocardial force level, indicating a negative inotropism (fig. 4). These effects upon myocardial mechanics of the intact canine left ventricle are qualitatively similar to those pro-

TABLE 2. Changes in Peak Force and Maximum Velocity before and during Methoxyflurane Anesthesia with and without Cardiac Sympathetic Nerve Stimulation

Exp. No.	Stimulation Frequency (cycle/sec.)	Change in Peak Force (F_0)				Change in Maximum Velocity (V_{max})			
		Control		Methoxyflurane		Control		Methoxyflurane	
		(Gm./cm. ²)	($\Delta\%$)	(Gm./cm. ²)	($\Delta\%$)	(cm./sec.)	($\Delta\%$)	(cm./sec.)	($\Delta\%$)
7	0	301	—	202	—	22.0	—	23.0	—
	.5	327	9	261	29	22.1	0.5	23.2	11.4
	2	360	20	262	30	26.5	20.5	24.3	10.5
	4	323	7	263	30	27.4	24.5	24.1	9.5
	6	332	10	270	34	27.3	24.0	23.9	8.6
9	0	323	—	174	—	23.0	—	22.5	—
	.5	370	15	250	44	23.1	0.4	22.1	-1.8
	2	500	55	285	121	25.8	12.2	26.3	16.9
	4	520	61	344	98	29.9	30.0	19.4	-13.8
	6	390	21	325	87	31.4	36.5	25.1	11.6
	8	335	4	245	41	23.7	3.0	25.0	11.1
10	282	-13	232	33	22.7	-2.2	20.3	-9.8	
10	0	202	—	149	—	19.7	—	20.0	—
	1	255	26	157	5	20.9	6.1	19.3	-3.5
	2	275	36	195	31	22.0	11.7	19.4	-3.0
	4	330	63	237	59	23.3	18.3	19.7	-1.5
	6	272	35	227	52	23.6	19.8	19.2	-4.0
	8	295	46	225	51	23.2	17.8	19.2	-4.0
11	0	355	—	138	—	14.6	—	13.0	—
	1	420	18	200	45	18.6	27.4	13.3	2.3
	2	428	18	235	70	19.6	34.2	14.5	11.5
	4	430	21	248	80	20.9	43.2	14.4	10.8
	6	433	22	227	64	18.2	24.7	13.2	1.5
	8	433	22	240	74	20.7	41.8	14.0	7.7
	10	422	19	267	94	20.8	42.5	14.0	7.7
Mean (range)	2 c.p.s.	32% (18-55)		63% (30-121)		20% (12-34)		9% (-3-17)	
	4	38% (7-63)		67% (30-98)		29% (18-43)		1% (-14-11)	
	6	22% (10-35)		59% (34-87)		26% (20-37)		4% (-4-12)	

duced by methoxyflurane in isolated cat cardiac muscle.²⁴

According to Laplace's law,²¹ myocardial wall force is a function of both intraventricular pressure and the radius of the ventricle. Thus, changes in myocardial force observed in the present study may be related to changes in intraventricular volume or the radius of the left ventricle at a given intraventricular pressure. However, the average change in left ventricular end-diastolic volume during anesthesia was -2.5 ± 10.3 per cent, not significant (table 1). Therefore, it seems reasonable to conclude that the observed changes in the myocardial force during methoxyflurane anesthesia were not complicated by change in left ventricular size.

It has been reported that direct electrical stimulation of the left stellate ganglion in dogs causes a positive inotropism,²⁵⁻²⁷ as evidenced by increase of myocardial contractile force, a more rapid and higher rise in ventricular pressure, increase of stroke work at any given end-diastolic pressure, and an increase in stroke volume. In the present study the stellate ganglion was stimulated electrically, and both maximum velocity of shortening (V_{max}) and peak force (P_0) increased in all of four experiments. These changes demonstrate a positive inotropism.

It has been suggested that the activity of the cardiac sympathetic nerve may play an important role in supporting myocardial performance during general anesthesia.^{1, 28-30} Plasma catecholamine concentrations are not significantly increased during methoxyflurane anesthesia in the dog.³¹ Apparently, the sympathetic nerve system does not play an important role in supporting the cardiovascular system during administration of methoxyflurane. The observed reduction of peak force during anesthesia may be related to the direct negative inotropism evoked by methoxyflurane without being complicated by the activity of the sympathetic nervous system. During the control state the sympathetic stimulation caused increases in both V_{max} and P_0 , indicating a positive inotropism. However, when the sympathetic stimulation was repeated during anesthesia there was an increase only in P_0 , not in V_{max} . It has been suggested that the

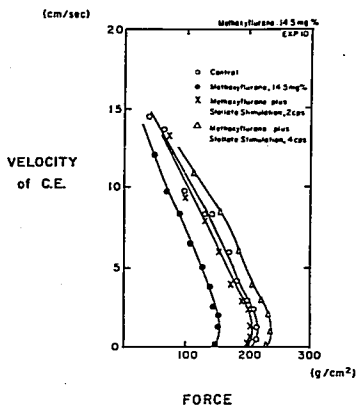


FIG. 5. Force-velocity relations before (open circles) and during (dots) a steady level of methoxyflurane anesthesia (arterial concentration 14.5 mg./100 ml.). There is an increase in the maximum force (P_0) when the stimulation of the left stellate ganglion was superimposed during anesthesia (triangles and x's).

change in V_{max} is a more sensitive indicator of the change in contractile state of the myocardium than the change in P_0 .^{5, 6} Podolsky postulated that V_{max} may be considered an experimental measure of the absolute rate of the force generating the chemical process of the muscle, whereas P_0 is a function of the number of active tension generating contractile sites.³² More recently, it has been suggested that an increase in the initial fiber length (pre-load) without changes in V_{max} may be due to the increased number of contractile sites available during the contraction.^{5, 6, 33} On the other hand, changes in the inotropic state (*i.e.*: norepinephrine or digitalis administration) accompany changes in V_{max} and may be related to alterations in the rate of force development at each contractile site.^{5, 6, 33} Therefore, the increase in P_0 occurring in response to the sympathetic nerve stimulation during anesthesia, without a change in V_{max} , may be considered an additional evidence that methoxyflurane evokes a direct negative inotropic effect on the myocardial contractility.

Summary

Evidence presented here indicates that methoxyflurane exerts a negative inotropic effect upon the intrinsic contractile state of the intact canine left ventricle, as determined by the force-velocity relations. Myocardial force-velocity relations were restored to the control levels when stellate ganglion stimulation was superimposed during methoxyflurane anesthesia. These findings may indicate that during methoxyflurane anesthesia sympathetic receptors in the heart can respond to the sympathetic transmitter, resulting in an augmentation of the maximum myocardial force.

APPENDIX

Calculation of End-diastolic Volume: Figure 6A represents a thermodilution curve recorded at the ascending aorta following a rapid injection of room-temperature saline (3-5 ml.) into the left ventricle. Only the portion of the curve during

a stepwise return of the aortic blood temperature was recorded in order to obtain full-scale sensitivity (0.10° C. per cm.).

The temperature readings at the beats n and $(n+1)$ were 36.12 and 36.27° C., respectively. The baseline aortic blood temperature was at 37.0° C. Thus, the temperature differences between the baseline temperature and those at n th and $(n+1)$ th beats were 0.88 and 0.73, respectively. Stroke volume (SV) derived from the blood flow rate curve was 14.1 ml. The end-diastolic volume (EDV) in ml was calculated from the following formula:

$$EDV = \frac{SV}{1 - \left(\frac{\Delta T_n + 1}{\Delta T_n} \right)} = \frac{14.1}{\left(1 - \frac{0.73}{0.88} \right)} = 70.7 \text{ (ml.)}$$

Calculation of Left Ventricular Radius (R): During an isovolumic contraction, there is no ejection of blood from the left ventricle. Thus, the left ventricular volume remains constant and equal to the end-diastolic volume (EDV). The radius (R) of the left ventricle may be calculated from the volume equation of a sphere (fig. 7).

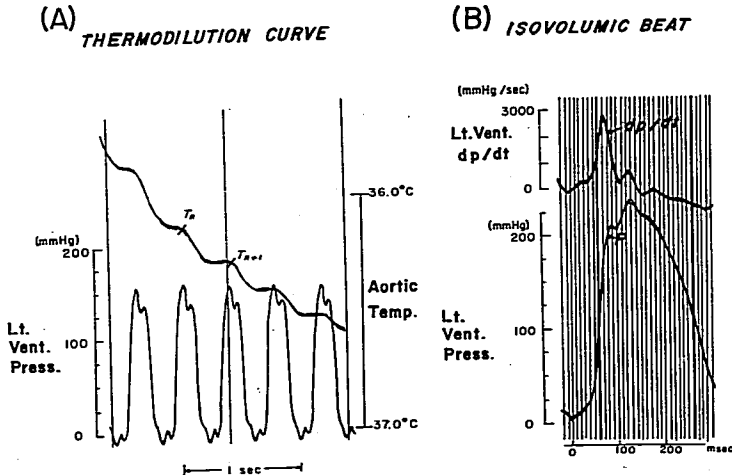


FIG. 6. A. The upper tracing is the exponential step function of the aortic blood temperature following an injection of saline solution at room temperature: downward deflection indicates increased temperature. The baseline aortic blood temperature was 37.0° C. T_n and T_{n+1} are temperatures at beats n and $n+1$ at the end-diastole phase, respectively. The lower tracing is the intraventricular pressure of the left ventricle. B. Recordings of the left ventricular pressure in mm. Hg and the first derivative of the left ventricular pressure in mm. Hg/sec. Paper speed: 200 mm./sec. (each interval equals 10 msec.).

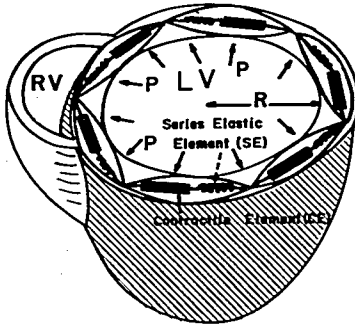


FIG. 7. Spherical configuration of the left ventricle (LV) with mathematical model of heart muscle according to A. V. Hill's muscle model. P: intraventricular pressure of left ventricle in mm. Hg; R: left ventricular radius in cm. Definitions of rate of myocardial force development, stiffness of the series elastic element (SE) and shortening velocity of the contractile element (CE) are shown as are various mathematical equations used for the calculations of total force, force per unit length of circumference and shortening velocity of the CE.

$$\text{Volume: } V = \frac{4}{3} \pi R^3$$

$$V = EDV = 4/3 \cdot (\pi R^3)$$

$$R = 3 \sqrt{\left(\frac{3}{4\pi}\right) \cdot (EDV)} = 3 \sqrt{0.24(70.7)} = 2.6 \text{ cm.}$$

Calculation of Myocardial Force: According to Laplace's law,²¹ if P represents the intraventricular pressure and R the radius, the total force (F_t) at the equatorial circumference that tends to separate the two hemispheres may be calculated as the product of P and the area of the circle at the equator using the following formula: $F_t = P \cdot \pi R^2$.

The total force (F_t) calculated in accordance with the above equation is a function of not only the intraventricular pressure (P) but also the radius (R). Therefore, in the present study, the myocardial force per unit length of circumference (F_c) in Gm./cm.² was used from the following equation:

$$F_c = \frac{P \cdot R \times 1.36}{2} \text{ (Gm./cm.)}^2$$

$$\text{Rate of Force Development: } \frac{dF_c}{dt}$$

$$\text{Dynamic Stiffness of S.E.: } \frac{dF_c}{dl}$$

$$\text{Shortening Velocity of C.E., } (V_{ce}): \frac{dl}{dt}$$

$$\text{Total Force, } F_t = P \cdot \pi R^2$$

$$\frac{\text{Force}}{\text{unit of } C}, F_c = \frac{P \cdot R}{2}$$

$$\frac{dl}{dt} = \frac{dF_c}{dt} / \frac{dF}{dl}$$

$$\frac{dF_c}{dl} = k F_c (F_c = \text{load}); k = 17.7$$

$$\frac{dF_c}{dt} = \frac{1}{2} \left(R \frac{dP}{dt} - P \cdot \frac{dR}{dt} \right)$$

$$P \cdot \frac{dR}{dt} = 0$$

Shortening Velocity of C.E.:

Isovolumic Contraction

$$V_{ce} = \left(\frac{dl}{dt} \right) 2\pi R = \frac{\pi R \cdot dp/dt}{8.9 \cdot P}$$

The factor of 1.36 was multiplied in order to convert pressure unit of mm. Hg into a gram/cm.² force unit.

The myocardial force per unit of circumference (F_c) was calculated at 10-msec. intervals in fig. 6B. The intraventricular pressure (P) at 80 msec. from the onset of an isovolumic contraction was 201 mm. Hg.

$$F_c = \frac{201 \times 1.36 \times 2.6}{2} = 351 \text{ (Gm./cm.)}^2$$

Calculation of Shortening Velocity of Contractile Element (V_{ce}): Analyses of the force-velocity relations were made using Hill's muscle model,²² in which the rubber-like, active, contractile element (C.E.) unites in series with a spring-like, passive, series elastic element (S.E.) (see fig. 7). Isovolumic contraction of the left ventricle was considered analogous to the isometric contraction (contraction without muscle fiber shortening) of the isolated heart muscle. Upon activation, chemical energy is converted into mechanical energy.

During isometric contraction, both ends of the muscle are fixed by external constraints and there is no apparent shortening. Force develops when the contractile elements start to shorten against the series elastic element. Therefore, during the isometric or isovolumic contractions, the shortening velocity of the contractile element was considered equal to the rate of lengthening (dl/dt) of the spring-like series elastic element. The shortening velocity of the contractile element (dl/dt) is directly proportional to the rate of force development (dF/dt) and inversely proportional to the stress-strain relationship (dF/dl ; stiffness) of the series elastic element (see fig. 7).

$$V_{cs} = \frac{dF/dt}{dF/dl}$$

where the stiffness of the series elastic element may be calculated from the following equation: $dF/dl = 17.7 F_c$. The rate of force development may be derived from the differentiation of the equation, $F_c = 1/2 (P - R)$

$$\therefore \frac{dF_c}{dt} = \frac{1}{2} \cdot \left(R \cdot \frac{dP}{dt} - P \frac{dR}{dt} \right)$$

In the isovolumic contraction, R remains constant and, therefore,

$P \cdot \frac{dR}{dt}$ becomes zero. Thus,

$$\frac{dF_c}{dt} = \frac{1}{2} R \frac{dP}{dt} \times 1.36 \text{ (Gm./cm.}^2\text{/sec.)}$$

The rate of intraventricular pressure development (dP/dt) is shown at the upper tracing of fig. 6B. The value of dP/dt at 80 msec. after the onset of isovolumic contraction is 2,257 mm. Hg/second. The shortening velocity of the contractile element is expressed for the entire circumference by multiplying $2 \pi R$:

$$\begin{aligned} V_{cs} &= \frac{2\pi R \times 1/2 R \cdot dP/dt \times 1.36}{17.7P \cdot R \times 1/2 \times 1.36} \\ &= \frac{\pi R \cdot dP/dt}{8.9P} \\ &= \frac{3.4 \times 2.6 \times 2257}{8.9 \times 201} = 10.2 \text{ (cm./sec.)} \end{aligned}$$

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Drugs

HEXOBARBITAL METABOLISM Slices of rat hepatoma failed to metabolize hexobarbital (Evipal) *in vitro*; slices of non-tumorous liver from host rats metabolized it at a lower rate than liver slices from normal animals. A corresponding *in vivo* difference was a prolonged hexobarbital sleeping time in tumor-bearing rats. The prolongation began only when the hepatoma became large enough to show areas of necrosis or ulceration. Surgical removal of the tumor restored sleeping time to normal. Since the tumor was implanted subcutaneously and did not invade the liver, it was suggested that a diffusible product of the tumor was responsible for the impairment of hexobarbital metabolism in the host liver. (*Hickie, R. A., and Kalant, H.: Modification of Hexobarbital Metabolism by Morris Hepatoma, Canad. J. Physiol.* 45: 975 (Nov.) 1967.)

MEPROBAMATE OVERDOSAGE Meprobamate intoxication is encountered frequently but is seldom a treatment problem. The relatively short duration of coma and the low mortality result from rapid endogenous metabolism of the drug. In most cases only supportive therapy is needed. However, when intoxication is severe or is complicated by intercurrent illness or other drugs, treatment with forced diuresis or hemodialysis should be considered. In the authors' experience, the best criteria of profound intoxication were the clinical state of the patient and a plasma meprobamate concentration approaching 20 mg./100 ml. (*Maddock, R. K., Jr., and Bloomer, H. A.: Meprobamate Overdosage: Evaluation of Its Severity and Methods of Treatment, J.A.M.A.* 201: 999 (Sept.) 1967.)