

# The Effects of Fluroxene and Enflurane on Contractile Performance of Isolated Papillary Muscles from Failing Hearts

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Effects of fluroxene and enflurane on myocardial mechanics of isolated papillary muscles obtained from cats with experimental congestive heart failure and from cats with normal hearts were compared. Significant impairment of myocardial performance, with elevated right ventricular pressure and reduced cardiac output, was observed in cats with congestive heart failure. At equipotent anesthetic concentrations (MAC in man) of fluroxene and enflurane, reductions of myocardial performance were similar in the two groups. When changes in maximal velocity of shortening ( $V_{max}$ ) and maximal developed force ( $F_m$ ) in muscles from hearts after congestive heart failure at MAC were compared with control values for normal hearts, depressions were 68 per cent and 70 per cent for fluroxene, and 72 per cent and 68 per cent for enflurane, respectively. These depressions, resulting from the combined effects of congestive heart failure and anesthetic, were similar to those caused by halothane and by isoflurane, but significantly greater than that caused by cyclopropane. (Key words: Anesthetics, volatile: fluroxene; Anesthetics, volatile: enflurane; Heart: myocardial mechanics: fluroxene; Heart: myocardial mechanics: enflurane.)

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RECENTLY we reported that the combined negative inotropic effects of general anesthetics (halothane,<sup>1</sup> isoflurane,<sup>2</sup> and cyclopropane<sup>3</sup>) and experimentally produced congestive heart failure result in more severe depression than that produced by anesthetics alone in normal heart muscle. The purpose of the present study was to determine whether fluroxene and enflurane have similar effects on muscular mechanics in failing hearts. Thus, the study was designed to compare the direct inotropic effects of fluroxene and enflurane on mechanics of muscular contraction in isolated papillary muscles obtained from cats with experimental congestive heart failure and from those with normal hearts.

## Materials and Methods

Normal adult cats (weighing 2.3 to 3.8 kg) were used. The method for producing congestive heart failure (CHF) has been described.<sup>1-4</sup> In brief, after anesthesia produced by intraperitoneal injection of sodium pentobarbital, right ventricular CHF was produced by constriction of the pulmonary artery in 25 cats. Fifteen cats with normal hearts (NH), not subjected to operation, were also studied and served as controls.

Four weeks after operation, the cats were anesthetized with sodium pentobarbital (30 mg/kg, ip, a dose that allowed them to breathe spontaneously). Aortic, right ventricular, right ventricular end-diastolic and central venous pressures and cardiac output were measured to meet the criteria for experimentally produced CHF.<sup>2</sup> After hemodynamic measurements, one or two papillary muscles were excised from a right ventricle and transferred to muscle chambers containing Krebs-Henseleit solution

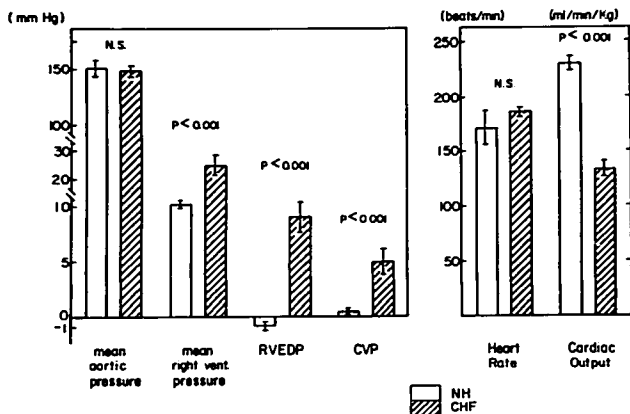


FIG. 1. Hemodynamic data in the two groups. Means  $\pm$  1 SE are shown. RVEDP = right ventricular end-diastolic pressure. CVP = central venous pressure. Cardiac output was normalized by dividing values by body weight. NS = not significant. NH = normal heart; CHF = congestive heart failure.

with 1 mg/ml of dextrose. The bathing solution was kept at a constant temperature of 32 C and bubbled with 95 per cent O<sub>2</sub>-5 per cent CO<sub>2</sub> gas mixture to maintain P<sub>O<sub>2</sub></sub> 580-600 mm Hg, P<sub>CO<sub>2</sub></sub> 38-40 mm Hg, and pH 7.39-7.41. After removal of the papillary muscles, the free right ventricular wall and left ventricle with the septum were weighed. Right and left ventricular weight per body weight ratios (RVwt/Bwt and LVwt/Bwt) were calculated.

Twenty-two papillary muscles from cats with normal hearts and 22 from those with CHF were obtained for measurements of isotonic and isometric muscular contractions.

Thirteen muscles from each group were treated with fluroxene; nine muscles from each group with enflurane. The apparatus for muscle preparations, isotonic and isometric measurements of muscle mechanics, and recording system are described in detail in our previous report.<sup>2</sup> Muscles were stimulated 12 times per minute by parallel platinum electrodes delivering 5-msec square-wave pulses at voltages 20 per cent above threshold. The muscle length was set by a small preload and kept constant throughout the procedure for each muscle study. Force-velocity relations were determined by stepwise increases in afterload

TABLE 1. Ventricular Weights in Two Groups of Cats\*

	Normal Heart	Congestive Heart Failure	Significant Difference
Right ventricular weight (g)	1.76 $\pm$ 0.14	2.64 $\pm$ 0.28	P < 0.001
Left ventricular weight (g)	6.80 $\pm$ 0.45	6.08 $\pm$ 0.34	NS
Right ventricular weight/body weight (g/kg)	0.60 $\pm$ 0.03	1.04 $\pm$ 0.09	P < 0.001
Left ventricular weight/body weight (g/kg)	2.41 $\pm$ 0.09	2.44 $\pm$ 0.09	NS

\* Mean values  $\pm$  1 SE are shown. NS = not significant.

TABLE 2. Values of Components of Muscle Mechanics before Administration of Anesthetics\*

	$V_{max}$ (ML/sec)	$F_m$ (g/mm <sup>2</sup> )	max dF/dt (g/mm <sup>2</sup> /sec)	TTF <sub>m</sub> (msec)
Fluroxene Normal heart (n = 13)	1.14 ± 0.08	3.9 ± 0.2	19.2 ± 1.3	292 ± 10
Congestive heart failure (n = 13)	0.61 ± 0.05†	2.2 ± 0.11	8.7 ± 0.8†	314 ± 15
Enflurane Normal heart (n = 9)	1.11 ± 0.05	3.2 ± 0.2	17.0 ± 0.8	288 ± 21
Congestive heart failure (n = 9)	0.56 ± 0.05†	2.2 ± 0.21	8.4 ± 0.6†	313 ± 21

\* Mean values ± 1 SE are shown. n = number of papillary muscles.  $V_{max}$  = maximal velocity of shortening at 0.4 g/mm<sup>2</sup>.  $F_m$  = maximal developed force. TTF<sub>m</sub> = time from the beginning of force development to  $F_m$ .

† Significant difference ( $P < 0.001$ ) compared with normal hearts.

‡ Significant difference ( $P < 0.01$ ) compared with normal hearts.

until the muscle became unable to shorten and maximal developed force ( $F_m$ ) was reached. Changes in muscle length and force of contraction with their derivatives (dl/dt and dF/dt) obtained by R-C differentiators, were recorded on a multichannel direct-writing recorder at a paper speed of 100 mm/sec. Time to maximal developed force (TTF<sub>m</sub>) was measured from the beginning of force development to  $F_m$  and expressed in msec. Maximal velocity of shortening

( $V_{max}$ ) was approximated by the value of the velocity of shortening at 0.4 g/mm<sup>2</sup> to avoid the errors inherent in extrapolation of the curve to zero load. Velocity of shortening was expressed in units of muscle length per second (ML/sec), and force was expressed in grams per unit of cross-sectional area (g/mm<sup>2</sup>).

After equilibration for two hours, control measurements, including 1)  $V_{max}$  (ML/sec), 2)  $F_m$  (g/mm<sup>2</sup>), 3) maximal dF/dt (g/mm<sup>2</sup>/sec), 4) TTF<sub>m</sub> (msec), were made. Fluroxene was ad-

TABLE 3. Effects of Fluroxene and Enflurane on  $V_{max}$ ,  $F_m$ , and Maximal dF/dt: Mean Percentage Depressions from Corresponding Control Values Shown in Parentheses\*

	$V_{max}$ (ML/sec)		$F_m$ (g/mm <sup>2</sup> )		Maximal dF/dt (g/mm <sup>2</sup> /sec)	
	Normal Heart	Congestive Heart Failure	Normal Heart	Congestive Heart Failure	Normal Heart	Congestive Heart Failure
Fluroxene (n = 13)						
MAC 0.5	0.98 ± 0.06 (14.8 ± 1.1)	0.51 ± 0.05 (17.6 ± 2.3)	2.98 ± 0.15 (22.9 ± 2.1)	1.67 ± 0.11 (24.7 ± 2.4)	15.46 ± 1.09 (18.6 ± 2.9)	6.35 ± 1.35 (26.4 ± 2.1)
MAC 1.0	0.78 ± 0.06 (31.5 ± 1.9)	0.37 ± 0.04 (39.0 ± 3.8)	2.17 ± 0.11 (44.7 ± 1.5)	1.16 ± 0.09 (46.5 ± 2.2)	11.48 ± 1.07 (43.6 ± 2.0)	4.33 ± 0.48 (50.6 ± 3.2)
MAC 1.5	0.55 ± 0.04 (53.0 ± 3.1)	0.22 ± 0.03 (65.3 ± 6.2)	1.41 ± 0.07 (63.1 ± 3.5)	0.72 ± 0.05 (66.4 ± 3.6)	7.11 ± 0.49 (62.2 ± 3.0)	2.70 ± 0.30 (71.5 ± 6.0)
Enflurane (n = 9)						
MAC 0.5	0.88 ± 0.03 (19.4 ± 3.0)	0.40 ± 0.04 (25.9 ± 3.2)	2.44 ± 0.16 (24.6 ± 3.6)	1.63 ± 0.11 (27.3 ± 4.8)	13.23 ± 0.69 (21.8 ± 3.0)	5.95 ± 0.44 (31.7 ± 5.5)
MAC 1.0	0.67 ± 0.05 (39.7 ± 2.9)	0.31 ± 0.03 (44.4 ± 3.2)	1.67 ± 0.08 (47.2 ± 1.9)	1.10 ± 0.12 (48.5 ± 3.8)	8.50 ± 0.52 (49.7 ± 2.9)	3.88 ± 0.41 (55.9 ± 3.1)
MAC 1.5	0.50 ± 0.03 (53.0 ± 6.8)	0.20 ± 0.02 (61.8 ± 5.7)	1.29 ± 0.10 (59.2 ± 6.7)	0.74 ± 0.20 (66.3 ± 6.5)	6.41 ± 0.40 (60.2 ± 6.8)	2.47 ± 0.45 (71.5 ± 6.0)

\* Mean values ± 1 SE are shown. There was no significant difference between percentage depressions in the two groups at any concentration of anesthetic.

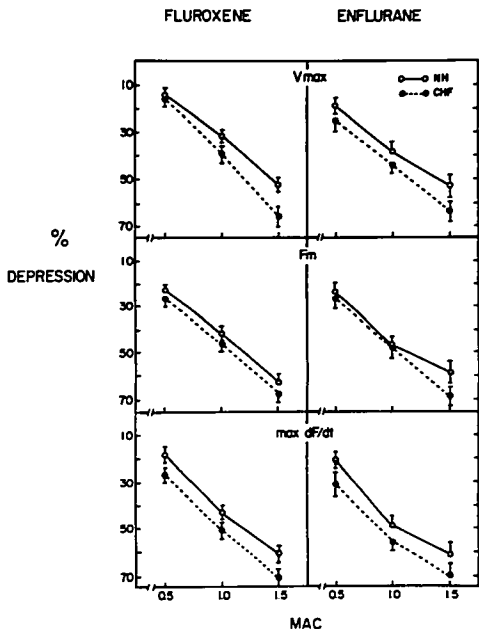


FIG. 2. Percentage depressions in  $V_{max}$ ,  $F_m$ , and maximal  $dF/dt$  produced by various concentrations of fluroxene (left) and enflurane (right) in normal hearts and in congestive heart failure. Vertical bars indicate  $\pm 1$  SE.  $V_{max}$  = maximal velocity of shortening at 0.4 g/mm<sup>2</sup>.  $F_m$  = maximal developed force.

ministered with a Pentec vaporizer, calibrated for the use of the anesthetic by gas chromatography; enflurane was administered with an Ethrane vaporizer. Determinations of the above components of muscle mechanics were repeated, at least 30 minutes after stabilization of contraction height, at concentrations equivalent to half the minimum alveolar concentration (0.5 MAC) in man,<sup>5,6</sup> at 1 MAC, and at 1.5 MAC. Anesthetic concentrations were measured by gas chromatography before and after each observation, and the chambers were completely rinsed between the anesthetic concentration changes. Control measurements without anesthetic were repeated, after which the weight and length of the muscle were measured and cross-sectional area calculated. Muscle preparations were included in these data only when repeat control measurements reached 90–100 per cent of original control values. All values were expressed as mean  $\pm$  1

SE and analyzed statistically by Student's *t* tests for paired and unpaired data. Values were considered significant when  $P < 0.01$  and probably significant when  $0.01 < P < 0.05$ .

## Results

### VENTRICULAR WEIGHTS AND HEMODYNAMIC DATA

Cats were divided into two groups: 1) 15 control cats with normal hearts (NH) and 2) 19 cats with congestive heart failure (CHF). Nineteen of the 25 cats subjected to pulmonary banding met the following criteria for CHF; a high right ventricular end-diastolic pressure ( $> 5$  mm Hg), low cardiac output ( $< 160$  ml/min/kg) and high RVwt/Bwt ratio ( $> 0.9$  g/kg). Of the 19 cats with CHF, ten had pleural fluid and ascites as well. The right ventricular weight and RVwt/Bwt in the CHF group were

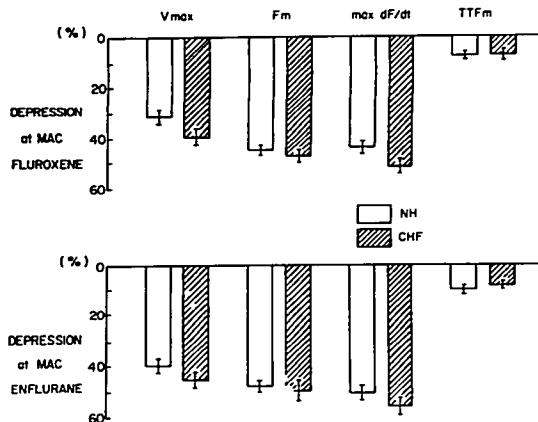


FIG. 3. Effects of fluroxene (upper panel) and enflurane (lower panel) on the components of muscle mechanics in normal hearts (open bars) and in congestive heart failure (solid bars) at 1 MAC. Percentage depression was calculated from corresponding control values.

significantly increased (table 1). There was no significant difference in left ventricular weight or LVwt/Bwt between the two groups. Hemodynamic data obtained from the two groups are summarized in figure 1. Average cardiac output in the CHF group was about 42 per cent less than that in the NH group. Mean right ventricular, right ventricular end-diastolic, and central venous pressures were significantly elevated in the CHF group, but there was no significant difference in heart rate or mean aortic pressure between the two groups.

#### MUSCLE MECHANICS AND RESPONSE TO ANESTHETICS

We selected muscles of similar lengths and cross-sectional areas from the two groups to minimize changes in muscle mechanics resulting from differences in muscle length and thickness.<sup>2</sup> The average lengths of 13 muscles from the NH group and 13 muscles from the CHF group were  $6.32 \pm 0.61$  mm and  $6.03 \pm 0.42$  mm for the fluroxene study ( $P > 0.5$ ). Nine muscles from the NH group and nine muscles from the CHF group used for the enflurane study were  $6.16 \pm 0.56$  mm and  $5.87 \pm 0.65$  mm long ( $P > 0.5$ ). Cross-sectional areas averaged  $1.17 \pm 0.13$  mm<sup>2</sup> for the NH group and  $1.24 \pm 0.09$  mm<sup>2</sup> for the CHF group

in the fluroxene study ( $P > 0.5$ );  $1.20 \pm 0.10$  mm<sup>2</sup> for the NH group and  $1.27 \pm 0.08$  mm<sup>2</sup> for the CHF group in the enflurane study ( $P > 0.5$ ).

The mean values for components of muscle mechanics in both groups before administration of fluroxene or enflurane are summarized in table 2.  $V_{max}$ ,  $F_m$  and maximal  $dF/dt$  were significantly lower in muscles of the CHF group ( $P < 0.001$ ,  $P < 0.01$ ,  $P < 0.001$ , respectively), while there was no significant difference in  $TTF_m$  between the two groups.

Fluroxene and enflurane caused similar dose-dependent depressions in the components of muscle mechanics (table 3, and fig. 2). Comparisons of percentage depressions of components of muscle mechanics of the NH and CHF groups at 1 MAC fluroxene and at 1 MAC enflurane are shown in figure 3. Fluroxene at 1 MAC (mean anesthetic concentration in the perfusate was  $14.3 \pm 0.18$  mg/100 ml) reduced  $V_{max}$  an average of 32 per cent in the NH group and 39 per cent in the CHF group.  $F_m$  was depressed 45 per cent for the NH and 47 per cent for the CHF group. Percentage depressions in maximal  $dF/dt$  were 44 for the NH and 51 for the CHF group. There was no significant difference between the changes in the two groups. Enflurane at 1 MAC ( $9.5 \pm 0.07$  mg/100 ml) reduced  $V_{max}$  an average of 40 per

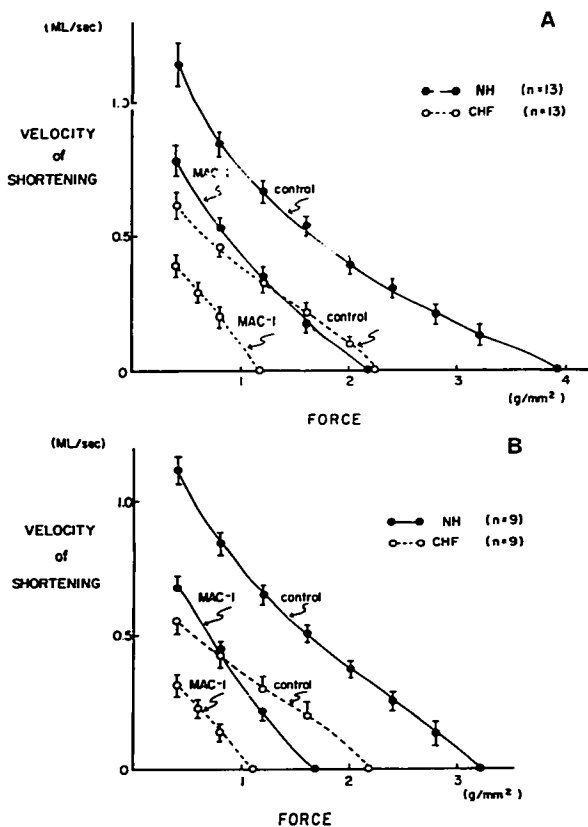


FIG. 4. A, mean force-velocity curves obtained from muscles from normal hearts and muscles from hearts after congestive heart failure before and during administration of fluroxene at 1 MAC ( $14.3 \pm 0.18$  mg/100 ml in the perfusate). B, comparable force-velocity curves before and during administration of enflurane at 1 MAC ( $9.5 \pm 0.05$  mg/100 ml in the perfusate). Ordinate, velocity of shortening expressed in muscle lengths per second (ML/sec); abscissa, force per unit of cross-sectional area in  $g/mm^2$ .

cent in the NH and 44 per cent in the CHF group. Average percentage depressions in  $F_m$  were 47 in the NH and 49 in the CHF group. Depressions in maximal  $dF/dt$  averaged 50 per cent in the NH and 56 per cent in the CHF group. There was no significant difference be-

tween the percentage changes in the two groups.  $TTF_m$  was decreased about 14 per cent in both groups for fluroxene and enflurane, but the difference was not significant. Figure 4 illustrates force-velocity relations in both groups of muscles before and during adminis-

tration of fluroxene and enflurane at 1 MAC. At each load, the velocity of shortening was less in muscles from cats with CHF, and the entire force-velocity curve was shifted downward and to the left. Administration of either fluroxene or enflurane caused a further shift in force-velocity curves obtained from the CHF group to the left and downward. It is also evident that the depressions caused by 1 MAC fluroxene or by 1 MAC enflurane in NH muscles are similar to those caused by CHF alone.

### Discussion

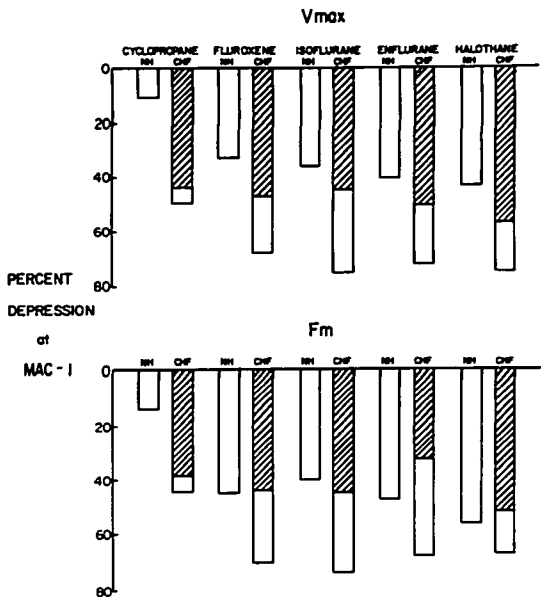
Findings of the present study show that both fluroxene and enflurane produced direct negative inotropic effects on isolated papillary muscles from cats with NH and those with CHF. These changes were dose-dependent and were reversible even for the muscles with depressed contractile performance from the CHF group within the anesthetic concentrations studied. The mechanical behavior of muscles of both groups in response to fluroxene and enflurane anesthesia can be considered qualitatively similar to that elicited by other anesthetics (e.g., halothane, isoflurane, cyclopropane). Both fluroxene and enflurane caused slightly greater depressions in CHF muscles than in NH muscles when the data were compared with their respective control values (table 3, and fig. 2). However, these differences were not significant, i.e., there was no potentiation of the negative inotropism of the anesthetics in the CHF group. Our data also show that when the already-depressed contractile performance of the myocardium caused by CHF was challenged further by another negative inotropic effect (anesthetic), the combined total depression was greater than that caused by the anesthetic alone in NH muscles. This is evident when  $V_{max}$  and  $F_m$  during administration of anesthetic in muscles with CHF are compared with NH control values (fig. 5). It should be emphasized that major portions of the depressions of both  $V_{max}$  and  $F_m$  in CHF muscles were due to experimental CHF. When changes in myocardial contractility in CHF muscles exposed to 1 MAC fluroxene or enflurane were compared with NH control values, total depressions in  $V_{max}$  and  $F_m$  averaged 68 and 70 per cent for fluroxene, and 72 and 68 per cent for enflurane,

respectively. These severe depressions resulting from combined effects of fluroxene or enflurane and CHF were similar to those caused by halothane or isoflurane and CHF, but quite different from the effect of cyclopropane and CHF (fig. 5). When percentage depressions in  $V_{max}$  and  $F_m$  in NH muscles exposed to various anesthetics at equipotent concentrations (1 MAC) are compared, cyclopropane has the least negative inotropic effect and halothane has the most.

We observed that the significant depression of contractile performance in papillary muscles of cats with CHF was accompanied by elevated right ventricular pressure and reduced cardiac output, which is in accord with our previous reports<sup>2,3</sup> and results of the study by Gold and co-workers.<sup>7</sup> Spann and associates<sup>8</sup> recently showed that cardiac output and stroke volume were maintained at close to normal levels in cats with experimental CHF despite marked depression of myocardial performance as reflected by force-velocity curve and length-active-tension curve. The performance of the heart as a pump is maintained by three principal compensatory mechanisms: 1) an increase in muscle mass by ventricular hypertrophy, 2) utilization of the Frank-Starling mechanism to increase contractile force, and 3) an increase in the contractile state by way of the cardiac sympathetic nerve system.<sup>9</sup> Spann and associates also suggested that at some point of reduced contractile state, perhaps after cardiac catecholamine stores have been depleted, circulatory compensations can no longer be maintained and cardiac output falls, with the clinical and hemodynamic manifestations of overt congestive cardiac failure.<sup>8</sup> We previously reported that cardiac catecholamines in myocardial tissues from cats with CHF were decreased significantly from values for NH.<sup>1</sup> It may be concluded, therefore, that the impaired myocardial performance in isolated papillary muscles of the CHF group with elevated right ventricular pressure and reduced cardiac output is found in advanced heart failure despite maximum utilization of compensatory mechanisms provided by the increase in muscle mass, and the Frank-Starling mechanism.

The circulatory effects of fluroxene have been ascribed to sympathetic nerve stimulation in man<sup>10,11</sup> and the cat.<sup>12</sup> Eger and associ-

FIG. 5. Percentage depressions of  $V_{max}$  and  $F_m$  by five anesthetics at equipotent concentrations (1 MAC) in muscles from normal hearts and muscles from hearts after congestive heart failure. Percentage depressions were calculated from the preanesthetic control values for normal hearts. Hatched areas of bars for cardiac failure values represent the depression caused by cardiac failure alone.



ates<sup>10</sup> reported that fluroxene, cyclopropane, and diethyl ether allowed cardiac output, stroke volume, and mean arterial pressure to remain near or above control values in healthy human volunteers. They concluded that this effect was due to stimulation of sympathetic activity. In contrast, halothane had only depressant effects, without any evidence of an increase in sympathetic activity. Skovsted and Price,<sup>12</sup> in their study of intact cats, concluded that fluroxene, like cyclopropane and diethyl ether, causes central sympathetic nervous excitation by depression of medullary depressor neurons. Dobkin and associates<sup>13</sup> reported that the circulatory effects of enflurane appeared relatively minor, suggesting a diethyl ether-like effect more than a halothane-like effect. However, this sympathetic nerve stimulation by certain anesthetics might not be evident in cases of advanced heart failure when catecholamine stores are depleted. Brown and Crout<sup>14</sup> reported that the effects of anesthetics (enflurane, halothane, methoxyflurane, cyclo-

propane, and diethyl ether) on isometric contraction of cat papillary muscles were not altered by propranolol. From this they concluded that the anesthetics did not directly stimulate  $\beta$ -adrenergic receptors in cat papillary muscles. Therefore, even if some anesthetics, such as fluroxene, have a sympathetic nerve-stimulating effect, the performance of isolated papillary muscles is not directly affected by humoral or other environmental factors existing *in vivo*.

The isolated muscle preparation provides excellent information on direct effects of anesthetics on myocardial performance. However, we should be aware that there are certain differences between an isolated muscle study and an intact study. These are 1) species differences, and 2) differences in experimental conditions such as a chamber temperature of 32 C, contraction frequency of 12/min, and provision of substrate and oxygen by diffusion.

At equipotent anesthetic concentrations (1 MAC) in normal hearts, cyclopropane has the



least negative inotropic effect and halothane the most. When combined negative inotropic effects of CHF and anesthetics at 1 MAC are compared, cyclopropane has the least depressant effect, and there is no essential difference among the other four anesthetics (halothane, enflurane, isoflurane and fluroxene).

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### References

1. Shimosato S, Yasuda I, Kemmotsu O, et al: Effect of halothane on altered contractility of isolated heart muscle obtained from cats with experimentally produced ventricular hypertrophy and failure. *Br J Anaesth* 45:2-9, 1973
2. Kemmotsu O, Hashimoto Y, Shimosato S: Inotropic effects of isoflurane on mechanics of contraction in isolated cat papillary muscles from normal and failing hearts. *ANESTHESIOLOGY* 39:470-477, 1973
3. Hashimoto Y, Kemmotsu O, Shimosato S: Effect of cyclopropane on contractile performance of cardiac muscle with experimental chronic heart failure. *Br J Anaesth*, in press, 1973
4. Spann JF, Buccino RA, Sonnenblick EH, et al: Contractile state of cardiac muscle obtained from cats with experimentally produced ventricular hypertrophy and heart failure. *Circ Res* 21:341-354, 1967
5. Munson ES, Saidman LJ, Eger EI II: Effect of nitrous oxide and morphine on the minimum anesthetic concentration of fluroxene. *ANESTHESIOLOGY* 26:134-139, 1965
6. Gion H, Saidman LJ: The minimum alveolar concentration of enflurane in man. *ANESTHESIOLOGY* 35:361-364, 1971
7. Gold HK, Prindle KH, Levey GS, et al: Effects of experimental heart failure on the capacity of glucagon to augment myocardial contractility and activate adenyl cyclase. *J Clin Invest* 49:999-1006, 1970
8. Spann JF, Covell JW, Eckberg DL, et al: Contractile performance of the hypertrophied and chronically failing cat ventricle. *Am J Physiol* 223:1150-1157, 1972
9. Spann JF: Heart failure and ventricular hypertrophy—altered cardiac contractility and compensatory mechanisms. *Am J Cardiol* 23:504-510, 1969
10. Eger EI II, Smith NT, Cullen DJ, et al: A comparison of the cardiovascular effects of halothane, fluroxene, ether and cyclopropane in man: A resumé. *ANESTHESIOLOGY* 34:25-41, 1971
11. Smith NT, Eger EI II, Cullen BF, et al: The cardiovascular responses to the addition of nitrous oxide to fluroxene in man. *Br J Anaesth* 44:142-149, 1972
12. Skovsted P, Price HL: Central sympathetic excitation caused by fluroxene. *ANESTHESIOLOGY* 32:210-217, 1970
13. Dobkin AB, Heinrich RG, Israel JS, et al: Clinical and laboratory evaluation of a new inhalation agent: Compound 347 (CHF<sub>2</sub>-O-CF<sub>2</sub>-ClHFCI). *ANESTHESIOLOGY* 29:275-287, 1968
14. Brown BR, Crout JR: A comparative study of the effects of five general anesthetics on myocardial contractility: I. Isometric conditions. *ANESTHESIOLOGY* 34:236-245, 1971

### Circulation

**DOPPLER METHOD FOR TIBIAL ARTERY** Determination of auscultatory blood pressure in the lower extremity is frequently difficult because of the large, difficult-to-fit cuff needed on the thigh or the absence of Korotkoff sounds in the popliteal or posterior tibial areas. Forty-four patients from 6.5 to 25 years old (weights, 17 to 91 kg) were studied, comparing blood pressures obtained by the Doppler method over the brachial and posterior tibial arteries. There was a difference of less than 0.5 inch

between the circumferences of the upper arm and the lower leg just above the ankle, so the same width of cuff was used for both sites. The paired data showed the systolic pressures in the leg to be slightly higher than those in the arm, with a mean difference of only  $\pm 2.66$  mm Hg (SD  $\pm 5.6$ ). Diastolic pressures were not significantly different. (*Hartmann, A. F., Jr., and others: Measurement of Blood Pressure in the Brachial and Posterior Tibial Arteries Using the Doppler Method. J. Pediatr.* 82: 498-500, 1973.)