The Effect of Ethrane on Cardiac Muscle Mechanics

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The inotropic effect of Ethrane on the intrinsic contractile state of the cat papillary heart muscle was studied in terms of mechanics of contraction. Negative inotropic responses to Ethrane were compared with those of methoxyflurane and halothane. Ethrane caused dose-dependent decreases in maximal velocity (V_{max}), peak force (F_m), power, and work during isotonic contraction, and was less depressant than halothane and methoxyflurane. A greater concentration of Ethrane (11 mg/100 ml) was required to produce the same degree of depression (50 per cent) in myocardial power as either methoxyflurane (4 mg/100 ml) or halothane (3 mg/100 ml). Similarly, a 50 per cent reduction in V_{max} required a higher concentration of Ethrane (233 per cent more than halothane and 18 per cent more than methoxyflurane). Therefore, Ethrane was less depressant to myocardial contractility than methoxyflurane or halothane. Probable mechanisms and significance of the change in the active state resulting from anesthetics are discussed.

ETHRANE (CHF_2-O-CF_2-CHFCl) (1,1,2-trifluoro-2-chloroethyl difluoromethyl ether)¶ has recently been introduced as a new, nonexplosive anesthetic agent. This compound, a potent anesthetic in both animals and man, does not produce gross disturbances in cardiohemodynamics.[1, 2] In view of the potential value of this agent, the present study was undertaken to obtain basic information related to the direct inotropic effect of Ethrane on the intrinsic contractile state of the isolated cat papillary heart muscle, as determined by force–velocity relations and the active state.

Materials and Methods

Papillary muscles were excised from the right ventricles of 11 normal cats (weighing 1.6–2.7 kg) anesthetized with chloralose intraperitoneally (80 to 100 mg/kg). Each heart muscle served as its own control. The isotonic lever system, muscle bath, perfusate, transducers and recording equipment have been described in detail.[3, 4]

All heart muscles were initially stimulated to contract isotonically at a frequency of 12 per min for at least 30 min at a level of less than 0.5 g. Measurements of the force–velocity relation and the active state were made before and after the administration of Ethrane.

Values were expressed as mean ± SEM and analyzed statistically by Fisher's t test.

Results

The directions and magnitudes of changes in the force–velocity relations in five heart muscles studied at 37 C were similar to those in six muscles studied at 22 C. Hence, the data obtained from muscles studied at the two temperatures were pooled.

Isotonic Contraction

In 11 heart muscles the peak force (F_m) always decreased during administration of Ethrane (concentration ranging from 1 to 29 mg/100 ml). The maximum velocity (V_{max}) decreased in all muscles when the concentration of Ethrane was higher than 3 mg/100 ml. In two muscles exposed to a low concentration (< 3 mg/100 ml), V_{max} increased (ranging from 12 to 32 per cent). During administration of Ethrane, force–velocity curves shifted to

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¶ Anesthetic Compound 347 supplied by Ohio Medical Products, a division of Air Reduction Company, Inc., Murray Hill, New Jersey 07971.

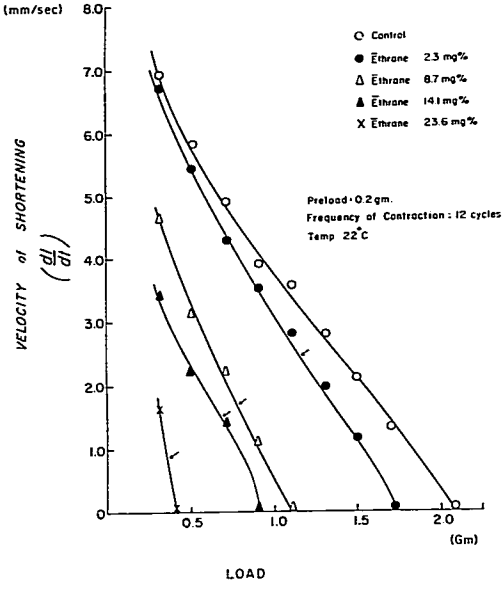

FIG. 1. Force-velocity curves obtained in cat papillary muscle before (open circles) and during exposure to the various concentrations of Ethrane at 37 C. The initial muscle length, 5.2 mm, was kept constant with a preload of 0.3 gm.

the left; the degree of leftward shift was dose-dependent (fig. 1). There were progressive decreases in net shortening, power and work, each given as a function of load, in the isotonically contracting heart muscle (fig. 2). Changes in V_{max}, F_m, maximal power and work were functions of increasing concentrations of Ethrane (fig. 3).

Correlation coefficients relating percentage changes in V_{max}, F_m, maximal power and work to anesthetic concentrations were −0.66, −0.76, −0.82 and −0.76, respectively. Concentrations of Ethrane necessary to produce 50 per cent depression in 11 heart muscles were calculated by deriving linear regression equations and were 20, 16, 19, and 11 mg/100 ml, respectively (table 1).

Isometric Contraction and Active State

The maximal rate of force development (max dF/dt) decreased progressively with increasing concentration of Ethrane in 11 heart muscles contracting isometrically (fig. 4). The correlation coefficient relating the percentage change in max dF/dt to anesthetic concentration was −0.83.

The times to peak isometric force (TTF_m) in 11 muscles before and during the administration of Ethrane averaged 356 ± 69 msec and 297 ± 28 msec, respectively. When values of TTF_m obtained during the control state were paired with those obtained during administration of Ethrane, the anesthetic agent significantly reduced the duration of contraction ($P < 0.01$).

Modulus of Elasticity (Stiffness)

The values of the modulus of elasticity (stiffness) of the series elastic element (dF/dl) of heart muscles exposed to Ethrane did not differ significantly from control values. The mean slopes of the dF/dl-load curves in five muscles before and during administration of

Ethrane were 3.18 ± 0.35 and 3.20 ± 0.23, respectively ($P > 0.5$).

Discussion

Results of the study demonstrate that Ethrane alters the intrinsic contractile state of cardiac muscle primarily by affecting its capacity to develop force and shorten, as reflected by decreases in the maximal velocity (V_{max}) and peak form (F_m) of muscle contracting isotonically, and by decreases in the maximal rate of force development (max dF/dt) in the isometrically contracting muscle. The negative inotropic response, as indicated by reductions in V_{max}, power, and work, varied directly with the concentration of the agent. These findings suggest that Ethrane exerts a direct negative inotropic effect on the contractility of the isolated heart muscle. However, it should be pointed out that greater concentrations of Ethrane than of either halothane or methoxyflurane were needed to produce 50 percent depressions in V_{max}, F_m, maximal power, maximal work and maximal dF/dt (fig. 5). Recent studies show that V_{max} indicates the intrinsic contractile state of the myocardium, independent of initial fiber length, and determines contractility of muscle at a given fiber length (preload) and the load that the muscle carries during a contraction (afterload).[5] Therefore, it seems reasonable to state that Ethrane is the least myocardial depressant of the three anesthetic agents under consideration.

In isotonic contraction, peak force (F_m) was reduced more than maximal velocity (V_{max}) in heart muscle exposed to Ethrane. The

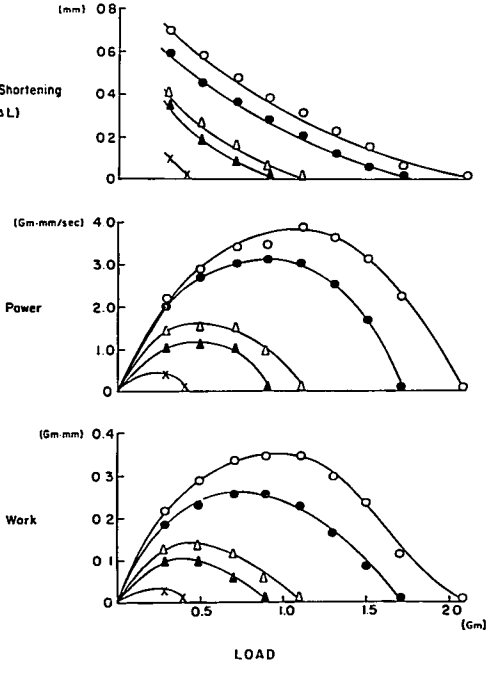

FIG. 2. Changes in net shortening (top), power (middle) and work (bottom) of one cardiac muscle were plotted against varying afterload (force) during isotonic contraction. *Note:* Ethrane caused a dose-dependent decrease in these parameters.

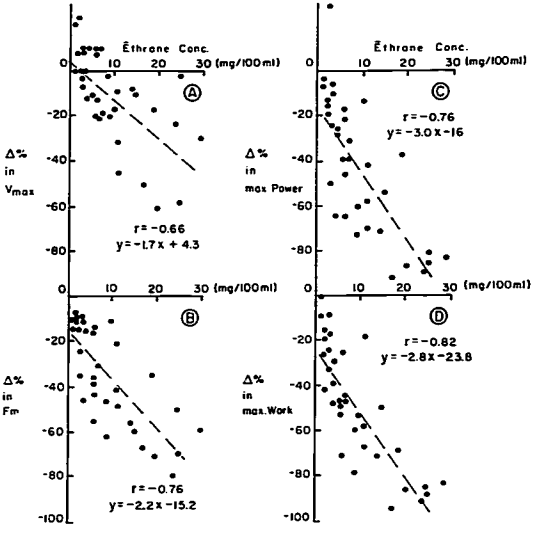

FIG. 3. Percentage changes in V_{max} (A), F_m (B), power (C) and work (D) were plotted against concentrations of Ethrane in mg/100 ml of Krebs–Henseleit solution in 11 heart muscles contracting isotonically. V_{max}: maximal velocity of shortening; F_m: peak isometric force.

finding of a leftward shift of the force–velocity curves with a substantial reduction in the F_m, associated with relatively little change in V_{max}, is comparable to those observed with methoxyflurane.[4] In contrast, halothane produces equivalent reductions in F_m and V_{max}.[3] Our recent studies of the intact dog heart reveal that both methoxyflurane and Ethrane cause greater changes in F_m than in V_{max},[5] whereas halothane causes equivalent decreases in both V_{max} and F_m.[6, 8] It has been postulated that V_{max} is related to the rate of the force-generating chemical process within the contractile sites, whereas F_m is a function of the number of force-generating sites participating in the contraction.[9] Therefore, it seems appropriate to state that the substantial decreases in F_m with small changes in V_{max} may indicate that Ethrane predominantly causes alterations in the actual numbers of active force-generating contractile sites, and has less effect upon the velocity of the chemical reactions involving the contractile proteins. It is apparent, therefore, that Ethrane depresses the contractile machinery of the heart muscle less than methoxyflurane and halothane.

TABLE 1. Concentrations of Ethrane, Methoxyflurane and Halothane to Produce 50 Per cent Reductions of Parameters of Myocardial Mechanics

	Concentration (mg/100 ml)		
	Ethrane	Methoxyflurane	Halothane
V_{max}	20	17	6
F_m	16	12	7
Maximal power	11	4	3
Maximal work	9	6	3
Maximal dF/dt	13	9	5
TTF_m	decreased	decreased	increased

It is interesting to note that changes in the time-to-peak force (TTF_m) with Ethrane and methoxyflurane differed from those with halothane. Both Ethrane and methoxyflurane[4] decreased TTF_m, whereas halothane either did not alter it or even caused prolongation.[3] Decreases in F_m were accompanied by decreases in dF/dt and TTF_m in heart muscles exposed

to Ethrane and methoxyflurane. In contrast, F_m was altered primarily by changes in dF/dt, while TTF_m remained almost constant in muscles exposed to halothane.[3] It has been shown that TTF_m may be used as a gross function of the duration of the active state and that dF/dt reflects the intensity of the active state. Thus, decreased dF/dt and F_m with relatively unaltered TTF_m caused by halothane may be related to the decrease in intensity of the active state alone. Concomitant decreases in F_m, dF/dt and TTF_m caused by Ethrane and methoxyflurane may be due to decreases in both intensity and duration of the active state.

It has been suggested that changes in the intensity of the active state may be due to alterations in excitation–contraction coupling and/or in the chemical interactions of the contractile proteins,[10] and may be related to changes in the quantity of calcium available for activation.[11] Changes in the duration of the active state, however, may be related to how fast the myocardial relaxing factors remove activating substances (calcium).[12] Therefore, decreased intensity of active state with and without changes in duration observed with the three anesthetic agents may be related either to changes in the calcium concentration around the contractile proteins during excitation–contraction coupling or to alteration in the myocardial relaxing factors causing inhibition of rapid removal of the activating substances.

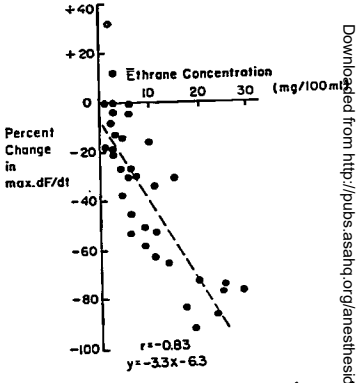

FIG. 4. Percentage changes in maximal rate of isometric force development (max dF/dt) were plotted against Ethrane concentration in mg/100 ml.

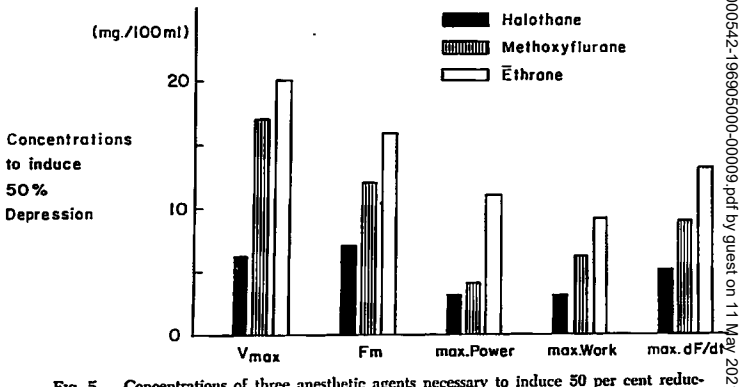

FIG. 5. Concentrations of three anesthetic agents necessary to induce 50 per cent reductions in V_{max}, F_m, maximal power, maximal work and maximal dF/dt were compared. Solid bars: halothane; vertical stripes: methoxyflurane; open bars: Ethrane. *Note:* In each parameter, a greater concentration of Ethrane is needed to produce 50 per cent depression.

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Drugs

BRONCHODILATORS In a double-blind crossover trial of responses of asthmatic patients to isoproterenol and metaproterenol, a significantly greater duration of action was found with metaproterenol. Fewer side effects appeared than after the administration of isoproterenol. (*Holmes, T. H.: A Comparative Clinical Trial of Metaproterenol and Isoproterenol as Bronchodilator Aerosols, Clin. Pharmacol. and Ther. 9: 615 (Sept.) 1968.*)

PLV-2 (OCTAPRESSIN) The systemic and renal hemodynamic effects of PLV-2 were studied in 11 patients with hypotension of decompensated hepatic cirrhosis. Intravenous infusion of PLV-2 resulted in dose-related increases in arterial pressure and systemic vascular resistance. Cardiac output and heart rate fell slightly, with no change in venous pressure. Low doses of PLV-2 (.004 to .02 units per minute) produced an increase in renal blood flow, a decrease in renal vascular resistance, and an increase in the renal fraction of cardiac output of from 9 to 14 per cent. Renal blood flow was somewhat lower at high than at low doses of PLV-2, but was still higher than predrug control values. No evidence of tachyphylaxis was seen during infusions lasting up to four hours. In hypotensive patients, PLV-2 produces renal vasodilatation and extrarenal vasoconstriction, resulting in redistribution of blood flow to the kidney. (*Cohen, J. N., and others: Systemic Vasoconstrictor and Renal Vasodilator Effects of PLV-2 (Octapressin) in Man, Circulation 38: 151 (July) 1968.*)