Anesthesiology
69:464-471, 1988

Comparative Effects of Halothane, Enflurane, and Isoflurane at Equipotent Anesthetic Concentrations on Isolated Ventricular Myocardium of the Ferret. II. Relaxation

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The effects of halothane, enflurane, and isoflurane on myocardial relaxation were compared in papillary muscles of the right ventricle of adult male ferrets at 30° C. The sensitivity of cardiac relaxation to the loading conditions was determined by examining the time course of relaxation before, during, and after exposure to incremental concentrations of halothane (n = 9 muscles), enflurane (n = 9 muscles), and isoflurane (n = 9 muscles) in steps of 0.25 MAC up to 1.5 MAC of halothane and of enflurane and up to 2.0 MAC of isoflurane. Load sensitivity of relaxation was quantified by comparing force and time coordinates at the onset of the isometric relaxation phase in several afterloaded isotonic twitch contractions with relaxation of the isometric twitch. Load sensitivity of relaxation, which is of particular benefit during early rapid filling of the heart, was decreased in a dose-dependent reversible fashion by halothane, enflurane, and, to a lesser extent, by isoflurane. These anesthetics abbreviated isometric relaxation, yet prolonged the time course of muscle lengthening which is suggestive of an impairment of calcium uptake by the sarcoplasmic reticulum and of a decrease in calcium sensitivity of the contractile proteins. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Heart: contractility; relaxation.)

IT IS WELL ESTABLISHED that in global or regional ventricular ischemia abnormalities of relaxation occur before contraction has become inadequate.[1-6] Similarly, abnormalities of relaxation are typically present in diseases such as ventricular hypertrophy,[7] hypertrophic cardiomyopathy,[8] and idiopathic hypertrophic subaortic stenosis.[9] Likewise, pharmacological interventions such as activation of the β-adrenoceptor[10,11] can modify relaxation of the heart. It may well be that drugs used in the practice of anesthesiology influence relaxation, but there is little information on the subject. In chronically instrumented dogs, isoflurane depressed diastolic filling and function by slowing relaxation and decreasing the diastolic filling period.[12]

Physiological studies on relaxation in mammalian cardiac muscle have introduced the concept that relaxation of cardiac muscle with extensive and active sarcoplasmic reticular systems is sensitive to loading conditions.[13-16] Load-sensitivity of relaxation relates to the observations that: 1) when the force traces of isometric relaxation phases of afterloaded contractions against different afterloads are superimposed, they are separated in time from each other and from the isometric twitch; and 2) when an abrupt increase in load is imposed during mid-to-late-systolic isotonic shortening, it induces isometric relaxation that occurs sooner than that of the control twitch. On the other hand, relaxation is load-insensitive (or load-independent, as originally described) when superimposed force traces during isometric relaxation coincide in time, irrespective of the load during the contraction phase. Relaxation is independent of load or load-insensitive in single mammalian cardiac cells without functional sarcoplasmic reticulum,[14] in rat and cat papillary muscle twitch after caffeine[16] and/or hypoxia,[17,18] in tetanized mammalian cardiac muscle,[16] and in intact frog ventricular cardiac muscle.[15,16] In all of these, the sarcoplasmic reticulum is either inactivated or sparsely developed. Load-sensitivity of relaxation requires, therefore, the presence of effective calcium-sequestering membrane systems, in particular, the sarcoplasmic reticulum. Relaxation is also load-sensitive in intact canine[19,20] and human heart.[11]

The volatile anesthetic agents halothane, enflurane, and isoflurane are potent myocardial depressants. This results from the combination of actions on the surface membrane,[21-23] on Ca^{2+} handling by the sarcoplasmic reticulum,[24-27] and on the Ca^{2+}-sensitivity of contractile proteins.[25-28] Because of their effects on subcellular organelles, one would anticipate that halothane, enflurane, and isoflurane modify myocardial relaxation, and possibly to varying extents because their effects on contractility differ. We have tested this hypothesis in this study by examining the time course and load-sensitivity of relaxation in the presence of halothane, enflurane, and isoflurane in isolated ventricular myocardium of the ferret.

This article is accompanied by an editorial. Please see: Rusy BF: Anesthetic action in heart muscle: Further insights through the study of myocardial mechanics. ANESTHESIOLOGY 69:445–447, 1988.

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Received from the Department of Anesthesiology, Mayo Clinic and Foundation, Rochester, Minnesota 55905. Accepted for publication April 27, 1988. Supported in part by USPHS GM36365, the International Anesthesia Research Society and the Puritan-Bennett Foundation. Doctor Housmans was funded in part by a 1986 B. B. Sankey Anesthesia Advancement Award (I.A.R.S.) and was a Parker B. Francis Investigator in Anesthesiology for 1986. Presented in part at the International Anesthesia Research Society, San Diego, California, March, 1988.

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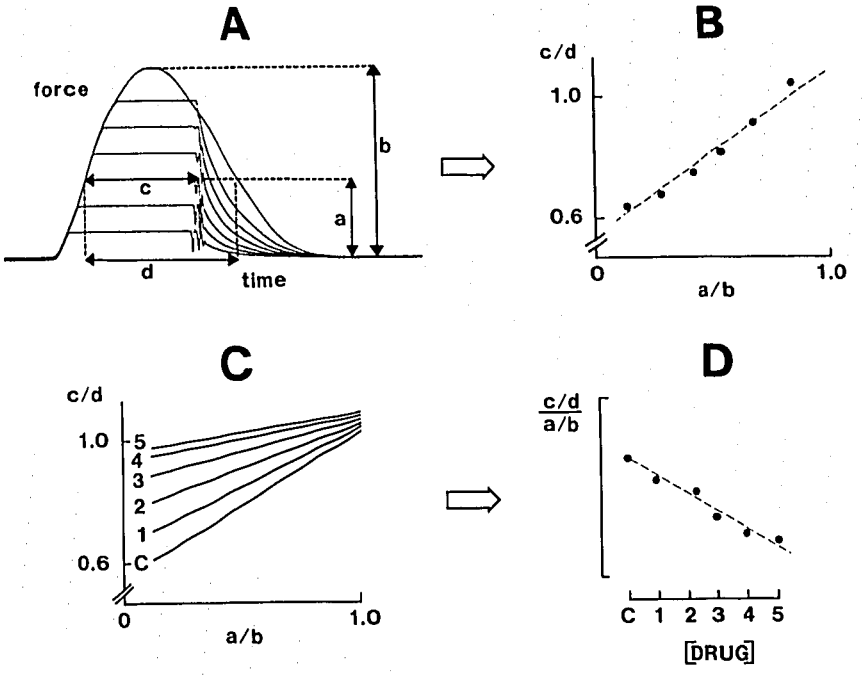

FIG. 1. Methods of analysis of load-sensitivity of relaxation as a function of drug concentration in cumulative dose-response experiments. *Panels A and B.* Method to quantify load-sensitivity of relaxation. Superimposed force traces as a function of time (*panel A*) of an isometric and of six afterloaded isotonic twitch contractions. Relative force (a/b) and time (c/d) coordinates at the onset of isometric relaxation were plotted in panel B to produce a relative time *versus* force curve. *Panels C and D.* During a cumulative dose-response experiment in a single muscle, a family of curves is obtained, one for control (C) and one for each drug concentration (1 to 5). The slope of each of these curves, *i.e.*, load-sensitivity $\frac{(c/d)}{(a/b)}$ is then plotted in panel D as a function of drug concentration. The dotted line in panel D is the regression line fitted by means of least squares linear regression.

Materials and Methods

Twenty-seven papillary muscles from the right ventricle of adult male ferrets (weighing 1100–1500 g, and 16–19 weeks of age) were used in this study. These muscles were the same as those used in an associated study on effects of anesthetics on myocardial contractility, and data for both studies were obtained simultaneously. The experimental apparatus, stabilization protocol, methods of delivery of anesthetic, and measurement techniques have been extensively described in the associated study on contractility.[29]

Load-sensitivity of relaxation was determined from an isometric twitch and six afterloaded isotonic twitches, each with a different afterload (fig. 1A). Load-sensitivity of relaxation was quantified (fig. 1A, B) by plotting force of an afterloaded isotonic twitch (a) as a fraction of peak developed force (b) of the isometric twitch against the ratio of the time to initiation of isometric relaxation in that isotonic twitch (c) to the time it took for force in the isometric twitch to decline to the same force levels (d). Only *developed* force was taken into calculations, and all times were measured from the onset of isotonic shortening. This procedure eliminates effects of changes in resting force and of inotropic state.[18] The resulting plot of relative time *versus* force coordinates at the onset of isometric relaxation produces a curve of the type shown in figure 1B. The steeper the slope $\frac{(c/d)}{(a/b)}$ of this curve, the more load-sensitive was relaxation. Therefore, the slope $\frac{(c/d)}{(a/b)}$ was taken as the quantitative indicator of load-sensitivity of relaxation. Figure 1C shows schematically a "family" of relative time *versus* force curves, as would be obtained during a cumulative dose-response type experiment. In a further transformation, the slope of each of these curves, or, in other words, load sensitivity $\frac{(c/d)}{(a/b)}$, was plotted as a function of drug concentration (fig. 1D). In this last representation, one can easily evaluate dose-dependent changes in load-sensitivity of relaxation.

This approach was used for the determination of load-sensitivity of relaxation during cumulative dose-response experiments for halothane, enflurane, and isoflurane, respectively, in three separate groups of nine muscles each. Load-sensitivity of relaxation was also determined in a non-anesthetic control group of six muscles. The seven twitches that were required to construct a plot of relative force-time coordinates of the type in figure 1B were recorded between 18–23 min of exposure to a particular anesthetic concentration. In order to eliminate effects of loading in preceding beats, each of those seven test contractions was separated by seven isotonic twitches against preload only.[30–32] To minimize effects of release of endogenous catecholamines in ferret cardiac muscle,[29] β-adrenoceptor blockade was achieved by the administration of (±)-bupranolol hydrochloride (10^{-6} M), a competitive β-blocking agent that is more potent than propranolol and apparently devoid of agonistic effects in heart muscle.[33,34] The following incremental anesthetic concentra-

TABLE 1. Load-sensitivity—Mean ± SD of Individual Slopes (c/d)/(a/b)

	Halothane (n = 9)		Enflurane (n = 9)		Isoflurane (n = 9)		Control (n = 6)	
	Slope (Mean ± SD)	r^2 (Median)	Slope (Mean ± SD)	r^2 (Median)	Slope (Mean ± SD)	r^2 (Median)	Slope (Mean ± SD)	r^2 (Median)
Control	0.691 ± 0.102	0.943	0.631 ± 0.051	0.972	0.667 ± 0.099	0.954	0.704 ± 0.101	0.971
0.25 MAC	0.657 ± 0.099	0.946	0.593 ± 0.060	0.984	0.684 ± 0.110	0.964	0.710 ± 0.112	0.963
0.50 MAC	0.577 ± 0.111	0.961	0.509 ± 0.111	0.970	0.686 ± 0.147	0.953	0.713 ± 0.086	0.962
0.75 MAC	0.527 ± 0.126	0.969	0.445 ± 0.127	0.957	0.631 ± 0.165	0.949	0.738 ± 0.084	0.965
1.00 MAC	0.450 ± 0.151	0.940	0.373 ± 0.127	0.956	0.626 ± 0.179	0.972	0.733 ± 0.094	0.962
1.25 MAC	0.369 ± 0.166	0.916	0.178 ± 0.146	*	0.542 ± 0.170	0.931	0.741 ± 0.095	0.956
1.50 MAC	0.230 ± 0.215	*	0.083 ± 0.100	*	0.509 ± 0.152	0.939	0.752 ± 0.080	0.962
1.75 MAC	—	—	—	—	0.471 ± 0.169	0.966	0.752 ± 0.093	0.958
2.00 MAC	—	—	—	—	0.357 ± 0.163	0.963	0.748 ± 0.082	0.962

* Mean (±SD) standard error of estimate ($s_{y.x}$) for halothane (1.5 MAC) 0.029 ± 0.012, for enflurane (1.25 MAC) 0.022 ± 0.010, and 0.017 ± 0.014 at 1.5 MAC.

tions were used: for halothane and enflurane, from 0 to 1.5 MAC in steps of 0.25 MAC; and for isoflurane, from 0 to 2 MAC in steps of 0.25 MAC. MAC values in ferrets at 37° C had been determined in a previous study.[35] This experimental design allowed us to compare effects on relaxation at equipotent anesthetic concentrations. After the highest concentration, the vaporizer was switched off and the reservoir bag was emptied. Muscle recovery was followed in identical conditions for 60 min and load-sensitivity of relaxation was measured at 15, 30, and 60 min of recovery.

STATISTICAL ANALYSIS

For each muscle, a plot of relative time *versus* force coordinates was obtained at control and at each anesthetic concentration (fig. 1C). Each curve was either linear, or curvilinear with a slight upward or downward curvature. For the purpose of analysis, each of these individual curves was subjected to least squares linear regression analysis. This model gave the best fit for the majority of the muscles; for all muscles, the correlation coefficient was >0.85, and even >0.95 for most muscles. The slope $\frac{(c/d)}{(a/b)}$ of each of these lines represents load-sensitivity: the larger the numeric value of the slope $\frac{(c/d)}{(a/b)}$, the more load-sensitive was relaxation. For each muscle, the values of these slopes were plotted as a function of anesthetic concentration (fig. 1D). Subsequently, for each muscle, the relation between the load-sensitivity slope $\frac{(c/d)}{(a/b)}$ and MAC was analyzed and expressed in a linear relation obtained by least squares error linear regression. Values of slope of this relation were obtained in each muscle of the four groups (halothane, enflurane, isoflurane, and non-anesthetic control), and were tested for differences between groups with one-way analysis of variance (one-way ANOVA). Pairwise comparisons between means of two groups were made with the least significant difference method at the 95% confidence level.

Results

Relaxation of the ferret papillary muscle was sensitive to load during control conditions. Between muscle groups (halothane, enflurane, isoflurane, and non-anesthetic control), there were no differences for load-sensitivity of relaxation at time zero as judged by the slope of the linear relation between relative force (a/b) and time (c/d) (table 1, one-way ANOVA, $P = 0.29$). Figure 2 illustrates that relaxation of ferret papillary muscle became less sensitive to load as anesthetic concentration was increased. This effect was dose-dependent and reversible. Figure 3 is similarly constructed as figure 1C and illustrates relative time *versus* force curves between 0 and 1.5 MAC (halothane and enflurane) and between 0 and 2 MAC (isoflurane). Halothane, enflurane, and isoflurane shifted these curves upward and to the left in a dose-dependent fashion. At equi-MAC concentrations, the effect of isoflurane was less pronounced. Even at 2 MAC of isoflurane, the curve had

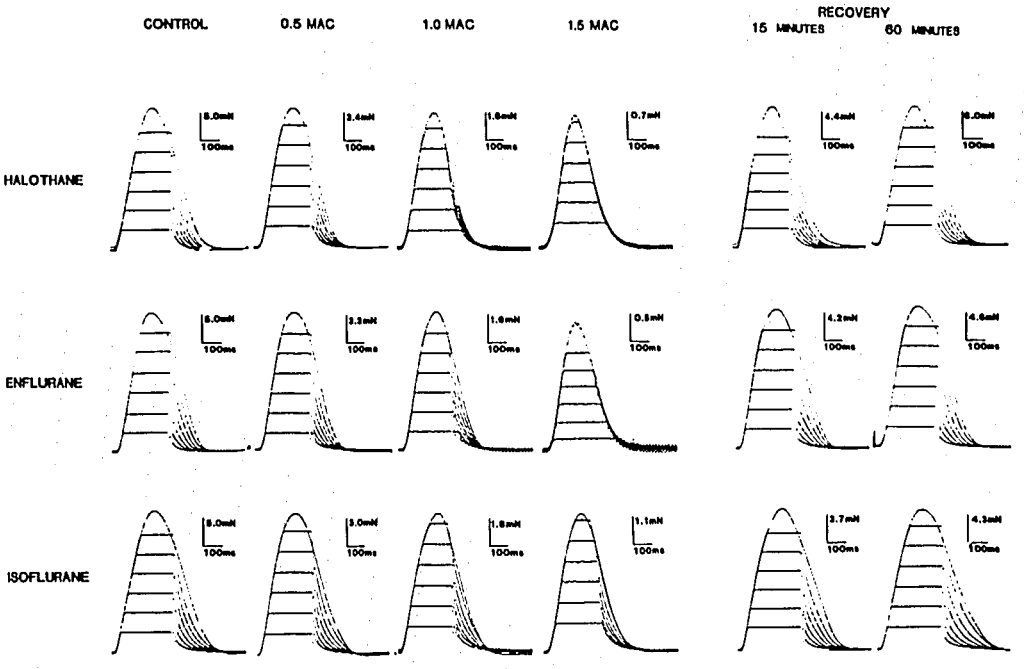

FIG. 2. Load-sensitivity of relaxation before, during, and after exposure to cumulative concentrations of halothane, enflurane, and isoflurane in one representative muscle each. In each panel, force traces of one isometric and of six afterloaded isotonic twitches were superimposed. There was a dose-dependent decrease in peak developed force with each anesthetic, and the reverse was true during recovery (see force scales in each panel). Therefore, for ease of comparison, force traces were electronically adjusted to the same height. In control conditions, the isometric relaxation phases of isotonic twitches at different loads were well separated from each other and from the isometric twitch. This temporal dissociation of isometric relaxation gradually disappeared when the concentration of anesthetic was increased. At 1.5 MAC of halothane and enflurane, all isometric relaxation phases coincided in time, and relaxation was therefore load-insensitive. By contrast, at 1.5 MAC of isoflurane, relaxation was still load-sensitive. Muscle characteristics: (halothane) L_{max} 6.0 mm, mean cross-sectional area (CSA) 0.55 mm^2, ratio of resting to total tension (R/T) 0.230; (enflurane) L_{max} 6.0 mm, CSA 0.55 mm^2, R/T 0.119; (isoflurane) L_{max} 4.5 mm, CSA 0.51 mm^2, R/T 0.163.

shifted less than at 1.5 MAC of either halothane or enflurane. The mean (±SD) values of individual slopes of each of these curves and median values of coefficients of determination (r^2) are shown in table 1. All coefficients of determination (r^2) were close to unity, the smallest median r^2 being 0.916. The mean (±SD) values of these slopes (load-sensitivity) (table 1) were plotted as a function of MAC in figure 4. This illustrates that each of the three anesthetics caused a dose-dependent decrease in load-sensitivity $\frac{(c/d)}{(a/b)}$. There were statistically significant differences between muscle groups (halothane, enflurane,

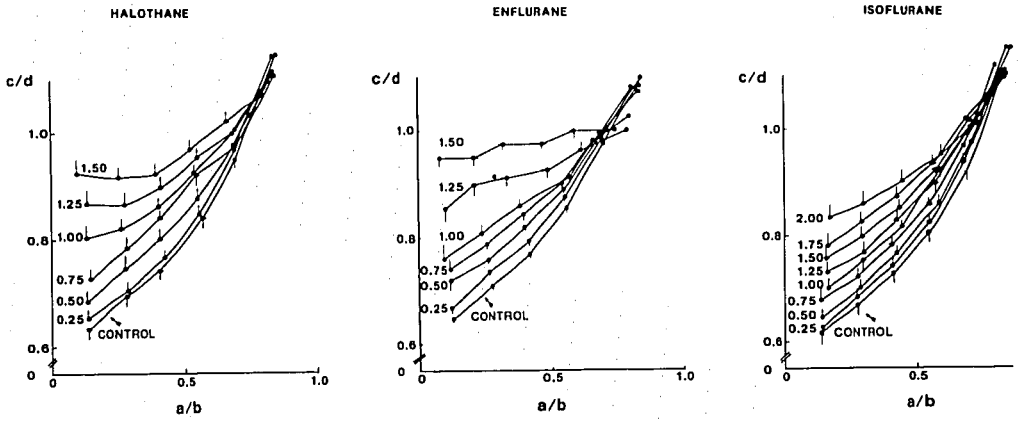

FIG. 3. Load-sensitivity of relaxation with halothane, enflurane, and isoflurane. See figure 1 for details. Each of the three anesthetics caused a dose-dependent up- and left-ward shift of the relative time *versus* force curve. At equipotent anesthetic concentrations this shift toward lesser load-sensitivity was comparable for halothane and enflurane, but less for isoflurane. Data are mean ± SEM. For reasons of clarity, SEM bars were omitted for values in the upper right corner of each graph. Similarly, data of recovery (at 15, 30, and 60 min) were not displayed since they were identical to control.

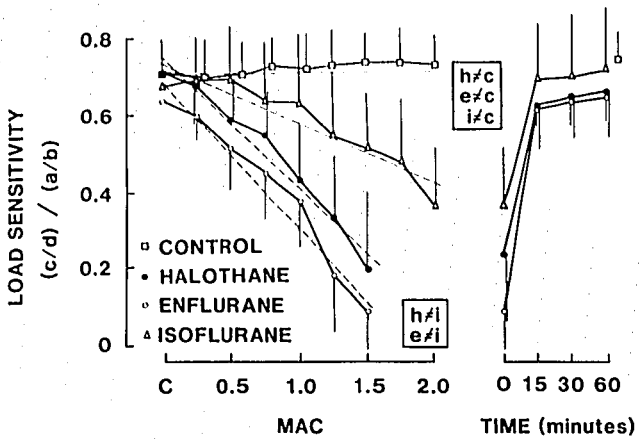

FIG. 4. Mean (±SD) values of load-sensitivity $\frac{(c/d)}{(a/b)}$ were plotted as a function of anesthetic concentration (MAC) during cumulative exposure, and as a function of time during recovery. The dotted lines represent the mean of linear regressions on individual muscles. The regression equations and coefficients of correlation were for halothane, $y = -0.338x + 0.745$ ($r = 0.984$, $P < 0.01$); for enflurane, $y = -0.373x + 0.681$ ($r = 0.954$, $P < 0.01$); for isoflurane, $y = -0.155x + 0.730$ ($r = 0.937$, $P < 0.01$); for the non-anesthetic control, $y = 0.000317x + 0.707$ ($r = 0.938$, $P < 0.01$). Points at time zero of recovery are those obtained at the highest concentration of the corresponding anesthetic agent.

isoflurane, non-anesthetic control) for individual slopes $\frac{(c/d)/(a/b)}{MAC}$ of this relationship (one-way ANOVA, $P < 0.001$). The decrement of load-sensitivity per unit of MAC was smaller for isoflurane than for either halothane ($P < 0.001$) or enflurane ($P < 0.001$). There was no difference between halothane and enflurane. The decrement of load-sensitivity per unit of MAC was larger for halothane, enflurane, and isoflurane when each of these was compared to the non-anesthetic control.

Upon termination of anesthetic exposure, relaxation became load-sensitive again (fig. 2). Recovery of load-sensitivity was already complete at 15 min, yet at this time contractility remained depressed when compared with pre-anesthetic levels.[29] There were no differences between values of load-sensitivity at the onset of the experiment (control), and after 15, 30, and 60 min of recovery in each group (non-anesthetic control: time zero and 60 min recovery only) (one-way ANOVA, see table 2), nor between groups at 15, 30, and 60 min (one-way ANOVA, see table 2).

Discussion

Relaxation of mammalian ventricular muscle is normally sensitive to loading conditions.[13-16] The concept of "load sensitivity" of relaxation originates from a series of observations made on isolated feline papillary muscles in which it was demonstrated that isotonic contractions against progressively smaller loads manifest progressively shorter overall durations than the control isometric twitch. The reduction in duration of the isotonic twitches is confined to an abbreviation of the relaxation phase, so that the isometric relaxation phases of several afterloaded isotonic twitches are separated in time from each other and from the isometric twitch (fig. 1A). An additional illustration of load-sensitive relaxation is that a mid-shortening increase in load produces a premature relaxation, whereas a mid-shortening decrease in load delays relaxation (fig. 5). Load-sensitive relaxation was demonstrated in mammalian ventricular muscle equipped with an effective calcium sequestering system, in particular, the sarcoplasmic reticulum, but it did not appear to be a property of frog ventricular muscle (in which the sarcoplasmic reticulum is sparsely developed), nor was it present in mammalian myocardium (rat) that had been made hypoxic or treated with caffeine.[13-18] In those conditions, the decline of myoplasmic calcium would be slower, activation of the contractile proteins would persist, and relaxation becomes load insensitive.[13-16] There is then little or no temporal dissociation in isometric relaxation between contractions against various loads, and abrupt alterations of load have

TABLE 2. Load-sensitivity of Relaxation during Recovery after Exposure to Anesthetics. Mean ± SD of Individual Slopes (c/d)/(a/b); P Values were Obtained by One-way ANOVA

	Halothane (n = 9)		Enflurane (n = 9)		Isoflurane (n = 9)		Control (n = 6)		
	Slope (Mean ± SD)	r^2 (Median)	Slope (Mean ± SD)	r^2 (Median)	Slope (Mean ± SD)	r^2 (Median)	Slope (Mean ± SD)	r^2 (Median)	P
Control	0.691 ± 0.102	0.943	0.631 ± 0.051	0.972	0.667 ± 0.099	0.954	0.704 ± 0.101	0.971	0.29
15 min	0.622 ± 0.116	0.958	0.611 ± 0.039	0.954	0.689 ± 0.162	0.943	—	—	0.33
30 min	0.642 ± 0.114	0.930	0.630 ± 0.061	0.962	0.695 ± 0.179	0.959	—	—	0.53
60 min	0.657 ± 0.126	0.923	0.641 ± 0.056	0.953	0.713 ± 0.178	0.950	0.750 ± 0.081	0.964	0.19
P	0.63		0.66		0.94		0.59		

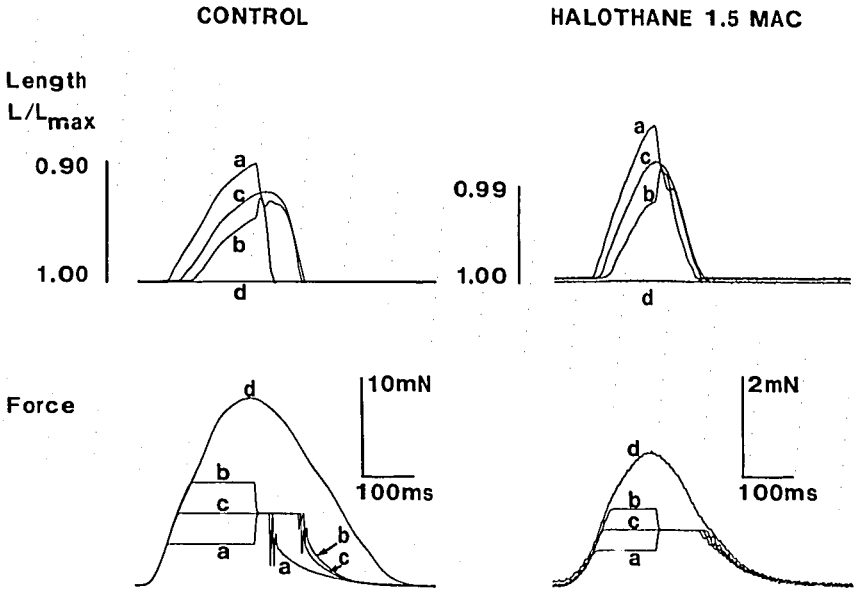

FIG. 5. Length (upper) and force (lower) traces of a loading (contraction a) and an unloading step (contraction b) of the same magnitude and imposed at the same time during contraction. Both contractions were clamped to the same afterload. The control afterloaded isotonic contraction (contraction c) to which the muscle was clamped and the control isometric twitch (d) are also shown. Although the load after the load step was the same in contractions (a), (b), and (c), the subsequent course of contraction and relaxation was greatly affected in control conditions (left) and hardly at 1.5 MAC of halothane (right). Ferret right ventricular papillary muscle, L_{max} 6.0 mm, mean cross-sectional area 0.6 mm^2, ratio of resting to total tension (R/T) 0.200.

little or no influence on the onset of isometric relaxation (fig. 5). The concept of load sensitivity of myocardial relaxation was recently confirmed in intact canine heart[19,20] and in humans.[11]

Halothane, enflurane, and isoflurane cause relaxation to become less load-sensitive, even load-insensitive at the higher anesthetic concentrations. In view of the evidence presented above, it seems plausible to present the hypothesis that volatile anesthetics decrease load-sensitivity of relaxation in a dose-dependent manner by impairing Ca^{2+} accumulation by the sarcoplasmic reticulum (SR). The discussion henceforth will focus on a few caveats. First, it has been shown that volatile anesthetics increase the initial rate of Ca^{2+} uptake by the SR, albeit with a concomitant decrease in SR capacity.[24] The decreased velocity of relaxation (lengthening velocity) tends to suggest that the capacity of the SR is sufficiently depressed to mask any effect of increased rate of Ca^{2+} uptake, or that SR Ca^{2+} uptake mechanisms become saturated and rate limiting in the presence of anesthetics (*vide infra*). Depletion of the SR is a definite possibility in view of the decrease in the peak of the Ca^{2+} transient with halothane in cat papillary muscle,[36] and of evidence of at least transient enhancement of Ca^{2+} release by halothane.[21,37,38] Second, it is conceivable that load-sensitivity is decreased as a consequence only of the fact that the amplitude of contraction is reduced by anesthetics. When the amplitude of contraction is reduced by other means, *e.g.*, by lowering extracellular Ca^{2+} concentrations from 2.50 mM to 0.375 mM in cat papillary muscle, load-sensitivity of relaxation is somewhat decreased.[18] Yet, in the ferret myocardium, it remains to be determined whether volatile anesthetics have a proper effect on relaxation in addition of that which may exist as a consequence of their effects on contraction. Third, a decrease in load-sensitivity of relaxation can result from an abbreviation of isometric relaxation, from a slowing of isotonic relaxation, or from both. Both effects are seen concurrently with volatile anesthetics, albeit that isoflurane has minimal effects on isotonic relaxation.[29]

Myocardial relaxation is a complex process, the time course of which depends upon: 1) the rate of decline of cytoplasmic calcium concentration (a reflection of the pumping activity of the sarcoplasmic reticulum); 2) the release of calcium from the regulatory protein troponin C (determined by the affinity of troponin C for Ca^{2+}); 3) myofibrillar responsiveness for a given occupancy of Ca^{2+}-binding sites of troponin C; and 4) dynamics of attachment and detachment of actomyosin cross-bridges. Of these four factors, at least one is known to be affected by the mode of contraction and may be responsible for differences in the time course of contraction and relaxation of the isometric *versus* isotonic twitch: the affinity of troponin C for calcium is less during shortening at low loads than at comparable times during force development.[39-43] Consequently, less calcium will remain bound on myofilaments after a period of shortening than after a period of force development, and calcium is more likely to come off troponin C when muscles are contracting at low loads than at high loads,[41-42] as cross-bridge attachment modulates calcium binding.[43] Hence, the dissipation of force, or isometric relaxation, will be much slower than isotonic lengthening against low loads, and the time course of isotonic relaxation will, therefore, reflect the pumping ability of the sarcoplasmic reticulum. The time course of isometric relaxation will reflect to a substantial degree the calcium sensitivity of the contractile proteins, possibly the affinity of troponin C for calcium. A diminution of load sensitivity of relaxation such as shown in figure 4 can, therefore, result from a slower or later occurring calcium sequestration and, hence, a delayed isotonic relaxation,

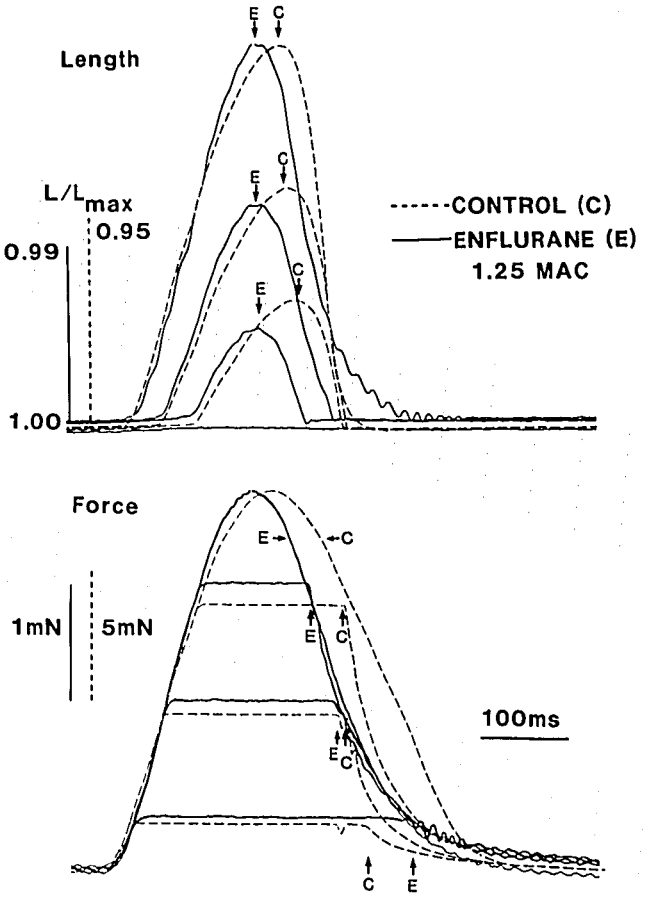

FIG. 6. Length (upper) and force (lower) traces of an isometric twitch and of three afterloaded isotonic twitches before (dotted lines), and during exposure to 1.25 MAC of enflurane (solid lines). Force and length scales are different for control (right) and enflurane (left). Muscle characteristics: L_{max} 4.2 mm, mean cross-sectional area 0.24 mm^2, ratio of resting to total tension (R/T) 0.174.

and/or from an accelerated disappearance of cross-bridges consequent to a reduced myofibrillar calcium sensitivity and, hence, an earlier isometric relaxation. Halothane, enflurane, and isoflurane accelerate the time course of isometric relaxation[29] (fig. 6), an effect that is most likely due to a decrease in myofibrillar calcium sensitivity.[26,27,29] The acceleration of isometric relaxation is not necessarily related to the concomitant decrease in peak force, as it was previously shown that time to half isometric relaxation did not change over a range of extracellular calcium concentrations from 1.25–10 mM in the cat papillary muscle.[44] Effects on isotonic relaxation depend on the load against which muscles were constrained to contract. At loads close to isometric force, the duration of the isotonic twitch was abbreviated with respect to the control, and isotonic relaxation occurred earlier (fig. 6). At loads approximately halfway between preload and isometric, the duration of the isotonic twitch was not affected by anesthetics, but this was the resultant of the fact that the duration of isotonic shortening was abbreviated and that of isotonic lengthening prolonged. At low loads close to the preload, the anesthetics greatly prolonged total duration of shortening; again, it was the relaxation phase (isotonic lengthening) that was prolonged. It is conceivable that in the absence of anesthetics, the dissociation of Ca^{2+} from troponin C is normally the rate limiting step of (or at least markedly modifies) isometric relaxation. Yet, in the presence of anesthetics, Ca^{2+} would dissociate more rapidly from troponin C and the SR Ca^{2+} uptake processes may become saturated and rate-limiting, which would reflect itself in a slowing of isotonic lengthening.

In summary, halothane, enflurane, and, to a lesser extent, isoflurane interfere with normal myocardial relaxation in a reversible dose-dependent fashion. The decrease in load sensitivity of relaxation with these anesthetics was due to a slowing of isotonic lengthening and an abbreviation of the isometric relaxation. This may result from the anesthetics' actions to: 1) produce a relative insufficiency of calcium sequestering systems, and 2) reduce the affinity of troponin C for calcium and/or the myofibrillar responsiveness to Ca^{2+}. How is this information applicable to the clinical situation? Load-insensitive relaxation implies that halothane, enflurane, and, to a lesser extent, isoflurane diminish the adaptability of ventricular myocardium to changes in vascular impedance because the time course of relaxation becomes fixed irrespective of afterload or peripheral loading. Second, since these anesthetics slowed isotonic lengthening at any load, one could predict that rapid ventricular filling will be slowed or even impeded to some extent in the intact heart during anesthesia. At the present time, there is one report that diastolic filling was depressed and relaxation slowed by isoflurane in chronically instrumented dogs.[45] The effects of halothane and enflurane on myocardial relaxation of the intact heart remain to be established.

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