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Electrical Stimulation and Digitalis Drugs: Repetitive Response in Diastole.* (32545)

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Electrical shock, such as is employed in cardioversion, may induce serious cardiac arrhythmias in the digitalized patient(1). In the experimental animal, digitalization lowers the electrical threshold for ventricular tachycardia by a factor of 2000(2). The change in electrical threshold develops when about 85% of the toxic glycoside dose has been administered. Since in these studies the electrical discharge was administered transthoracically, it is uncertain whether the digitalis-induced sensitization resulted from the high energies employed. If digitalization similarly alters the response to small pacemaker stimuli delivered directly to the heart, utilization of this phenomenan may provide a method for estimating the degree of digitalization.

The present experiments demonstrated that small pacemaker stimuli, when administered to the digitalized animal, evoke repetitive ventricular responses. It was also noted that during digitalization the ventricular cycle becomes strikingly differentiated in its sensitivity to small test pulses.

Materials and methods. Fifteen mongrel dogs of both sexes, weighing 18 to 22 kg, were anesthetized by intravenous sodium pentobarbital in a dose of 30 mg/kg. Artificial respiration with room air was accomplished by a Harvard ventilatory pump through a cuffed endotracheal tube. A multistrand insulated steel electrode wire with a platinum tip of 0.5 mm in diameter was introduced through the jugular vein and floated into the

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heart, with electrocardiographic monitoring ascertaining entry into the ventricle. In 4 animals a second unipolar electrode was placed into the myocardium. This was Teflon-coated 00 Surgalloy multistrand wire which was introduced percutaneously into the heart and anchored to the free wall of the left ventricle.

A direct current cathodal pulse was employed for stimulation. The indifferent electrode was on the left chest. The pulse was derived from a 16 microfarad oil-filled capacitor discharging through an inductor of 100 millihenries and 20 ohms internal resistance. At the range of energies used for intracardiac stimulation, 1 microjoule (μJ) to 0.4 Joule (J), the discharge wave form is overdamped. The discharge was synchronized to the R wave of the surface electrocardiogram and timed in the cardiac cycle through an adjustable delay permitting variation from 10 to 400 msec with an accuracy of $\pm$ 3 msec. The result was monitored by standard electrocardiographic amplifier and oscilloscope. The input of the amplifier was protected by a high-pass RC filter. In one animal a Medtronic square wave pulse generator† was used to produce 2 msec wide, current-regulated pulses.

Of the 15 animals, 5 served merely to test the response to internal shock, while 10 were studied before and after digitalization. In the digitalized animal the experiment consisted of 3 phases: 1) control phase, to establish threshold energies for propagated ventricular responses and to assess the presence of repetitive ventricular response (RVR) after a single stimulus; 2) a digitalization phase; and 3) a restudy of threshold energies for single and repetitive responses following digitalization.

The threshold energy required to produce an extrasystole was determined when stimuli were applied at various times in the cardiac cycle. Stimuli were separated by intervals of 10 msec. Testing was carried out from the onset of the T wave in the absolute refractory period and continued in diastole until a constant energy level was reached. In 4 animals stimuli were delivered through electrodes both in the right ventricular cavity and in the left ventricular myocardium.

Digitalization was accomplished by administering ouabain intravenously in a priming dose of 0.5 mg and followed by 0.1 mg increments at 30 minute intervals until the development of ventricular tachycardia. After each dose, testing for RVR was carried out. The initial testing energy was at 1 μJ. If no RVR occurred, the energy was progressively doubled until either such a response occurred or an energy of 0.05 J was reached. Within 5 minutes after the animal recovered from ouabain-induced ventricular tachycardia, retesting was carried out as in the control phase. The cardiac cycle was reexplored at 30 minute intervals until RVR was no longer obtainable.

Results. Control studies. In the nondigitalized animal a single electrical discharge resulted in a single propagated response. In order to obtain RVR from a single stimulus delivered directly to the myocardium during diastole, energies of several J were required. Thus in 5 control dogs the lowest mean energy for RVR after a single unipolar endocardial stimulus was 5.9 J. In 4 of 10 animals prior to digitalization large energy shocks were delivered by intracardiac electrodes without producing a repetitive response. As the large energy shocks induced currents of injury, an energy of 0.04 J was not exceeded in the remaining 6 dogs.

Digitalized animals—threshold for single response. Digitalization did not alter the energy necessary to produce a single ventricular ectopic beat during diastole. The mean energy in the control period, during digitalization and after recovery from toxicity, was 4.4 $\pm$ 6.1 μJ, 4.2 $\pm$ 4.0 μJ and 4.5 $\pm$ 3.0 μJ, respectively.

Threshold for RVR. The animal receiving ouabain showed a remarkable reduction in the threshold for RVR. In 9 animals, after the administration of ouabain, RVR was produced at a mean energy of 5.2 $\pm$ 4.3 μJ (Table I). In one animal in which a square wave pulse was employed and current rather than energy was measured, during the control period 100 ma did not result in repetitive response; after ouabain, however, with

† Model 5736 with Medtronic Model 4028 constant current cardiac stimulator.

TABLE I. Comparison of Threshold Energies for Repetitive Ventricular Response (RVR) After a Single Endocardial Discharge in 10 Animals Before and After Administration of Ouabain.

	Control	Ouabain effect
Dog	Highest energy without RVR (μJ)	Energy threshold for RVR (μJ)
1	200,000	10
2	400,000	15*
3	400,000	4
4	40,000	4
5	40,000	2
6	40,000	6
7	40,000	2
8	40,000	2
9	40,000	2
10	100 ma	2.5 ma

* Testing limited to period of ouabain administration, since animal died from overdigitalization.

the lowest available current of 2.5 ma there was a consistent repetitive response. The same low threshold was obtained whether stimulation was carried out through the right ventricular cavity electrode or through the wire imbedded in the left ventricular myocardium. The onset of RVR was first observed when 70% of the toxic dose of ouabain was administered. The initial manifestation consisted of 2 ventricular ectopic beats (Fig. 1). As more ouabain was infused, instead of

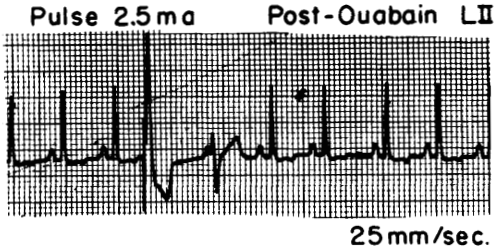

FIG. 1. After recovery from ouabain-induced ventricular tachycardia, a single 2.5 milliampere (ma) discharge through a right ventricular cavitary electrode produces a coupled ventricular extrasystole. This dual response was the first manifestation of ouabain-induced toxicity.

a dual response, multiple ectopic beats and paroxysms of ventricular tachycardia resulted (Fig. 2). The morphology of the ectopic impulses was similar to those resulting from ouabain alone.

Location within cardiac cycle. The initial development of RVR, when measured from the onset of the QRS and expressed as a

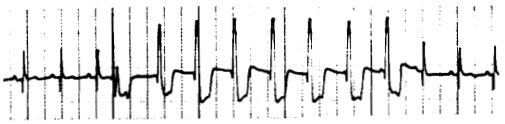

FIG. 2. In digitalized animal a single 2 μJ discharge (4th complex) delivered in diastole results in a paroxysm of ventricular tachycardia. The morphology of the arrhythmia was indistinguishable from that resulting from ouabain alone. In the control period 40,000 μJ did not produce a repetitive response. (Paper speed 25 mm/sec).

ratio of cycle length, had a mean and median value of 0.50. This was well beyond the usual location of the ventricular vulnerable period which coincides in time with the apex of the T wave in the surface electrocardiogram (3). As more ouabain was given, RVR could be evoked from progressively later periods in diastole. With near toxic doses, the RVR zone extended nearly to the P wave. RVR could be elicited in 6 of 9 animals for more than 4 hours after recovery from ouabain-induced ventricular tachycardia. In one dog it persisted for 7 hours.

Discussion. Digitalization with ouabain did not change the diastolic excitability threshold for single response. However, it consistently lowered the threshold for RVR by about 6 orders of magnitude. In the nondigitalized animal, similar repetitive responses can at times be obtained by electrical stimulation in the vulnerable period. The energy required is just below the threshold for ventricular fibrillation, or about 10,000 μJ. This is 4 orders of magnitude above the threshold for eliciting RVR in the digitalized animal. Another aspect of the phenomenon was the observed widening of the zone of diastolic sensitivity as a function of the degree of digitalization.

Repetitive ventricular response has been observed in digitalized patients undergoing cardioversion(1). Castellanos and coworkers (4) subjected 16 patients to low energy shocks before and after acute digitalization. In 4 patients after receiving digoxin, the electrical discharge unmasked latent ventricular arrhythmias. Thus in patients as well as in animals electrical stimulation of the digitalized heart evokes RVR. The development

of a repetitive response to a single stimulus delivered during diastole is related to the amount of digitalis glycoside administered. At present there exists no clinical method for assessing the degree of digitalization. Adaptation for clinical use of the phenomenon of repetitive ventricular response to single stimuli provides a possible approach to this important problem.

Summary. In the nondigitalized animal, a unipolar stimulus to the endocardium or myocardium discharged during diastole resulted in a single response unless energies greater than 5 J were used. During digitalization employing ouabain, the diastolic threshold energy for a repetitive ventricula response (RVR) was reduced by 6 orders of magnitude. RVR was first noted after 70% of the toxic dose of ouabain had been given and consisted of 2 ventricular ectopic beats. With advancing degrees of digitalization, a single stimulus evoked paroxysms of ventricular tachycardia. The most sensitive part of the cardiac cycle followed immediately after inscription of the T wave. As toxicity was approached, the zone of lowered threshold extended throughout most of the diastolic interval.

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A Simple Device to Orientate Rat Brain for Cutting According to De Groot's Atlas.* (32546)

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Most experimental work involving microscopic examination of the rat brain is done with the help of De Groot's Stereotaxic Atlas (1). In the stereotaxic apparatus the upper jaw of the rat is placed on the upper incisor bar at a height of 5 mm above the level of the interaural line. The horizontal zero plane is tangent to the upper surface of the incisor bar, and passes intracerebrally through the anterior and posterior commissures. The vertical zero plane is taken perpendicularly to the horizontal plane. The atlas is composed of tracings taken from transverse sections parallel to the chosen vertical plane. De Groot states that he has chosen this plane because it effects a somewhat equal distribution of important centers on either side in the regions of the diencephalon and telencephalon.

Duplication for brain cutting of the angle found in the atlas is the keynote to easy and rapid comparison of histological sections with the tracings. This angle can easily be achieved in every rat brain that is serially cut if the simple device shown in Fig. 1 is used to cut the anterior tip of the brains which have been fixed for 24 hours in formalin. The angle at which the brain is positioned in the stereotaxic apparatus can be duplicated after the brain has been removed from the skull by placing it on a wooden block which has an angle of 28°. A sharp blade can then be lowered perpendicularly to the base of the instrument. This produces a transverse section which slants posteriorly and forms an angle of approximately 118° with the ventral surface of the brain (Fig. 2). Embedding, after the fixation has been completed, is done by placing this anterior cut surface on the bottom of the embedding dish. When the block is later set up on the microtome, almost no adjustment is necessary to obtain the exact orientation described in the atlas. Thus no long experience is needed

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