

Cardioversion and Digitalis Drugs: Changed Threshold to Electric Shock in Digitalized Animals

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■ Cardioversion is now widely accepted as the method of choice for terminating a number of atrial, nodal and ventricular arrhythmias.¹⁻⁶ The technique consists of administering from a capacitor a specific underdamped monophasic electrical pulse across the intact chest.⁷ When the heart is exposed to electrical energy, there is a risk of producing ventricular fibrillation. With this new technique, such risk is minimized by programming the discharge to fall outside the ventricular vulnerable period of the cardiac cycle. In 450 patients reverted to sinus rhythm during the past three years at the Peter Bent Brigham Hospital, there has not been a single episode of cardiac standstill, ventricular fibrillation or death. Transient arrhythmias, however, have been frequently noted after delivery of the electric shock. These have consisted of varying degrees of A-V block, atrial, nodal and ventricular extrasystoles occurring either singly or assuming a bigeminal pattern, nodal rhythm, nodal tachycardia and rarely paroxysms of ventricular tachycardia. In reviewing the cardioversion experience at the Peter Bent Brigham Hospital, it was found that patients with evidence of digitalis toxicity were more prone to manifest "shock induced" disorders of rhythm.⁸

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The present experiments on dogs were undertaken to clarify the relationship between the digitalized state and the effects of cardioversion and were designed to answer three questions. 1) Can digitalis-induced arrhythmias be treated successfully by cardioversion? 2) Does overdigitalization alter cardiac response to electric discharge? 3) Is the ventricular vulnerable period altered by digitalization?

Methods

Mongrel dogs, 44 in number, including both sexes, and weighing from 20 to 30 kg were anesthetized by intravenous sodium pentobarbital in a dose of 30 mg/kg. Artificial respiration with room air was given by a Harvard respiratory pump through a cuffed endotracheal tube. Minute volume was adjusted to maintain arterial oxygen saturation over 95%. In all animals two defibrillator electrode paddles measuring 9 cm in diameter were covered generously with conductive paste ("Redux") and applied with pressure on either side of the shaved chest at the level of the apex thrust. This position gives the most consistent results and requires the lowest energy levels for defibrillating the heart. The paddles were held in place by clamps. The electrical discharge was delivered from a 16 microfarad capacitor through a 100 millihenry inductor; this provides a 2.5 millisecond underdamped pulse.⁹

Capacitor discharges (DC) were given at 30-second intervals. The endpoint of shock was ventricular tachycardia defined as four or more consecutive ventricular beats of abnormal QRS configuration at a rate in excess of 60 per minute occurring within three seconds after discharge. The electrical shock was synchronized to occur during the QRS complex or shortly after its completion.* In selected experiments to be described the shock was delivered in oth-

*The instrument employed was the "Lown Cardioverter" supplied by the American Optical Company.

er parts of the cardiac cycle. The energy of the initial electrical discharge was set at 10 watt-seconds (WS). If ventricular tachycardia occurred, the energy was reduced by about 50% after each shock until no arrhythmia resulted. If ventricular tachycardia did not follow the 10 WS discharge, the energy was increased progressively to 50, 100, 200, 300 and 400 WS. The shock at the energy setting which resulted in ventricular tachycardia was repeated three times. If ventricular tachycardia occurred in all three trials, this was defined as the threshold energy. If ventricular tachycardia did not occur in each of the three trials, the next highest energy level was tried. This method was found to yield reproducible results.

The dogs were digitalized with acetyl strophanthidin (AS)* or ouabain to an endpoint of ventricular tachycardia, defined as the occurrence of four or more consecutive ventricular beats of abnormal QRS morphology. In a number of experiments both drugs were employed together. AS was given intravenously by means of a constant infusion pump at a rate of 123 $\mu\text{g}/\text{min}$. Ouabain was administered intravenously in an initial dose of 750 μg followed by 100 μg every 20 to 30 min. When both drugs were given together, ouabain was administered as a single injection in a dose of approximately 60% of the anticipated toxic dose. This was followed within minutes by constant infusion of AS, which was administered until ventricular tachycardia developed.

CAPACITOR DISCHARGE

In four of the 44 animals the sole procedure consisted of administering capacitor shocks at increasing energy levels until three consecutive discharges each resulted in ventricular tachycardia. This procedure was repeated hourly over a seven-hour period. The objective was to determine whether the repeated production of ventricular tachycardia by means of high energy discharge reduced the myocardial threshold for electrical provocation of ventricular tachycardia.

REVERSION OF DIGITALIS-INDUCED ARRHYTHMIAS

Five animals were digitalized without prior control shocks. Ouabain, in a dose of 750 μg , was administered intravenously within 30 seconds. After 30 minutes, AS was infused until ventricular tachycardia occurred. As soon as this arrhythmia developed, an attempt was made to restore sinus rhythm by shocking transthoracically with 100 WS discharges given every five minutes. Reversion was attempted 39 times during 184 minutes

of ventricular tachycardia. In each of 11 additional animals reversion of digitalis-induced ventricular tachycardia was attempted with shocks as high as 400 WS.

As soon as these five animals recovered spontaneously from the combination of ouabain and AS-induced ventricular tachycardia, the response to further electrical shock was studied. A total of 130 shocks at energies of 10 and 50 WS was administered throughout the cardiac cycle, but the ventricular vulnerable period was avoided.

In each of these five animals ventricular fibrillation was produced during the episode of digitalis-induced ventricular tachycardia by delivering transthoracic low energy capacitor discharges triggered to fall during the ventricular vulnerable period. Once ventricular fibrillation occurred, the minimal energy for defibrillation was determined. This value was compared with the energy required for defibrillation when ventricular fibrillation was induced during sinus rhythm. In three of these dogs, after completing the above procedures, an excess of AS was infused until ventricular fibrillation developed. Defibrillation was attempted at increasing energies until a level of 400 WS was reached; thereafter three rapid shocks were delivered at this energy.

THRESHOLDS TO ELECTRICAL SHOCK BEFORE AND AFTER DIGITALIZATION

In 35 dogs, during a control period, the minimal DC energy for the production of ventricular tachycardia was determined. Thereafter these thresholds were restudied during digitalization or after recovery from digitalis-induced ventricular tachycardia. In eight animals thresholds were determined during digitalization with ouabain. The energy level which produced ventricular tachycardia was checked before administering each additional dose of ouabain. Capacitor shocks were delivered at two intervals in the cardiac cycle: during the absolute refractory period, 40 msec after the QRS complex; and during the diastolic phase, between the T and QRS waves of the electrocardiogram. In 27 dogs, these thresholds were studied after recovery from digitalis toxicity; shocks were administered at frequent intervals until control energy level requirements to produce ventricular tachycardia were re-established. Of the 27 animals, 11 received ouabain, 12 received AS, and 4 received both drugs.

In eight of the above animals the duration and threshold of the ventricular vulnerable period were studied before digitalization with AS and at varying intervals after recovery from ventricular tachycardia. The beginning of the vulnerable period was determined by administering repeated 10-WS discharges during inscription of the ascending limb of the T wave,

*Kindly supplied by Dr. G. C. Chiu of the Eli Lilly Company, Indianapolis, Indiana.

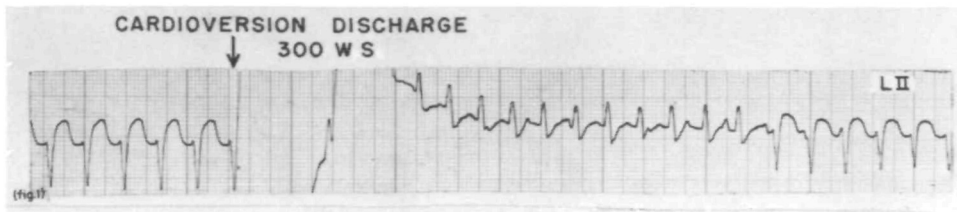


FIGURE 1

Ventricular tachycardia induced by acetyl strophanthidin responds after 300 watt-seconds (WS) synchronized (DC) discharge with transient supraventricular tachycardia. This is followed immediately by resumption of ventricular tachycardia.

and then by progressing at 10-msec intervals toward the apex of the T wave. The first occurrence of ventricular fibrillation defined the beginning of the vulnerable period. By exploring similarly the descending limb of the T wave, i.e., starting at the end of the T wave and working backward toward its apex, the end of the vulnerable period was defined. Using this technique, only two episodes of ventricular fibrillation were required to locate the time limits of this period for the energy setting employed. The range of energy which resulted in ventricular fibrillation was determined by fixing the synchronizer to discharge in the center of the vulnerable period and by administering shocks at increasing energies beginning below the threshold for ventricular fibrillation. The initial development of ventricular fibrillation defined the lower energy limit.

The upper limit was explored by starting at 50 WS; depending upon the occurrence of ventricular fibrillation, the energy setting was either increased or decreased until this limit was defined. In order to deliver discharges of energy of less than 1 WS, a three-range voltage dividing network was connected between the defibrillator and the experimental animal. This device permitted division of the output voltage of the defibrillator by 10, 100 or 1000 depending upon the energy level selected. As energy delivered is proportional to the square of the applied voltage, the energies available at the output of the network were respectively 10^{-2} , 10^{-4} and 10^{-6} of the input into the voltage divider.

Results

CARDIOVERSION OF DIGITALIS-INDUCED ARRHYTHMIAS

Cardioversion of digitalis-induced ventricular tachycardia was attempted 63 times in 16 dogs. Ventricular tachycardia was produced by ouabain in four dogs, by AS in seven, and by a combination of both drugs in five. In only one case was reversion of ventricular tachycardia achieved for more than a few

seconds. In this single case, atrial fibrillation appeared, lasted for a minute, and then was followed by resumption of ventricular tachycardia. In four other animals, transient sinus rhythm or supraventricular tachycardia appeared and lasted for less than five seconds (fig. 1). The remaining 58 attempts to revert ventricular tachycardia were unsuccessful even after repeated high energy shocks. In a few instances electrical discharge accelerated the rate transiently or changed the morphology and direction of the QRS complex (fig. 2). In no case was lasting reversion achieved even though shocks of 400 WS were administered; this represents over five times the average energy level required to defibrillate the dog's heart during ventricular fibrillation. Reversion was equally ineffective whether ventricular tachycardia was induced by AS or by ouabain.

When ventricular fibrillation was produced during digitalis-induced ventricular tachycardia by discharging the electrical pulse at the apex of the T wave, defibrillation could be accomplished readily. The result, however, was reinstatement of ventricular tachycardia rather than restoration of sinus rhythm (fig. 3). The energy required for abolishing ventricular fibrillation was essentially the same whether ventricular fibrillation was initiated during sinus rhythm or during digitalis-induced ventricular tachycardia.

In five animals with sinus rhythm, 29 episodes of ventricular fibrillation were induced by discharge during the vulnerable period of the cardiac cycle. The mean defibrillating energy was 58 WS. In these same animals, 25 episodes of ventricular fibrillation were pro-

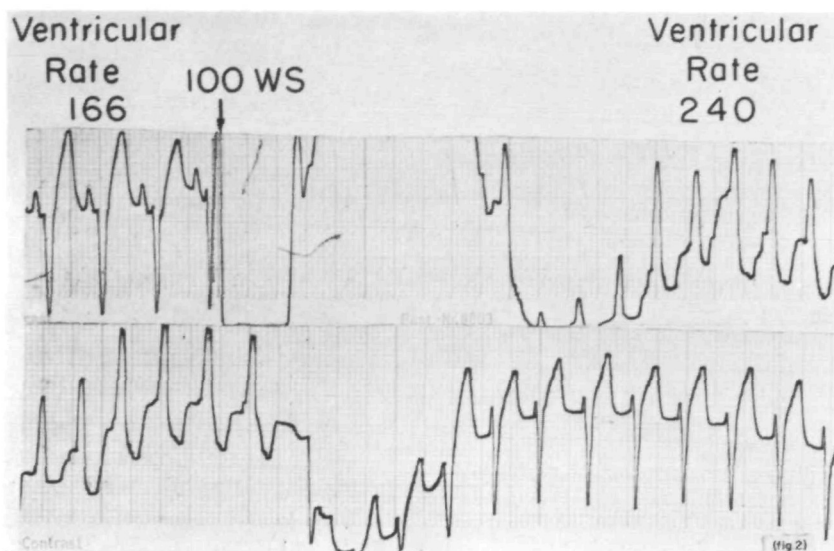


FIGURE 2

Ventricular tachycardia induced by acetyl strophanthidin with synchronization between atria and ventricles. A single 100 watt-second DC discharge accelerates the rate and changes direction of the ventricular complex.

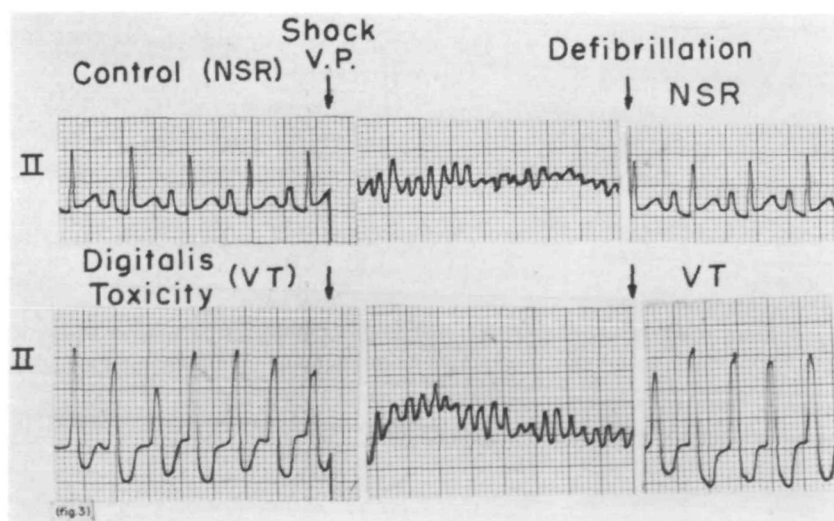


FIGURE 3

In the presence of normal sinus rhythm (NSR), ventricular fibrillation is defibrillated to sinus rhythm. When defibrillation is done against a background of digitalis-induced ventricular tachycardia (VT), the abnormal rhythm persists. In both cases ventricular fibrillation was induced by delivering a small energy electrical discharge in the vulnerable period of the cardiac cycle.

duced electrically during ventricular tachycardia caused by AS and ouabain; the mean defibrillating energy was 42 WS. The difference in defibrillating energies is not statistically significant. In three of these animals AS

was given to the point of ventricular fibrillation. This arrhythmia could not be reverted even transiently, although multiple high energy shocks were administered. These experiments indicate that digitalis-induced

ventricular arrhythmias in the dog cannot be terminated by condenser discharge.

RESPONSE OF THE DIGITALIZED ANIMAL IN SINUS RHYTHM TO DC SHOCK

Control thresholds for production of ventricular tachycardia by transthoracic shock were determined in 35 dogs. These shocks were delivered outside the ventricular vulnerable period. In 12 of these animals ventricular tachycardia was not produced even at 400 WS, the upper limit of energy available for testing. The median energy for ventricular tachycardia was 400 WS. The lowest level was 100 WS and this was noted in only one animal. The distribution of energies is illustrated in table 1.

Repeated DC shock did not lower the threshold for ventricular tachycardia. In four dogs tested at hourly intervals for seven hours, the electrical threshold remained constant, even though supplementary pentobarbital anesthesia was given as needed in an uncontrolled fashion.

In an initial phase of these experiments, five dogs were given 10-WS shocks after recovery from combined ouabain and AS-induced ventricular tachycardia. These electrical shocks were delivered outside the ventricular vulnerable period and produced ventricular tachycardia in each of the five animals. A total of 100 shocks was administered to these five dogs; 36 were followed by ventricular tachycardia, 18 by frequent ventricular premature beats, five by atrial fibrillation and four by 2:1 heart block. The arrhythmias following shock usually lasted from 3 to 15

seconds. The abnormal response to low energy shocks occurred only within the first seven minutes following the termination of drug-induced ventricular tachycardia.

Because these experiments showed sensitivity to a fixed level discharge following digitalis intoxication, a more detailed exploration of this phenomenon was undertaken. In twelve animals the electrical thresholds for ventricular tachycardia were determined prior to digitalization and immediately after recovery from AS-induced ventricular tachycardia. In seven animals the electrical threshold for ventricular tachycardia was reduced significantly, in four it remained unchanged and in one animal it increased. In the seven animals showing a decrease, the median energy decreased from 250 WS during the control period to 7 WS when testing was done within ten minutes after recovery from AS-induced ventricular tachycardia. This sensitivity to DC discharge was of short duration. The animals that did not show a reduced threshold to shock may have been tested too late, i.e., after the brief effect of AS had worn off.

Since sensitivity to electric shock after AS was of short duration, further exploration of this phenomenon involved the use of the longer acting drug, ouabain. Control thresholds to electric shock, i.e., the lowest discharge energies producing ventricular tachycardia, were determined in 11 of the 44 dogs. These animals were then tested every ten minutes following recovery from ouabain ventricular tachycardia. The median control energy value was 400 WS. When the 11 dogs were retested immediately after recovery from ouabain ventricular tachycardia, the median value was 0.2 WS, a 2000-fold reduction. The episode of ventricular tachycardia following shock generally lasted for three to 30 seconds. One of the 11 dogs required 100 WS, one 5 WS, while the remaining nine developed ventricular tachycardia after 0.2 WS or less (fig. 4). The lowest energy setting resulting in ventricular tachycardia was 0.05 WS. During control testing in this animal, ventricular tachycardia could not be produced with a discharge of 400 WS. In this dog a greater than 8000-

TABLE 1

Control Thresholds for the Production of Ventricular Tachycardia (VT) by Condenser Discharge (DC) in Thirty-five Dogs

Energy for VT	Number of animals
watt-sec	no.
100	1
200	8
300	7
400	7
> 400	12
Median 400	Total 35

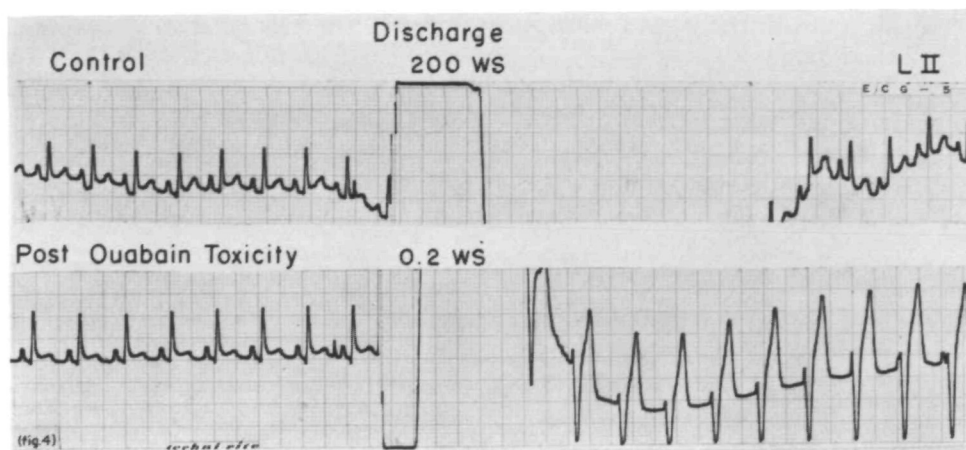


FIGURE 4

Prior to ouabain a 200 watt-second discharge does not alter heart rhythm. Immediately after recovery from ouabain-induced ventricular tachycardia 0.2 watt-second provokes ventricular tachycardia.

TABLE 2

Electrical Threshold (in watt-seconds) for Production of Ventricular Tachycardia in Ten Dogs at Varying Intervals Following Recovery from Ouabain Toxicity

Dog no.	Control before ouabain	After ouabain				
		0 to 4 min*	5 to 29 min*	30 to 59 min*	60 to 89 min*	90+ min*
1	300	0.1	0.5	200.0	200.0	300.0
2	400	5.0	5.0	5.0	5.0	5.0
3	300	0.2	1.0	50.0	300.0	300.0
4	300	0.1	0.2	0.1	10.0	200.0
5	400	0.2	1.0	10.0	400.0	400.0
6	400	1.0	1.0	1.0	400.0	400.0
7	300	0.2	0.5	1.0	50.0	300.0
8	200	0.2	0.2	0.2	0.2	200.0
9	400	50.0	400.0	400.0	400.0	400.0
10	300	0.5	0.5	0.5	0.5	400.0
Median	300	0.2	0.5	1.0	50.0	300.0

*Time in minutes after recovery from ouabain-induced ventricular tachycardia.

fold increase of sensitivity to electric shock occurred after administration of a toxic dose of ouabain.

To determine the duration of sensitivity to shock, the electrical threshold was determined periodically following ouabain-induced ventricular tachycardia in ten of the above animals. Eight dogs had threshold levels of 1 WS, or below, for about 30 minutes (table 2 and fig. 5). Five dogs were sensitive to 5 WS, or less, for one hour. At 90 minutes three animals were sensitive to 10 WS, or less, and one of these animals still developed ventricular

tachycardia after a discharge of 0.2 WS. One animal continued to show sensitivity to 5 WS beyond 90 minutes.

The degree of reduction in energy threshold after ouabain was not related to the duration of drug-induced ventricular tachycardia. Recovery, having once begun, generally took five to ten minutes to reconstitute the control electrical threshold. As time elapsed from recovery of ouabain toxicity, electric shock ceased to provoke ventricular tachycardia but produced merely single or multiple ventricular ectopic beats, at times bigeminal in form.

TABLE 3

Threshold Changes for Production of Ventricular Tachycardia (VT) by Means of Electrical Discharge During Digitalization With Ouabain

Dog no.	Control threshold watt-sec	Total dose of ouabain for VT μg	Per cent of toxic dose ouabain to changed threshold %	Energy for VT at change in threshold watt-sec
1	300	1250	92	0.2
2	400	1350	85	300.0
3	400	1550	94	20.0
4	300	2150	82	10.0
5	300	1150	91	5.0
6	400	1300	92	300.0
7	300	1500	100	200.0
8	400	1200	100	0.2

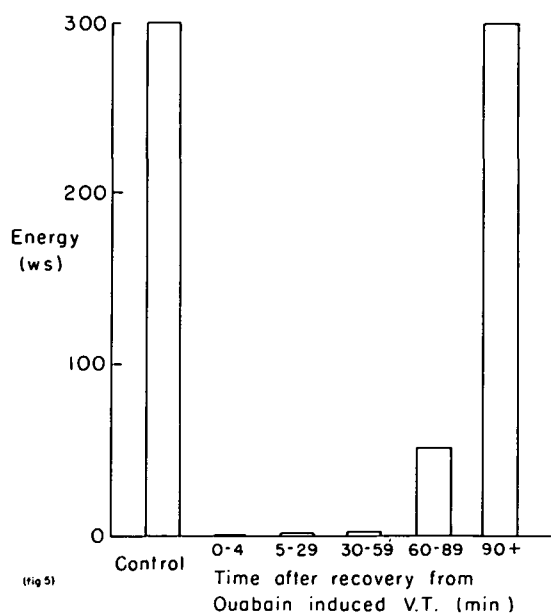


FIGURE 5

Median electrical threshold (ws) for ventricular tachycardia in 10 dogs. Lowering of the electrical threshold for ventricular tachycardia following ouabain toxicity persists for over 60 minutes. Recovery of control threshold, once it begins, is rapid.

In four animals electrical thresholds were determined following toxic doses of AS. When control thresholds were re-established these animals were restudied after toxic doses of ouabain. Change of electrical threshold occurred in all four after ouabain and in three of the animals after AS. As compared with results after ouabain, the changes in electrical threshold following AS were less marked and less

long-lasting. Since AS toxicity persists for ten to twenty minutes, while that of ouabain persists for one or more hours, it appears that the duration of sensitivity to electrical shock is a function of the rapidity of drug disappearance by destruction or excretion.

In eight animals response to electric discharge was tested during incremental digitalization with ouabain. The objective was to determine the fraction of the toxic dose at which electrical sensitivity became evident and also to determine whether such sensitivity depended upon the prior production of digitalis-induced ventricular tachycardia. Two animals required less electrical energy for ventricular tachycardia only after a full toxic dose of ouabain had been administered. The electrically induced arrhythmia was transient and was followed immediately by sustained ventricular tachycardia. In the remaining six dogs reductions of energy threshold were noted before a full toxic dose had been given (table 3 and fig. 6). Administration of at least 83% of the toxic dose of ouabain was required before lowering of the threshold was demonstrable. The mean dose of ouabain at which a change occurred was 92% of the toxic dose. In three of these animals, threshold was lowered progressively by additional increments of ouabain (dogs no. 2, 3, and 4, table 3). Thus in dog no. 2 after 1150 μg of ouabain, the threshold was reduced from over 400 WS during control testing to 300 WS. After an

additional 100 μg , the threshold was 20 WS, and when a total of 1350 μg had been given, 0.2 WS induced sustained ventricular tachycardia. The response was similar in dogs 3 and 4.

The ventricular tachycardia following elec-

trical shock in the overdigitalized animal was similar, in QRS complex morphology, direction, and rate, to that which was provoked by digitalization alone (fig. 7). This was the case whether ouabain or AS was the digitalizing drug.

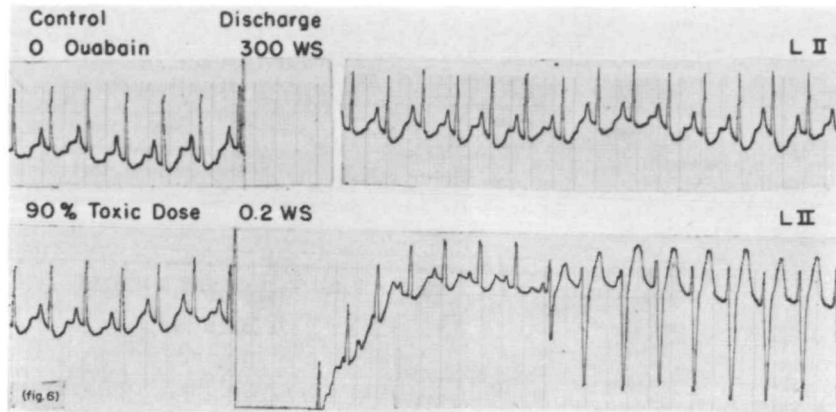


FIGURE 6

A discharge of 300 watt-seconds does not change cardiac rhythm in the undigitalized animal. After administration of 90% of the dose of ouabain necessary to produce ventricular tachycardia, a 0.2 watt-second electrical shock produces ventricular tachycardia after brief delay.

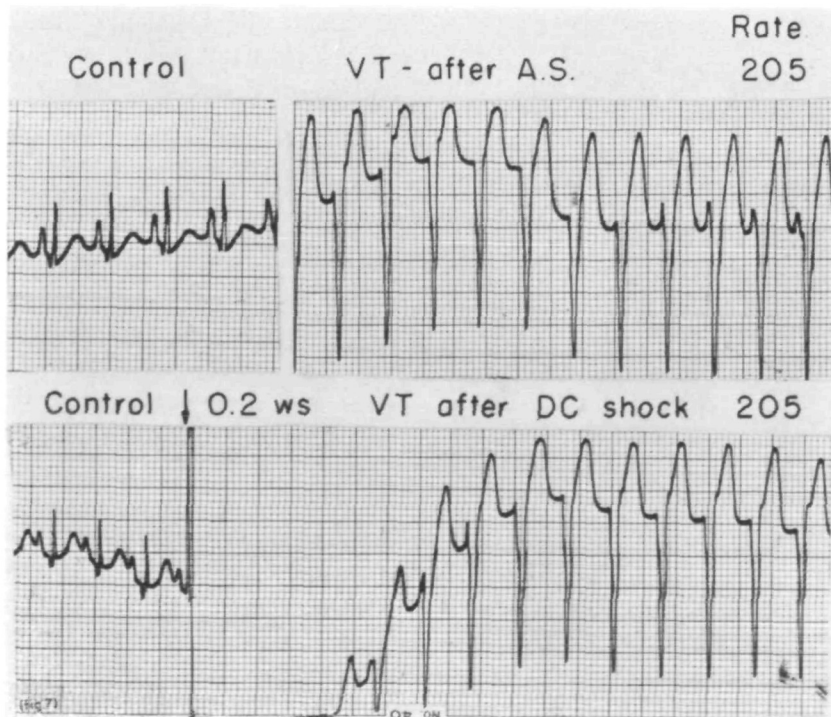


FIGURE 7

Ventricular tachycardia (VT) after digitalization with acetyl strophanthidin (AS) is similar in morphology and direction and identical in rate to the arrhythmia occurring after 0.2 watt-second (WS) discharge given shortly after recovery from digitalis intoxication.

VULNERABLE PERIOD AND EXCITABILITY CHANGES

In the experiments reported above, electrical discharges were delivered outside the vulnerable period of the cardiac cycle. The energy required to provoke ventricular tachycardia after digitalization was in the range of energy most effective in producing ventricular fibrillation when administered during the ventricular vulnerable period. It was therefore possible that with digitalization, the phase of vulnerability expands into what is normally the absolute refractory period of the cardiac cycle. In five animals this was tested by delivering capacitor shocks at multiple intervals of the cardiac cycle immediately after recovery from AS-induced ventricular tachycardia. It was found that the reduction in threshold was identical throughout the cardiac cycle. In eight other dogs, during digitalization with ouabain, the shock was delivered at two points in the cardiac cycle, namely the absolute refractory period (indi-

cated by the QRS complex) and during the period of diastolic excitability (between terminal portion of T wave and onset of QRS complex). As digitalis toxicity was approached, the reduction in threshold was identical at these points (fig. 8).

The duration of the vulnerable period was determined before and immediately after recovery from AS toxicity in eight dogs. The onset of the ventricular vulnerable period was 0.14 sec after the beginning of the QRS complex both before and after AS. The mean duration of ventricular vulnerability was 28 msec before and 31 msec after digitalization. This difference is not statistically significant. Four other animals were digitalized with ouabain to an endpoint of ventricular tachycardia. Just preceding the onset of ventricular tachycardia, the duration of ventricular vulnerability, and the lower and upper energy levels for ventricular fibrillation were studied.

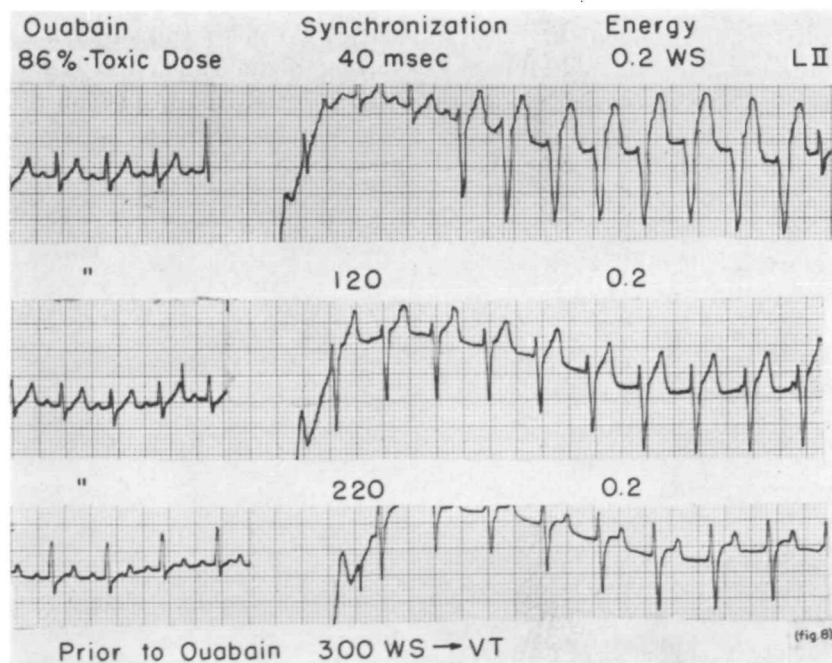


FIGURE 8

Discharges in three points of the cardiac cycle after administration of 86% of toxic dose of ouabain produces ventricular tachycardia in each instance at the same energy of 0.2 watt-second. In the top strip with a synchronization of 40 msec, the discharge entered during the absolute refractory period. In the middle strip with a synchronization of 120 msec, the shock was triggered during the relative refractory period. In the bottom strip after 220 msec, the shock was delivered during the period of diastolic excitability.

TABLE 4
Duration and Threshold of Ventricular Vulnerable Period Before and During Digitalization With Ouabain

Dogs	Duration		Lower energy limit		Upper energy limit	
	Control	Ouabain	Control	Ouabain	Control	Ouabain
	msec		watt-sec		watt-sec	
D1	40	35	0.75	0.35	40	30
D2	55	60	0.30	0.30	50	60
D3	30	30	0.60	0.80	20	20
D4	30	20	0.60	0.50	40	50
Mean	39	37	0.56	0.49	37	40

As shown in table 4, no difference in duration or threshold was found.

Discussion

The use of cardioversion to terminate ectopic tachycardia in man is based on two suppositions: first, that the factors which initiate an abnormal mechanism are transient and, second, that an arrhythmia once initiated may be self-sustaining. The electrical shock by depolarizing the entire heart, erases recirculating wave fronts of excitation, thereby permitting the sinus node, having the highest discharge rate, to resume as pacemaker. It would follow that if the initiating cause continued to operate, transient depolarization of the heart would be ineffective in abolishing an arrhythmia. This is the case with abnormal mechanisms due to digitalis where the inciting agent remains within the heart. Since the shock would not dislodge the glycoside, one would not expect an electrical discharge to abolish a digitalis-induced arrhythmia. The consistent failure to revert ouabain or AS-induced ventricular tachycardia or ventricular fibrillation is in accord with this view.

An alternative explanation for the failure of cardioversion of arrhythmias due to digitalis is that these disordered mechanisms are not caused by re-entry of circulating wave fronts, but rather by repetitive discharges from an individual focus. A single electrical depolarization of such an abnormal site would not be expected to terminate the disorder. Indeed when ventricular fibrillation was precipitated electrically during digitalis-induced ventricular tachycardia, the condenser shock reverted the ventricular fibrillation to ventricu-

lar tachycardia but did not restore sinus rhythm. When, however, ventricular fibrillation was induced by digitalis alone, condenser shock could not defibrillate the heart. This implies that the critical factor is the presence of digitalis toxicity rather than the mechanism of the arrhythmia.

The degree of sensitization to electric shock that accompanies digitalization to a level approaching toxicity is the most striking yet observed. Coronary occlusion, significant K^+ or Mg^{++} deficits, or severe degrees of anoxia do not result in such changes.¹⁰ Following digitalization the electrical threshold was reduced from a median of 400 WS during the control period to 0.2 WS and represents a 2000-fold enhancement of response to transthoracic electrical shock. This phenomenon is not related to the timing of the discharge within any specific part of the cardiac cycle. It can be demonstrated when the shock is delivered in the absolute refractory period, the relative refractory period, and during diastole. It is not related to the ventricular vulnerable period. When the digitalized animal exhibits a lowered threshold to electrical discharge, no change is detected in location, duration and threshold of the ventricular vulnerable period. The lowering of threshold to electric shock occurs in the absence of any overt manifestations of overdigitalization, and requires 83% or more of the toxic dose of ouabain. As digitalis toxicity is approached, there is a rapid lowering in the level of energy which provokes ventricular tachycardia. The rise in threshold when the animal recovers from digitaliza-

tion, once it begins, is equally rapid and abrupt. The duration of sensitivity to shock lasts longer after ouabain than after AS. In these experiments, in no instance, did the shock-induced ventricular tachycardia progress to ventricular fibrillation. However, in two digitalized animals, high energy discharges did result in ventricular fibrillation. The infrequency of ventricular fibrillation may have been due to the absence in these animals of cardiovascular disease or electrolyte derangements.

An explanation for the sensitization to electrical discharge in the digitalized animal will not be forthcoming until the mechanism of digitalis action is fully understood. For the present, one can only speculate in one of several directions; e.g., the electric shock, 1) may mobilize catecholamines, 2) may disrupt the supply or utilization of metabolic energy within the cardiac cell, or 3) may alter cell membrane permeability or transmembrane transport of various ions.

In the presence of increased norepinephrine, the toxic threshold of digitalis glycosides is lowered. The electrical discharge may release catecholamines from various sites, thereby reactivating digitalis-induced ventricular tachycardia. However, administration of a β -adrenergic blocking agent does not annul or modify this phenomenon.¹⁰

Electric shock may disorganize intracellular metabolism and thereby sensitize the heart to digitalis. This would presuppose that the glycosides affect cardiac automaticity or excitability by altering energy supply or energy utilization within the cell. There is no decisive evidence to support the view that the effects of digitalis depend upon altered metabolic function within the cell.¹¹ Glycoside-induced changes in the excitable properties of the myocardium appear to be related to drug action on the cell membrane.¹²

The excitable properties of the cardiac cell relate to the transmembrane resting potential and generation of the action potential.¹³⁻¹⁵ These are determined by transmembrane ionic concentration gradients which depend on active and passive transport of ions across a selec-

tively permeable membrane. Digitalis in toxic or near toxic doses causes a net loss of potassium from the myocardial cell and the occurrence of ectopic ventricular arrhythmias.^{16, 17} A possible explanation for the arrhythmias, following low energy shocks in the digitalized animal, is that the electrical discharge changes ion transport characteristics of the membrane and thereby promotes a net loss of potassium from the cell. Since arrhythmias will occur with high energy shocks, it is possible that the K^+ loss induced by digitalis lowers the threshold for shock-induced arrhythmia. An alternative explanation is that the shock injures the membrane and promotes re-establishment of digitalis intoxication. This need not be an immediate effect. Indeed in many digitalized animals after the shock, there was a brief episode of normal rhythm before the onset of ventricular tachycardia. That the abnormal mechanism was a digitalis type of toxic arrhythmia is suggested by the great similarity of the contour and rate of the ventricular tachycardia following low energy shock to the ventricular tachycardia produced by overdigitalization (fig. 7).

In overdigitalized patients, the delay between the cardioversion discharge and ensuing arrhythmia is even longer than in the experimental animal.⁸ This may be explained on the basis that patients are not usually at the point of digitalis toxicity as was the case with the dogs in the present experiments. In patients the arrhythmias occurring after electrical discharge have been found to be more prolonged. This may occur because of the higher energy levels used with cardioversion and also because digitalis preparations employed clinically have a longer duration of action than AS and ouabain.

The clinical significance of the present study is to emphasize the dangers of cardioversion even when borderline states of digitalis toxicity exist. The simplicity of cardioversion and its high rate of success have popularized this method of therapy. The most frequently treated arrhythmia is chronic atrial fibrillation. Almost invariably the patient is receiving one of the digitalis drugs. A number of ar-

ticles have appeared reporting complications following cardioversion.¹⁸⁻²⁰ Some of the patients exhibiting serious arrhythmias were overdigitalized.²⁰ Early in the use of cardioversion, it was noted that ectopic beats were especially likely to follow the electrical discharge in patients with atrial fibrillation who had slow ventricular rates. In the first 250 reversions of atrial fibrillation, there were two episodes of ventricular tachycardia, both occurring in patients who were on digitalis and who previously had exhibited marked sensitivity to the drug.

In clinical practice, it is therefore necessary to make certain that the patient is not overdigitalized prior to electrical reversion. If the ventricular rate is less than 70 per minute, if there is a regulated ventricular response, ventricular ectopic beats, or nodal escape beats, then cardioversion should be postponed. A low serum potassium is an additional indication for delay of elective reversion. The hazard of digitalis arrhythmias is further diminished by omitting digitalis drugs for one to two days prior to cardioversion. The duration of the period during which digitalis should be withheld would depend on whether digoxin, for example, or a longer acting agent had been employed.

Summary

The relationships between the action of digitalis drugs and the effects of cardioversion were studied in 44 dogs. Ventricular tachycardia provoked by either acetyl strophanthidin (AS) or ouabain could not be reverted to sinus rhythm by DC shock. When ventricular fibrillation was induced electrically during digitalis toxicity, defibrillation could be accomplished readily but the toxic arrhythmia due to digitalis remained unaltered. When ventricular fibrillation was induced by AS, it was also unaffected by repeated high energy discharges.

In control animals the median energy to produce ventricular tachycardia by electrical discharge was 400 watt-seconds. Repeated electrical shocks did not change the level of energy required to produce ventricular

tachycardia. However, following recovery from ouabain-induced ventricular tachycardia, the electrical threshold for ventricular tachycardia was 0.2 watt-second. A similar but less consistent response was noted after AS-induced ventricular tachycardia. The sensitization to electrical shock lasted for five to ten minutes after AS and for approximately one hour after recovery from ouabain toxicity. This same phenomenon of sensitization to electrical discharge was observed during digitalization. About 80% of the potentially toxic dose of ouabain had to be administered before the electrical threshold was lowered.

The sensitivity to DC shock in the digitalized animal was not related to any specific phase of the cardiac cycle. Digitalization did not change the duration, location or energy limits of the ventricular vulnerable period.

These experiments lead to the following conclusions of clinical importance: 1) Cardioversion will not be effective in arrhythmias induced by digitalis toxicity and 2) in the presence of overdigitalization cardioversion discharge may provoke serious disturbance of rhythm.

References

1. LOWN, B., PERLROTH, M. G., KAIDBEY, S., ABE, T., AND HARKEN, D. E.: "Cardioversion" of atrial fibrillation: A report on the treatment of 65 episodes in 50 patients. *New Engl. J. Med.* 269: 325, 1963.
2. KILLIP, T.: Synchronized DC precordial shock for arrhythmias: Safe new technique to establish normal rhythm may be utilized on an elective or an emergency basis. *J. Am. Med. Assoc.* 186: 1, 1963.
3. ORAM, S., DAVIS, J. P. H., WEINBREN, I., TAGGART, P., AND KITCHEN, L. D.: Conversion of atrial fibrillation to sinus rhythm by direct-current shock. *Lancet* 2: 159, 1963.
4. BROWN, K. W. G., WHITEHEAD, E. H., AND MORROW, J. D.: Treatment of cardiac arrhythmias with synchronized electrical counter-shock. *Can. Med. Assoc. J.* 90: 103, 1964.
5. LOWN, B.: "Cardioversion" of arrhythmias. *Mod. Concepts Cardiovascular Disease* 33: 863, 1964.
6. MORRIS, J. J., KONG, Y., NORTH, W. C., AND MCINTOSH, H. D.: Experience with "cardioversion" of atrial fibrillation and flutter. *Am. J. Cardiol.* 14: 94, 1964.

7. LOWN, B., AMARASINGHAM, R., AND NEUMAN, J.: New method for terminating cardiac arrhythmias: Use of synchronized capacitor discharge. *J. Am. Med. Assoc.* 182: 548, 1962.
8. KLEIGER, R., AND LOWN, B.: Cardioversion and digitalis drugs. II Clinical studies. In preparation.
9. LOWN, B., NEUMAN, J., AMARASINGHAM, R., AND BERKOVITS, B. V.: Comparison of alternating current with direct current electroshock across the closed chest. *Am. J. Cardiol.* 10: 223, 1962.
10. Unpublished observations.
11. WOLLENBERGER, A.: Digitalis action on metabolism and the contractile system. In *Enzymes and Drug Action*. ed. by J. L. Morgan, and A. V. S. De Reuck, Boston, Little, Brown and Company, 1962, p. 127.
12. WEATHERALL, M.: Action of cardiac glycosides or ionic movements. *Ibid.* p. 115.
13. BROOKS, C. McC., HOFFMAN, B. F., SUCKLING, E. E., AND ORIAS, O.: *Excitability of the Heart*, New York, Grune and Stratton, Inc., 1955.
14. WEIDMANN, S.: *Electrophysiologie der Herzmuskelfaser*, Bern, Huber, 1956.
15. HOFFMAN, B. F., AND CRANFIELD, P. F.: *Electrophysiology of the Heart*. New York, McGraw-Hill Book Company, Inc., 1960, p. 20.
16. HOLLAND, W. C., GREIG, M. E., AND DUNN, C. E.: Factors affecting the action of lanatoside C on the potassium content of isolated perfused guinea pig hearts. *Am. J. Physiol.* 176: 227, 1954.
17. HELLEMS, H. K., REGAN, T. J., AND TALMERS, F. N.: Influence of acetyl strophanthidin on myocardial electrolyte exchange. *J. Clin. Invest.* 34: 915, 1955.
18. LEMBERG, L., CASTELLANOS, A. J., SWENSON, J., AND GOSSELIN, A.: Arrhythmias related to cardioversion. *Circulation* 30: 163, 1964.
19. WILLIS, W. H.: Letter to editor, *Am. Heart J.* 67: 575, 1964.
20. RUBBINO, M. D., LIKOFF, W., AND DREIFUS, L. S.: Complications and limitations of direct-current countershock. *J. Am. Med. Assoc.* 190: 417, 1964.

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