ABSTRACT

Left atrial strips and right ventricular papillary muscles of kittens and left atrial strips of guinea pigs, rabbits, dogs, and chickens were exposed to ouabain, acetylstrophanthidin, or digoxin at 37°C during rest or while contracting at frequencies from 0.06 to 60/min. Both the positive inotropic effect and increases in resting tension developed fully in all preparations exposed to the three drugs during complete quiescence. Contraction frequency had some influence on the rate of development of these effects, but this influence was not the result of the number of beats during exposure. In ventricular myocardium, exposure times required for the attainment of the maximum positive inotropic effect and for the induction of contracture at different contraction frequencies were proportional to the increase in tension development. It is concluded that the development of the myocardial effects of digitalis-like compounds does not require cardiac activity. The limited influence of contraction frequency on the rate of development of these effects may be partly due to frequency-dependent changes in the functional state of the myocardium which affect the magnitude of the positive inotropic action of cardiac glycosides.

KEY WORDS positive inotropism acetylstrophanthidin contracture digoxin hypodynamicity rabbits cats interval-strength relationship ouabain guinea pigs

The magnitude of the positive inotropic effect of cardiac glycosides varies greatly with the frequency of myocardial contraction (1-5). Contraction frequency also influences the concentrations of glycosides required to produce the maximum positive inotropic effect or to induce contracture (3, 6-9). The effect of contraction frequency on the rate of development of cardiac glycoside action remains at issue.

Observations on frog ventricles (10), guinea pig ventricle strips (11) and rabbit atria (4) suggested to some that the positive inotropic action of cardiac glycosides is contraction dependent and does not occur in resting myocardium. Others reported that the positive inotropic effect and contracture develop during exposure to glycosides of quiescent myocardium of frogs (6), cats (3), guinea pigs (5), and rabbits (12). Most investigators have noted some influence of contraction frequency on the rate of approach to the maximum positive inotropic action of a cardiac glycoside, but this was found in several studies not to be related to the number of beats during exposure to the drug (2, 3, 5). Studies with tritiated digoxin showed no effect of contraction frequency on its uptake and the same myocardial concentrations and half-lives in contracting and quiescent myocardium (13, 14).

This paper describes the effect of myocardial activity on the time course of the mechanical response of isolated myocardium to cardioactive steroids. The experiments were designed to answer three questions. (1) Are the mechanical effects of cardiac glycosides on the myocardium contraction dependent or do they develop during rest? (2) To what extent does contraction frequency influence the rate
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35

40 60 80 100 120

EXPOSURE TIME — minutes

FIGURE 1

Time course of development of positive inotropic action of ouabain at four contraction frequencies in kitten myocardium exposed to ouabain, 2 \( \times \) 10^{-7}M; means and standard errors of 14 to 18 preparations.

of onset of the myocardial effect of cardiac glycosides? (3) Is this influence due to the number of contractions during exposure or to other factors?

Methods

Papillary muscles were obtained from the right ventricles of 52 kittens with a median weight of 610 g. Only papillary muscles of less than 0.6 mm^2 cross-sectional area were included in order to minimize inadequate oxygenation of the central fibers (15, 16) and to ensure rapid diffusion of glycosides from the perfusing solution throughout the interstitial fluid. Cross-sectional area was estimated on the basis of weight at the end of each experiment, assuming the muscle to be a cylinder with a specific gravity of one. Length of the muscles was measured under the resting tension employed throughout the experiment and averaged 7 mm. Atrial strips were taken from the left atria of kittens, guinea pigs, rabbits, dogs, and chickens. They averaged 0.5 mm thick, 10 mm long, and 5 mm wide.

The animals were killed by a sharp blow on the skull and the hearts were immediately dissected in oxygenated solution at room temperature. Suitable papillary muscles were removed together with a small button of adjacent ventricular wall and a short piece of chorda tendinea. The mural end of each muscle was fixed to a muscle holder by a plastic clamp and the tendinous end was tied with a short silk thread to a wire extending upward to a Statham transducer model G7B-0.75-350. The long axis of the atrial strips was similarly fixed. Resting tension of all preparations was maintained at about one half of that determined at the beginning of the experiment to be associated with maximum development of tension. It varied between 100 and 300 mg depending on the cross-sectional area of the preparation.

Isometric mechanograms were recorded on a Sanborn model 984 oscillographic recording
Development of positive inotropic action of ouabain related to number of contractions during
exposure. Same preparations as in Figure 1.

Results

Rate of Development of Positive Inotropic Action.—Atrial strips and papillary muscles of
kittens stimulated at one of four frequencies were exposed to 2 × 10^{-7} M ouabain, until the
drug had produced its full inotropic effect and tension development no longer increased.

Since the positive inotropic effect of ouabain

system equipped with model 350-1100B carrier preamplifiers. All measurements of developed
tension were made after a steady state for the particular frequency of stimulation had been
reached. The preparations were quiescent unless excited electrically. Electrical stimuli were deliv-
ered through two punctate platinum electrodes contacting the surface of the muscle just above
the point of clamping. The stimuli were delivered

The muscles were suspended in 50 ml of a
modified Krebs solution of the following composit-
ion (before equilibration with CO₂): Na⁺ 140
mEq/liter, K⁺ 3 mEq/liter, Ca²⁺ 4.5 mEq/liter,
Mg²⁺ 2 mEq/liter, Cl⁻ 98.5 mEq/liter, SO₄²⁻ 2
mEq/liter, HCO₃⁻ and H₂CO₃ 29 mM, HPO₄²⁻ and
H₂PO₄⁻ 1 mM, fumarate 5 mM, pyruvate 5
mM, l-glutamate 5 mM, glucose 10 mM, and
insulin 5 IU/liter. The solution was continuously
oxygenated and stirred by passage of finely
divided bubbles of a mixture of 95% O₂ and 5% 
CO₂. After equilibration with this mixture, the
pH was 7.4. The perfusing solution was replaced
by fresh solution at 1-hour intervals or whenever
the concentration of a drug was changed. The
solution was always maintained at a temperature
of 37.5 ± 0.1°C.

Ouabain, acetylstrophanthidin, and digoxin
were added directly to the organ bath after
dilution of stock solutions. Dilutions were made in
such a way that the volume of drug solution
added never exceeded 0.1% of the organ bath
volume.
first appears and later reaches its maximum in an asymptotic fashion, no attempt was made to time these events. Instead, the exposure time to ouabain required to achieve 10, 25, 50, 75, and 90% of the maximum increase in developed tension was determined (Fig. 1). Frequency of contraction clearly influences the rate of development of the positive inotropic action of ouabain on kitten myocardium. For atrial muscle, the relationship is straightforward: the lower the contraction frequency the greater the time required to reach any fraction of the maximum inotropic effect. For papillary muscles, the rate of onset of the inotropic action is slower at the intermediate frequencies of 0.6 and 6 beats/min than at 60 and 0.06 beats/min. In both types of myocardium, the effect of contraction frequency on the development of the positive inotropic action of ouabain is relatively minor. A thousand-fold decrease in frequency slows the achievement of 90% of the maximum effect in papillary muscle by only 30% and in atrial strips by 100%.

Figure 2 shows that the rate of development of the inotropic action of ouabain is not related to the number of contractions during exposure. When intervals between beats are 1000 seconds, 90% of the maximum inotropic effect is reached with the ninth or tenth beat. With 1-second intervals between contractions, this occurs only after more than 5000 beats. In both atrial and ventricular muscle exposed to ouabain, the number of beats prior to the achievement of any fraction of the maximum inotropic effect increases sharply with contraction frequency.

The findings presented in Figure 3 demon-
state further that the rate of appearance of the positive inotropic action of ouabain is independent of the number of beats. Atrial strips and papillary muscles were stimulated at one of two frequencies during exposure to ouabain. Half of the preparations were stimulated continuously; in the other half, 5-minute periods of stimulation were alternated with 5-minute periods of complete quiescence. This experimental procedure would have detected any effect of the number of beats during exposure on the rate of development of ouabain action. At all times after exposure to ouabain shown in Figure 3, the continuously stimulated preparations had contracted twice as many times as the preparations stimulated at the same frequency but with pauses. In either type of kitten myocardium, the number of contractions during exposure to ouabain had no effect on the rate of development of the positive inotropic effect at either contraction frequency.

The results of a third experimental approach to separating the effects of contraction frequency and of number of beats during exposure to ouabain are shown in Figure 4. During exposure to ouabain, each atrial strip was stimulated in continuous rotation for 5 minutes at the three frequencies of 0.6, 6, and 60/min. At any time after exposure, each strip had therefore contracted the same number of times. Nevertheless, in all preparations, the higher the contraction frequency, the earlier was any fraction of the maximum inotropic effect of ouabain reached. Tension development at the lower frequencies continued to increase after the maximum inotropic effect had been reached at 60 beats/min. The effect of frequency on the rate of development of the positive inotropic effect of ouabain was the
same as during the experiments shown in Figure 1, where the number of beats during exposure in each preparation was determined by the contraction frequency. The results of these three experimental approaches indicate that frequency of contraction influences the rate of onset of ouabain action, that this effect is not related to the number of beats during exposure to the drug, and that the number of beats does not influence the rate of development of the positive inotropic effect.

It remained possible that some contractions were necessary for the development of the changes in the myocardium which are responsible for the inotropic effect of ouabain. Single stimuli were applied at 10-minute intervals to 10 atrial strips and 12 papillary muscles. The strength of contractions preceded by intervals of such length is independent of previous beats (rested-state contractions, 19). Further prolongation of the preceding interval has therefore no effect on the strength of contraction. After five such rested-state contractions of identical strength, ouabain (2 x 10^{-7}M) was added to the perfusing solution. The preparations were then not stimulated for 3 hours but continuously monitored to ensure that no spontaneous contractions occurred. In each instance, the first contraction after the 3-hour quiescent exposure to ouabain showed the full positive inotropic effect of ouabain on rested-state contractions. Evidently, the ouabain-induced change in atrial and ventricular muscle which results in enhanced myocardial contractility develops in the total absence of any contractile activity.

Magnitude and Rate of Development of Positive Inotropic Action.—The frequency of contraction influences not only the rate of development of the positive inotropic effect of ouabain but also its magnitude. Figure 5 shows the basal strength of contraction of...
kitten atrial strips and papillary muscles and the maximum tension development after addition of $2 \times 10^{-7}$M ouabain at four contraction frequencies. In papillary muscles the largest absolute positive inotropic effect occurred when they contracted 6 times/min, and the smallest when beating 60 times/min. At these contraction frequencies, the rate of approach to the maximum inotropic effect was slowest and fastest, respectively (Fig. 1). This suggests that in ventricular myocardium the influence of contraction frequency on the rate of development of ouabain action expressed as percent of maximum may be related to the variation with frequency of the magnitude of this action.

The possibility that the absolute magnitude of the positive inotropic response of ventricular myocardium is a major determinant of the exposure time required to achieve the maximum effect is supported by the relationship shown in Figure 6. Here, exposure time to ouabain is related to the ouabain-induced absolute increase in tension development at four contraction frequencies. The time required to achieve any given absolute increase in active tension appears quite independent of frequency. The greater the maximum inotropic effect of ouabain at a given frequency, the more slowly is it reached. This simple relationship does not hold for kitten atrial muscle. In this tissue, the rate of onset of ouabain action decreases with decreasing contraction frequency from 60 to 0.06/min, but the magnitude of the absolute inotropic effect first increases and then decreases (Figs. 1 and 5).

Effect of Hypodynamism.—The positive inotropic effect of the maximally effective concentration of ouabain is greater in hypody-
Influence of perfusate \([\text{Ca}^2+]\) on development of positive inotropic effect of ouabain, \(2 \times 10^{-7}\)M; contractions, 60/min. Means and standard errors of 11 to 15 preparations of kitten myocardium.

Development of Contracture.—During exposure of heart muscle to sufficiently high concentrations of ouabain the period of maximum positive inotropic effect of the drug is followed by a progressive decrease in tension development associated with an increase in resting tension. These changes gradually approach complete contracture and absence of contractile activity. The frequency of contraction influenced the time from exposure to ouabain to the first increase in resting tension and to marked contracture (Fig. 8). In atrial muscle ouabain-induced contracture occurred sooner the higher the frequency of contraction. As with the positive

Figure 7

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inotropic effect of ouabain, the cause of this cannot lie in the number of beats during exposure, which varied more than 500-fold.

In papillary muscles, increases in resting tension also appeared most quickly at the highest frequency of contraction (Fig. 8). In muscles beating 0.06 times/min during exposure to $2 \times 10^{-7}$M ouabain, contracture never developed. The rate of onset of contracture at the intermediate frequencies of 6 and 0.6/min was almost identical. Similarly, little difference had been found between these frequencies in the magnitude (Fig. 5), and the rate of development (Fig. 1) of the positive inotropic effect of ouabain.

The interspersion of rest periods at any contraction frequency did not influence the exposure time required for increases in resting tension to appear. When atrial strips or papillary muscles were exposed to $4 \times 10^{-7}$M ouabain, contracture developed fully during complete quiescence of the preparations and at a rate identical to that observed at 0.06 beats/min.

Other Species.—The relationship between contraction frequency and rate of development of ouabain action was examined in isolated heart muscle preparations of four other species. In guinea pig atrial strips, ouabain-induced increases in active tension appear much more quickly than in atrial muscle of kittens (Fig. 9). A tenfold change in contraction frequency had no significant effect on the exposure time required for the development of any fraction of the maximum positive inotropic effect. Contraction frequencies of 60 and 6 beats/min were chosen, since at these frequencies the mean basal strength of contraction and the average magnitude of the positive inotropic effect of ouabain (220%...
Development of positive inotropic effect of ouabain in guinea pig and rabbit atrial strips.

Means and standard errors of 12 preparations for each species and contraction frequency.

Note different time scale for 2 species. Ouabain concentration: guinea pig, $5 \times 10^{-7}M$; rabbit, $10^{-6}M$. Numbers over top of curves indicate mean number of beats from addition of ouabain to that point.

By the time 90% of the maximum positive inotropic effect was reached, the muscles contracting 60 times/min had beat nine times as often as those contracting only 6 times/min.

The findings with rabbit atrial strips were similar (Fig. 9). A tenfold decrease in frequency of contraction slowed the achievement of any given fraction of the maximum positive inotropic effect only slightly. The mean maximum absolute increase of active tension was 20% less at the higher frequency of contraction, and the exposure time required to achieve it was 28% shorter. Again, the number of beats during development of the ouabain effect were very different at the two frequencies.

The same general observations were made with atrial strips of dogs and chickens. In myocardium of all four species, contraction frequency had some influence on the exposure time required to achieve the maximum positive inotropic effect or any fraction thereof, but the differences were small. The number of beats during achievement of the maximum positive inotropic effect varied enormously at different frequencies. The first contraction after a sufficiently long quiescent exposure of
atrial muscle from these four species showed the full positive inotropic effect for rested-state contractions. Contracture always developed during exposure of resting preparations to sufficiently high concentrations of ouabain.

Other Cardiac Glycosides.—The rate of onset of the positive inotropic action of $4 \times 10^{-3} M$ acetylstrophanthidin and of $2 \times 10^{-3} M$ digoxin was examined in left atrial strips of guinea pigs and kittens and in kitten papillary muscles. The positive inotropic action of acetylstrophanthidin developed 1.58 times as fast, and that of digoxin 0.56 times as fast, as the action of ouabain. Changes in contraction frequency between 0.06 and 60 beats/min had no major effect on the rate of development of the positive inotropic effect of either compound. The time required to reach the maximum positive inotropic effect of both drugs in papillary muscles was proportional to the absolute increase in active tension. The number of contractions during development of the maximum inotropic effect of both compounds was very much greater at higher contraction frequencies. Both the positive inotropic effect and increases in resting tension developed during exposure of quiescent muscles to acetylstrophanthidin or digoxin.

**Discussion**

The results of our studies on the development of the positive inotropic action of digitalis-like compounds indicate that it is a time-dependent process which does not require myocardial activity. The changes responsible for the mechanical effects of cardiac glycosides develop fully in quiescent heart muscle, as reflected by the enhanced strength of the first contraction after resting exposure and by development of contracture during rest. The number of contractions during exposure to a glycoside does not affect the rate of development of its actions. The time required to achieve the maximum inotropic effect of a glycoside or any fraction thereof does vary somewhat with contraction frequency. The role of frequency cannot be related to the number of beats during exposure, since it is not altered by interspersion of rest intervals or by rotation of contraction frequencies in the same preparation. It may well be related to the marked influence of contraction frequency on the functional state of heart muscle.

Previous studies on the relationship between myocardial activity and the onset of cardiac glycoside action have yielded conflicting results. Weizsäcker (6, 19) reported that the toxic effects (negative inotropism and contracture) of ouabain and digitalin on frog ventricles appeared more quickly at high contraction frequencies at which basal contractility was high but developed fully in resting muscle. He concluded that increases in contraction frequency increase the susceptibility of myocardium to cardiac glycosides and thereby accelerate development of contracture. When comparing two contraction frequencies of frog ventricle at which contractility is about the same, von Isokutz (7) found no appreciable effect of frequency on the rate of development of contracture. Fischer (20) reached similar conclusions, but Wilbrandt et al. (10) reported that the positive inotropic effect of a 5-minute exposure of hypodynamic frog ventricles to K-strophantoside increased with contraction frequency.

The effect of contraction frequency on the rate of onset of glycoside action in mammalian myocardium was first reported by Garb and Penna (21). They found that any fraction of the maximum positive inotropic effect of ouabain was reached after the same exposure time in cat papillary muscles beating 12 or 60 times/min and concluded that the "latent period" of ouabain action was related to exposure time and not to the number of contractions during exposure. Sanyal and Saunders (11), on the other hand, observed that the approach to the maximum inotropic effect of ouabain on guinea pig right ventricular strips accelerated with frequency from 25 to 200 beats/min, while the magnitude of the effect decreased. They did not examine low contraction frequencies or quiescent myocardium but postulated that the inotropic action of ouabain "occurs only in contracting myocardium." Kruta et al. (2) noted that in...
guinea pig atrial strips stimulated in rotation 30, 60, and 120 times/min, the magnitude of the maximum positive inotropic effect of ouabain and the exposure time required to achieve it decreased with increasing contraction frequency. Since in their experiments the effect of frequency could not be due to the number of contractions during exposure, they concluded that each contraction frequency creates a different functional state in the myocardium which influences the magnitude of the glycoside effect and the time needed to reach it. Holland (22) found the exposure time required to reach the maximum positive inotropic effect of ouabain on rabbit atria to be inversely proportional to contraction frequency. Lock (23) reported that the rate of development of the positive inotropic action of ouabain in contracting hen atrial strips was not significantly altered by a brief preceding resting exposure.

Three recent studies examined the influence of myocardial activity on the rate of cardiac glycoside action in detail but came to different conclusions. Moran (4) found that the contractile force of rabbit left atria beating 15, 30, 60, and 120 times/min responded to ouabain in proportion to the number of contractions and not to the time of exposure. He postulated that the binding and the positive inotropic effect of ouabain are largely contraction dependent and that little or no reaction takes place during rest. However, low contraction frequencies and the occurrence of contracture in resting myocardium were not examined. In marked contrast, Vincenzi (5) observed that the rate of onset of ouabain action on guinea pig left atria was independent of contraction frequency from 0.2 to 20/min and was only moderately accelerated during higher frequencies at which the magnitude of the positive inotropic effect was less. The onset of ouabain action was independent of the number of beats in its presence, and ouabain produced its full positive inotropic effect on resting atria of guinea pigs and rabbits. Similarly, Byrne and Dresel (12) reported that ouabain exerted its positive inotropic action on quiescent rabbit atria and that this action developed more quickly at 120 beats/min than at rest.

Since conflicting results have been obtained on the same species (frog, guinea pig, rabbit) and with the same cardiac glycoside (ouabain), they cannot be explained by species differences or by different lipid/water partition coefficients of the drugs. The concentration of glycoside, the concentration of calcium in the perfusing medium, and the degree of hypodynamicity of the preparations may have influenced the results (3, 12). The experimental temperature may also account for some differences, because the effect of contraction frequency on the rate of onset of glycoside action apparently increases as the temperature is lowered below the physiological (4, 5, 12).

The contraction frequencies examined by different workers have almost certainly influenced their conclusions. The positive inotropic effect of glycosides is small at high contraction frequencies, and in isolated preparations the full manifestation of this effect may be prevented by limits on energy production determined by the maximum rate at which oxygen can diffuse into the tissue (8, 15, 16). Thus comparisons of the rate of onset of glycoside action at high contraction frequencies may be misleading. At contraction frequencies below 15/min, the increase in contractile force is far more prominent (3, 8) and is fully as sensitive an index of glycoside action as the "frequency reduction test" (4, 12, 14). Study of such frequencies is revealing, and it may be significant that they were not examined by those who concluded that the positive inotropic effect of glycosides is contraction dependent. Even more important is the study of the effect of glycosides on quiescent muscle. Whenever this was determined directly with the use of rested-state contractions or by the induction of contracture (3, 5, 7, 12), the effects were found to develop fully. Comparison of contractility at high frequencies after short exposures and washout of resting and active muscles is a less direct and sensitive index, but even this has always shown some action on resting muscle (4, 14,
The conclusion is inescapable that myocardial activity is not a sine qua non for the action of cardiac glycosides. It is equally certain that the exposure time required to achieve the full effect of cardiac glycosides varies with contraction frequency. The suggestion that this reflects contraction dependency of the binding of these drugs to heart muscle (4, 10) is in conflict with direct measurements of their myocardial uptake. As early as 1913, Werzäcker (19) concluded that myocardial activity did not influence the rate of binding of cardiac glycosides to frog ventricles, and Holland and Sekul (24) reached the same conclusion with rabbit atria. Using tritiated digoxin, Kuschinsky et al. (13) found that the uptake of digoxin by guinea pig atria was independent of contraction frequency and that resting atria took up as much digoxin as beating organs during a 3-hour exposure. Roth-Schechter et al. (14) observed that activity of guinea pig atria had no effect on myocardial uptake and concentration of digoxin or on the pharmacological and drug half-lives. Thus myocardial contraction does not appear to enhance glycoside binding. It has been suggested that cardiac glycosides act on, or interact with, processes which are influenced by contraction frequency. One such process is the influx of sodium with excitation. If glycosides act by inhibiting sodium efflux and thereby increase calcium influx with each beat, their action should develop at a rate directly proportional to contraction frequency (25). The actual influence of frequency is much less marked and the action develops at rest. Thus, the rate of onset of glycoside action must also be determined by a quantitatively important basal process which is independent of cardiac activity.

A likely explanation for the relatively small influence of contraction frequency on the onset of glycoside action lies in the profound effect of frequency on the functional state of the myocardium. The influence of contraction frequency on the strength of contraction of heart muscle is always marked, though it differs in atrial and ventricular muscle and among species (8, 16, 18). The inotropic effects of many drugs vary greatly with contraction frequency (8, 28). This is particularly true for the cardiac glycosides which diminish the influence of rate and rhythm on contractility (1-3, 8, 28).

The positive inotropic effect of maximally effective concentrations of glycosides is greatest during those contraction frequencies at which contractility is normally lowest (1, 3, 8, 26, 27). The lower the frequency-determined contractility, the higher the concentration of a glycoside needed to produce the maximum inotropic effect (3, 8). Low concentrations of glycosides solely increase contractility at all contraction frequencies (3, 9). Higher concentrations do so at low frequencies, but at high frequencies the initial positive inotropic effect is followed by the toxic effects of decreased active tension and increased resting tension (3, 6, 9). Still higher concentrations produce the same positive inotropic effects more quickly than low concentrations but ultimately cause toxic effects at all contraction frequencies and even in resting muscles (3, 6, 7). For each glycoside and species, the maximum concentration tolerated without toxic effects is inversely proportional to contraction frequency (7, 9).

A possible explanation for all these relationships is that the same factor in myocardial fibers which increases contractility is augmented by increases in contraction frequency and by cardiac glycosides. The changes in the functional state of the myocardium due to higher heart rates would act additively with cardiac glycosides in achieving greater degrees of activation of the contractile element. The factor involved may be the concentration of free calcium around the myofilaments (25, 28-31). The normally high contractility at high contraction frequencies and the uniformly high contractility at all contraction frequencies after exposure to maximally effective concentrations of glycosides may reflect the presence of nearly optimal concentrations of free calcium for development of active state. Thus, one would expect the opportunity for positive inotropic action of glycosides to be
greatest during contraction frequencies at which contractility and concentration of free intracellular calcium are low. Both the magnitude of the maximum positive inotropic effect and the concentration of glycoside required to achieve it would be high. In contrast, during contraction frequencies at which basal contractility is high, glycosides should have relatively little positive inotropic effect and concentrations required to produce the maximum inotropic action should be relatively low. This is exactly what has been found experimentally.

Similar considerations may explain why, at different contraction frequencies of ventricular myocardium, the time required for achievement of the full positive inotropic effect of cardiac glycosides is proportional to the magnitude of this effect (Figs. 5 and 6). The considerable time required for any nontoxic concentration of a glycoside to exert its full positive inotropic effect must reflect slow achievement of equilibrium between its concentration in the perfusing fluid and at its active site in heart muscle (32) or slow production of the change responsible for the positive inotropic action, or both. At contraction frequencies associated with high basal contractility the relatively small maximum increase in the strength of contraction may be achieved long before either of these processes is complete. In contrast, during frequencies which cause marked hypodynamicity, the strength of contraction may continue to increase until the final concentration of the glycoside at its site of action has been reached and its full effect exerted. With low concentrations of glycosides the time required to reach the full positive inotropic effect may decrease with increasing contraction frequency only at high frequencies (5), because at lower frequencies the maximum possible inotropic effect is not achieved. When, as in our and most previous studies, concentrations of glycosides are higher than those required to produce the maximum positive inotropic action, the influence of frequency on the rate of onset of action becomes more pronounced and extends over the entire frequency range. Since contraction induced by glycosides likely represents an excess of the same change in the myocardium which mediates their positive inotropic action (9, 25, 29), the influence of contraction frequency on both probably has the same basis.

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