

Inotropic Effects of Isoflurane on Mechanics of Contraction in Isolated Cat Papillary Muscles from Normal and Failing Hearts

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The inotropic effect of isoflurane (Forane) was studied in papillary muscles from cats with normal hearts (NH) and those with experimentally produced congestive heart failure (CHF). Mean maximal velocity of shortening (V_{max}) and mean maximal developed force (F_m) of CHF muscles were lower than in the normal heart. Isoflurane at the concentration equivalent to MAC in man reduced V_{max} an average of 36 per cent in NH and 51 per cent in CHF muscles. Average percentage decreases in F_m were 40 in NH and 52 in CHF muscles. When changes in myocardial contractility of CHF muscles exposed to isoflurane at MAC were compared with the NH control values, reductions of V_{max} and F_m were 75 and 74 per cent, respectively. The combined negative inotropic effects of isoflurane and CHF were more pronounced than that of isoflurane alone on the normal heart. (Key words: Isoflurane; Myocardial mechanics; V_{max} ; F_m ; Normal heart; Congestive heart failure.)

CARDIO-HEMODYNAMIC EFFECTS of isoflurane (Forane) have been studied in man and animals.¹⁻³ The studies have revealed that isoflurane produces minimal decreases in cardiac output with marked reduction in arterial blood pressure. However, there has been no report concerning effects of isoflurane on the basic

contractile properties of normal or diseased myocardium. Therefore, the present study was designed to determine the direct inotropic effect of isoflurane on the intrinsic contractile state of isolated papillary muscles from the normal heart (NH) of the cat, and to compare this effect with that in cats with experimentally produced congestive heart failure (CHF).

Materials and Methods

Twelve normal adult cats (weighing 2.5 to 3.8 kg) were anesthetized with sodium pentobarbital (30 mg/kg, ip). Following oral endotracheal intubation, respiration was controlled using intermittent positive pressure by means of an Ayre's T-piece. Anesthesia was maintained with halothane (0.5-1.0 vol per cent in N_2O and O_2 (50:50 vol per cent)). Via left thoracotomy, right ventricular congestive failure was produced through chronic pressure load by placing a circular clip (3.0-4.0 mm ID) around the proximal portion of the main pulmonary artery under sterile conditions, using the method described previously.³

Twenty-eight to 32 days after the operation the cats were again anesthetized with sodium pentobarbital (30 mg/kg, ip, a dose that allowed them to breathe spontaneously). In order to establish criteria for both NH and CHF, the following hemodynamic measurements were made. A catheter (17-gauge) was inserted in the ascending aorta through the right carotid artery for measurement of aortic pressure. Another catheter (18-gauge) was placed through the right external jugular vein into the right ventricle and superior vena cava for measurements of right ventricular and central venous pressures. These catheters were connected to Statham P23Db pressure transducers and pressures were recorded on a multichannel oscillograph (Sanborn 560 se-

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ries), together with the electrocardiogram. Cardiac output was determined by the indicator-dilution technique using indocyanine green dye, and was normalized by dividing the value of cardiac output by total body weight measured at the time of catheterization. In addition, aortic, right ventricular, and central venous pressures and cardiac output were measured in 11 control cats not subjected to operation in order to establish normal value ranges for comparison with CHF values.

After completion of these measurements, the heart was rapidly excised and one or two papillary muscles were removed from the right ventricle and transferred immediately to muscle chambers. Left and right ventricles were blotted dry and weighed and right ventricular weight per body weight ratio (RV wt/B wt) was calculated.

Nineteen papillary muscles from cats with NH and ten muscles from those with CHF were obtained for measurements of both isotonic and isometric muscular contractions. Papillary muscles were mounted between two

TABLE 1. Ventricular Weights in Two Groups of Cats*

| | Normal Heart | Congestive Heart Failure | P |
|------------------------------|--------------|--------------------------|--------|
| Right ventricular weight (g) | 1.60 ± 0.12 | 3.36 ± 0.14 | <0.001 |
| Left ventricular weight (g) | 6.20 ± 0.43 | 6.61 ± 0.16 | NS† |
| RV wt/B wt‡ | 0.63 ± 0.03 | 1.10 ± 0.05 | <0.001 |

* Mean ± 1 SE.

† Not significant.

‡ Right ventricular weight divided by body weight in g/kg.

metal spring clips and suspended in Krebs-Henseleit solution, which was bubbled with 95 per cent O₂-5 per cent CO₂ in order to maintain P_{O₂} at a mean level of 600 mm Hg, P_{CO₂} between 38 and 40 mm Hg, and pH 7.4. The bathing solution was maintained at a constant temperature of 32 C by means of a Haake pump connected in series with a Mode

TABLE 2. Hemodynamic Data in Two Groups of Cats*

| | Normal Heart | Congestive Heart Failure | P |
|--|--------------|--------------------------|--------|
| Heart rate (beats/min) | 204.5 ± 9.0 | 204.0 ± 4.8 | NS† |
| Mean aortic pressure (mm Hg) | 143.4 ± 9.5 | 140.0 ± 5.8 | NS |
| Mean right ventricular pressure (mm Hg) | 10.2 ± 1.0 | 26.1 ± 4.3 | <0.001 |
| Systolic right ventricular pressure (mm Hg) | 26.9 ± 1.2 | 47.4 ± 3.8 | <0.001 |
| Right ventricular end-diastolic pressure (mm Hg) | -0.81 ± 0.55 | 6.76 ± 1.26 | <0.001 |
| Central venous pressure (mm Hg) | 0.1 ± 0.5 | 4.0 ± 0.9 | <0.01 |
| Cardiac output normalized by dividing by body weight (ml/min/kg) | 221.9 ± 12.6 | 127.2 ± 11.2 | <0.001 |

* Mean ± SE.

† Not significant.

TABLE 3. Values of Components of Muscle Mechanics before Administration of Isoflurane*

| | Normal Heart | Congestive Heart Failure | P |
|---|--------------|--------------------------|--------|
| Maximal velocity of shortening (ML/sec) | 1.14 ± 0.09 | 0.57 ± 0.05 | <0.001 |
| Maximal developed force (F _m) (g/mm ²) | 3.13 ± 0.30 | 1.73 ± 0.11 | <0.01 |
| Maximal dF/dt (g/mm ² /sec) | 15.85 ± 1.48 | 7.12 ± 0.58 | <0.001 |
| Maximal work (g/mm ²) · (ML) | 0.14 ± 0.02 | 0.05 ± 0.01 | <0.01 |
| Maximal power (g/mm ²) · (ML/sec) | 0.91 ± 0.11 | 0.37 ± 0.04 | <0.01 |
| Time from beginning of force development to F _m (msec) | 276.1 ± 8.2 | 305.6 ± 8.2 | <0.05 |

* Mean ± 1 SE.

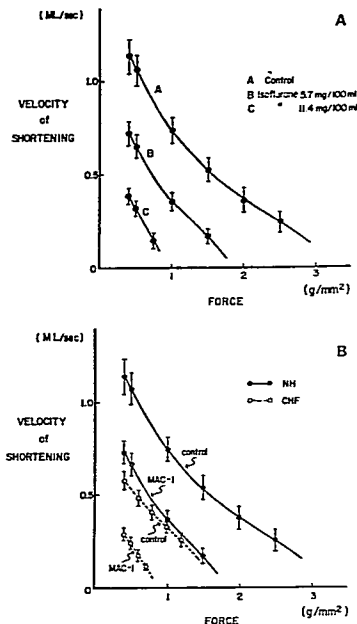


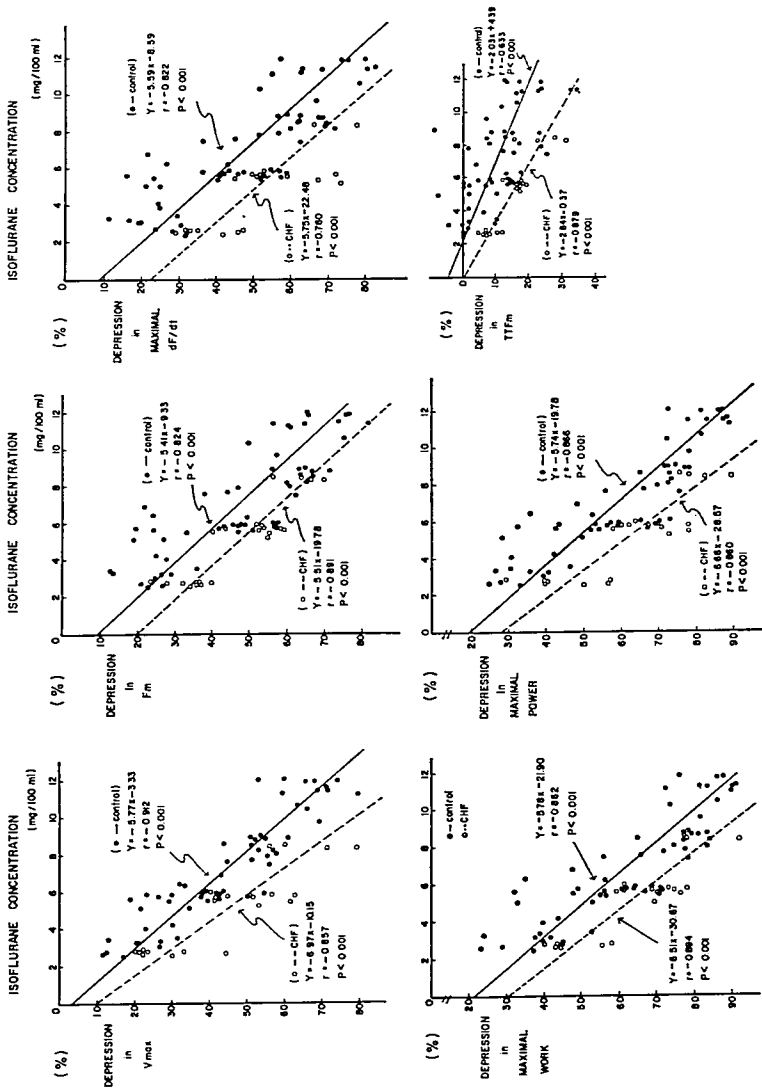
FIG. 1. A, mean force-velocity curves obtained from normal heart muscles before and during administration of isoflurane. B, comparison of mean force-velocity curves from NH and congestive heart failure (CHF) muscles at 1 MAC isoflurane (5.73 ± 0.12 mg/100 ml in perfusate). Ordinate: velocity of shortening expressed as a function of muscle lengths per second (ML/sec); Abscissa: force per unit of cross sectional area in g/mm^2 .

55005 heat exchanger. The lower spring clip was attached to stainless steel tubing (30-gauge) which passed through a mercury seal at the bottom of the muscle chamber and was connected to a force transducer (Statham, Model 7B-0. 75-350). The upper spring clip was attached by a silver chain (0.8 mm ID) to an isotonic lever arm in order to minimize artifacts related to maldistribution of developed force. The lever arm was made of Plexiglas (ratio: 16.3 to 1). Displacement of the lever was measured by a rotary variable differential transducer (Schaevitz Engineering,

Model R4BSS), which formed the fulcrum of the lever. Muscles were stimulated 12 times per minute by parallel platinum mass electrodes delivering 5-msec square-wave pulses at voltages 20 per cent above threshold. Initial muscle length was adjusted with a small load (preload) and kept constant by a micrometer stop during the entire study for each muscle. Force-velocity relations were determined by stepwise increases in the afterloads. Stimulation artifact, net shortening (ΔL), velocity of shortening (dl/dt), developed force (F), and first time derivative of force development (dF/dt) were recorded simultaneously on a direct writing multichannel recorder (Sanborn 7700 series). Both dl/dt and dF/dt were obtained by electrical differentiators (time constant: 0.5 msec) at a paper speed of 100 mm/sec. Net shortening of muscle (ΔL in mm) was converted to muscle lengths per contraction (ML) by dividing muscle length at any given load by initial muscle length. Velocity of shortening was expressed in units of muscle lengths per second (ML/sec). Maximal developed force (F_m) was obtained when the load was increased to a point where no more shortening occurred, and F_m was expressed in grams per unit of cross-sectional area (g/mm^2). In the present study, the velocity of shortening at a load of 0.4 g/mm^2 was used to approximate the maximal velocity of shortening (V_{max}) in order to minimize errors that might result from extrapolation of the force-velocity curve to zero load.

After two hours of equilibration time, the following control measurements were made: 1) V_{max} (ML/sec); 2) F_m (g/mm^2); 3) maximal dF/dt ($g/mm^2/sec$); 4) maximal work ($g/mm^2 \cdot ML$), calculated as the product of force development and net shortening; 5) maximal power ($g/mm^2 \cdot ML/sec$), calculated as the product of force development and the velocity of shortening; 6) TTF_m (msec) the time from the beginning of force development to F_m .

Isoflurane was administered with a Fluotec vaporizer which was calibrated for the use of isoflurane by gas chromatography, and determinations of the above components of muscle mechanics were repeated, at least 30 minutes



DEPRESSION in MAXIMAL df/dt ; TTFm; Fm; MAXIMAL POWER; V_{max} ; MAXIMAL WORK. Solid line = normal heart (NI) group; dotted line = congestive heart failure (CHF) group.

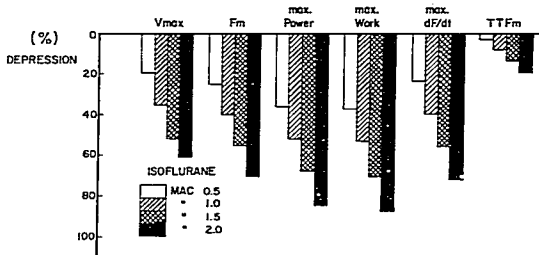


FIG. 3. Percentage depressions components of muscle mechanics in normal heart muscles at isoflurane concentrations equivalent to half MAC, MAC, 1.5 MAC, and 2 MAC.

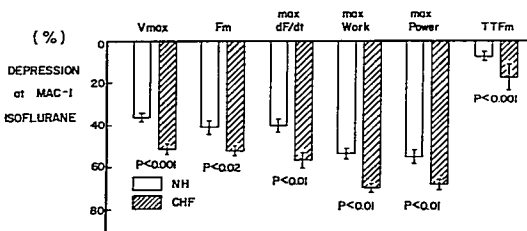


FIG. 4. Percentage depressions of muscle mechanics at 1 MAC, calculated from the control values for the normal heart and congestive heart failure groups.

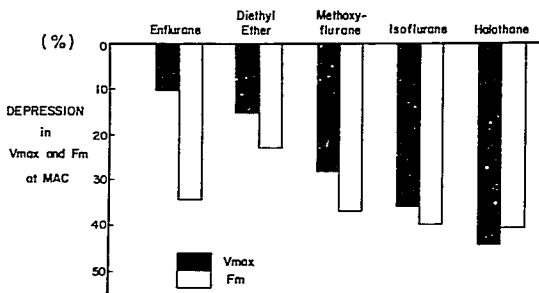
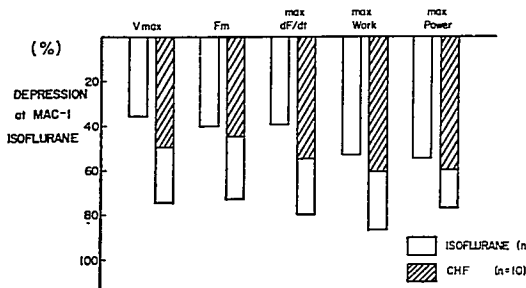


FIG. 5. Comparison of the inotropic effect of isoflurane on normal heart muscle with effects of four other anesthetics at equipotent levels (MAC).

after stabilization of contraction height, at concentrations equivalent to half MAC (minimum alveolar anesthetic concentration), MAC, 1.5 MAC, and 2 MAC in man.¹ Anesthetic concentrations were measured by gas chromatography before and after each observation, and the baths were completely rinsed between isoflurane concentration changes. Muscle preparations were included in these data only

when back-control measurements reached 90-100 per cent of control values. At the end of each experiment, the weight and length of the muscle between the spring clips were measured, and cross-sectional area was calculated. All values were normalized for muscle length and cross-sectional area. Student's *t* tests for paired and unpaired data were used for all statistical calculations. Values were consid-

FIG. 6. Percentage depressions of components of muscle mechanics during administration of isoflurane (1 MAC) in two groups. Comparisons were based on the pre-anesthetic value in the normal heart (see text). Congestive heart failure (hatched bar) caused most of the depression.



ered significant when $P < 0.01$ and probably significant when $0.01 < P < 0.05$.

Results

HEMODYNAMIC DATA AND VENTRICULAR WEIGHTS

The cats were divided into two groups: 1) 11 control cats with normal hearts (NH), and 2) nine cats with congestive heart failure (CHF). Nine of the 12 cats subjected to pulmonary-artery banding met the following criteria for CHF: high right ventricular end-diastolic pressure (> 5 mm Hg), low cardiac output (< 160 ml/min/kg), and high RV wt/B wt ratio (> 0.9 g/kg). Of the nine cats with CHF defined in this manner, five had pleural fluid and ascites as well. Table 1 shows that RV wt/B wt in the CHF group was significantly increased ($P < 0.001$). There was no significant difference between left ventricular weights in the two groups ($P > 0.5$). The average lengths of 19 papillary muscles from the NH group and ten muscles from the CHF group were 5.94 ± 0.28 mm and 5.76 ± 0.39 mm, respectively ($P > 0.7$). Cross-sectional areas averaged 1.15 ± 0.14 mm² for NH and 1.26 ± 0.09 mm² for CHF muscles ($P > 0.5$). Hemodynamic data obtained from the two groups are summarized in table 2. The mean right ventricular pressures and right ventricular end-diastolic pressures of the CHF group were significantly higher than those of the NH group ($P < 0.001$). Cardiac output was significantly lower in the CHF group ($P < 0.001$). There was no significant difference between heart

rates or mean aortic pressures in the two groups ($P > 0.5$).

MYOCARDIAL MECHANICS AND RESPONSES TO ISOFLURANE

Before administration of isoflurane, V_{max} , F_m , maximal dF/dt, maximal work, and maximal power were all significantly lower in muscle of the CHF group ($P < 0.01$ or $P < 0.001$) and TTF_m was prolonged ($P < 0.05$) (table 3).

Administration of isoflurane at all concentrations studied decreased both V_{max} and F_m in both groups. These changes resulted in dose-dependent shifts in the force-velocity curve downward and to the left (fig. 1). At any given isoflurane concentration, reductions in F_m were more prominent than those in V_{max} . There were concomitant dose-dependent decreases in maximal dF/dt, maximal work, maximal power, and TTF_m during administration of the anesthetic. The correlation coefficients relating percentage changes in each component of muscle mechanics to isoflurane concentrations were all highly significant for both groups (fig. 2). Figure 3 summarizes the effects of varying isoflurane concentration on muscle mechanics of the NH group. Figure 4 shows the differences between percentage depressions of the components in the two groups at MAC isoflurane (mean anesthetic concentration in the muscle chamber was 5.73 ± 0.12 mg/100 ml). Percentage depressions in each component were all significantly greater in the CHF group ($P < 0.001$, $P < 0.01$, or $P < 0.02$).

Discussion

Results of the present study showed that isoflurane had a direct negative inotropic effect on isolated papillary muscles from cats with normal hearts and those with congestive heart failure. Reductions in each component of myocardial mechanics were directly proportional to increases in isoflurane concentration. The decreased ability of the heart muscle to develop force and to shorten was shown by decreases in V_{max} , which may be considered an appropriate index of myocardial contractility at the present time.⁴ Reductions in F_m were accompanied by decreases in both maximal dF/dt and TTF_m , suggesting that isoflurane affects both intensity and duration of changes in the active state of heart muscle.⁵ These findings were in accordance with those reported previously for halothane,⁶ methoxyflurane,⁷ enflurane,⁷ and diethyl ether,⁸ which suggested that they produce direct myocardial depression in a similar manner. Figure 5 compares the negative inotropic effect of isoflurane on normal heart muscle with those of four other anesthetics at equipotent levels (MAC), causing direct myocardial depression in the following order of severity: halothane > isoflurane > methoxyflurane > diethyl ether > enflurane.

Another finding of the present study is that marked depression of myocardial contractility was observed in isolated papillary muscles with CHF before exposure to the anesthetic. This decrease in the basic contractile state of heart muscle was indicated by a downward and leftward shift in force-velocity curves, substantial decreases in V_{max} , and concomitant decreases in other components of myocardial mechanics. These findings are similar to those reported previously.^{2, 9}

The relationship between cardiac hypertrophy with overt congestive heart failure and decreased myocardial contractility has not yet been completely elucidated. Several groups of investigators¹⁰⁻¹² have suggested four possible areas where CHF-related disturbances could originate: 1) the level of transmembrane electrical potential, 2) the process of excitation-contraction coupling, 3) the contractile machinery itself, and 4) the biochemical energy-producing system.

Bing and co-workers¹⁴ have suggested that normalization of force on a muscle weight basis is misleading, since a short, thick muscle of a given weight would develop less force than a longer, thinner one of the same weight. The reason for this is not clear, but they suggested it may result from hypoxia of the core of the thick muscle preparation. Since the average cross-sectional area of CHF muscles is usually greater than that of NH muscles, core hypoxia might be a factor in decreased contractility as well as decreased developed force. In our experiments, we selected muscles of similar lengths and similar cross-sectional areas from both groups to minimize any discrepancy that might result from different muscle thicknesses.

Isoflurane caused greater depression in CHF muscles than in NH muscles when the data were compared with control values (fig. 4). This potentiation of the negative inotropism caused by the anesthetic was not found with halothane.⁹ When changes in myocardial contractility in CHF muscles exposed to isoflurane at MAC were compared with the NH control values, depressions in V_{max} and F_m averaged 75 and 74 per cent, respectively (fig. 6). This severe depression caused by the combined effects of isoflurane and cardiac disease was similar to that caused by halothane and CHF (for halothane and CHF, depressions in V_{max} and F_m were 74 and 67 per cent, respectively).⁹

As reported previously,^{1, 15-17} isoflurane has the following advantages over halothane: 1) lower blood/gas partition coefficient (this means that induction and emergence from anesthesia will be more rapid than with halothane);¹⁵ 2) less sensitization of the heart to epinephrine;¹⁶ 3) less cardiovascular depression,¹ and 4) excellent muscle relaxation.¹ Our data showed that the negative inotropic effect of isoflurane on NH muscle is slightly less than that of halothane. However, this effect is potentiated in CHF muscle, which is not the case with halothane.

Since these experiments were performed *in vitro* at a temperature of 32 C, conclusions may not be directly applicable to clinical situations. However, the data suggest that halothane might be preferable for patients with severe cardiac diseases when compensatory

mechanisms are no longer adequate. Our preliminary data concerning cardiocirculatory effects of isoflurane anesthesia in normal healthy volunteers at normal P_{aCO_2} revealed that this anesthetic at MAC (end-tidal concentrations: 1.25 vol per cent) increased cardiac output and heart rate in the presence of hypotension.¹² Therefore, the direct negative inotropic effect of isoflurane on the performance of individual heart muscles may be counteracted *in vivo*, and the performance of heart as a pump may not be impaired. Both isoflurane and halothane, however, must be used with caution in patients with cardiac disease.

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