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A Noninvasive Means for Assessing Glycoside Toxicity: Mechanically Induced Repetitive Ventricular Response[1] (39973)

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Introduction. The digitalis glycosides have now been in continuous clinical use for nearly two centuries. Yet to date there exist no effective means for assessing the degree of digitalization. Measurement of serum glycoside concentration defines the blood level at the specific time of sampling, but does not provide information on myocardial responsiveness to the particular dose being administered.

Lown and associates (1, 2) have described a method for assessing the electrophysiologic effect of digitalis drugs on the heart. In animals digitalized with varying glycosides (3), an early electrical stimulus of threshold intensity for a ventricular extrasystole results in a repetitive ventricular response (RVR). The RVR phenomenon can be elicited consistently after administration of 50–60% of the dose of glycoside that produces ventricular tachycardia (VT). With increasing dose of drug the number of repetitive responses to a single stimulus increases and the zone in diastole for eliciting RVR widens. A limitation of this method is that it requires invasive cardiac catheterization.

A sharp thump to the chest has been shown by our group to be effective in terminating ventricular tachycardia in both man and experimental animals (4). The delivery of a precordial thump, designated as "thump-version," provides, through electromechanical transduction, a low-energy current which evokes a propagated ventricular response that apparently depolarizes a segment of a reentry pathway and extinguishes the arrhythmia. Recently, Zoll *et al.* (5) have developed a mechanical device which can deliver an external thump to the chest and evoke a ventricular premature beat. We, therefore, undertook to examine whether a repetitive ventricular response could be evoked by a mechanical thump to the chest and thereby provide a method for the noninvasive assessment of the degree of digitalization.

Materials and methods. General. Five healthy mongrel dogs of either sex weighing between 10 and 20 kg were studied. The animals were anesthetized with sodium pentobarbital, 30 mg/kg, administered intravenously. Ventilation was maintained via a cuffed endotracheal tube attached to a Harvard constant-volume pump. Sufficient oxygen was admixed with room air to maintain arterial pO_2 in the range of 90–150 mm Hg. The respiratory rate was set at 14 per minute and the tidal volume adjusted to maintain arterial pH in the range of 7.35 to 7.45. Abdominal aortic pressure was determined via a large lumen cannula inserted through a right femoral arteriotomy and connected to a Statham P23ID pressure transducer. The ECG was recorded from limb lead II and monitored continuously on an oscilloscope. A femoral vein was cannulated for intravenous infusion of acetyl strophanthidin.

Acetyl strophanthidin infusion. Acetyl strophanthidin[4] (AS), 100 μg/ml, was infused into a femoral vein with a Harvard constant-rate infusion pump at a rate of 123 μg/min. The infusion was stopped upon the occurrence of four successive ventricular beats defined as ventricular tachycardia.

Cardiac testing for repetitive ventricular response. Both a mechanical and an electri-

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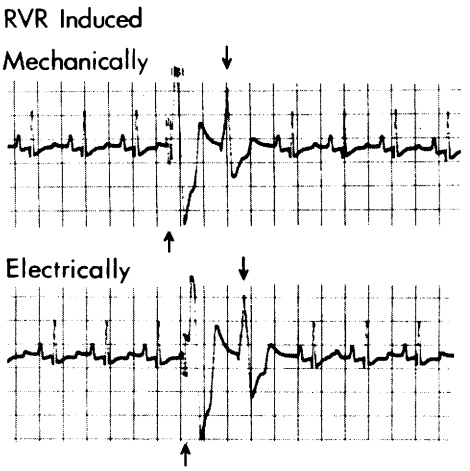

FIG. 1. A repetitive ventricular response (RVR) induced mechanically and electrically. Upward arrow indicates stimulus. Downward arrow indicates repetitive ventricular response.

cal means of cardiac testing were used to confirm the presence of a repetitive ventricular response during the same AS infusion in each dog.

(i) A repetitive ventricular response was induced electrically by delivering stimuli of twice mid-diastolic threshold intensity and a pulse width of 2 msec through a Medtronics bipolar catheter inserted via the right external jugular vein and positioned at the apex of the right ventricle under fluoroscopic control. Diastole was explored by increasing the interval from the R-wave to the stimulus by 10-msec increments until a repetitive ventricular response was encountered.

(ii) A repetitive ventricular response was evoked mechanically by delivering a quick thump to the chest with an industrial electric tacking device[5] that was modified to accept a plunger with a hard rubber stopper on its tip.[6] This device delivers a sharp, quick thump at a predetermined delay after the QRS. The trigger mechanism for the electric solenoid was connected to a precision delay generator, synchronized to the electrocardiographic R-wave. An external plastic housing permitted firm positioning of the solenoid on the animal's chest. The thump was delivered to the region of the lower sternum while the dog was in a supine position.

Experimental protocol. The absence of a repetitive ventricular response prior to an acetyl strophanthidin infusion was confirmed by both mechanical and electrical testing. The presence of RVR was determined by both methods every 2 min after initiating the AS infusion. This was continued until onset of ventricular tachycardia. The infusion was then stopped. Following termination of ventricular tachycardia, mechanical and electrical testing for the presence of a repetitive ventricular response resumed until RVR could no longer be elicited by either method.

Results. A repetitive ventricular response (RVR) was exposed prior to the onset and after termination of ventricular tachycardia with both mechanical and electrical stimulation of the myocardium in five dogs (Fig. 1). RVR was exposed mechanically at 6.4 ± 0.7 (mean ± standard error of the mean) min and electrically at 7.0 ± 1.0 min after the start of AS infusion. Ventricular tachycardia occurred at 8.6 ± 0.7 min after onset of AS administration and persisted for 12.6 ± 6.2 min. The average dose was 1.03 ± 0.09 mg. After the termination of ventricular tachycardia, RVR was exposed mechanically for 29.1 ± 12.2 min and electrically for 29.6 ± 11.9 min. There was no significant statistical difference between the duration of RVR exposed by either mechanical or electrical stimulation (Table I).

Discussion. A mechanical thump to the chest can evoke repetitive ventricular response (RVR) in animals receiving digitalis

TABLE I. COMPARISON OF MECHANICAL AND ELECTRICAL OCCURRENCE OF REPETITIVE VENTRICULAR RESPONSE (RVR) DURING AND FOLLOWING ACETYL STROPHANTHIDIN ADMINISTRATION.[a]

Testing method	RVR times (min)		
	Onset	Offset	Duration
Electrical	6.4 ± 0.7[b]	50.8 ± 18.2	44.5 ± 18.0
Mechanical	7.0 ± 1.0	50.3 ± 18.6	43.3 ± 18.0

[a] None of the results differs significantly.
[b] Mean ± SE.

[5] Duo Fast Corporation, Franklin Park, Illinois 60131.

[6] The tacking device was prepared by Mr. Nicholas Jordan.

drug. The development of RVR during and following an infusion of acetyl strophanthidin, a synthetic ester of a cardioactive aglycone, is related to the amount of drug administered and provides an electrophysiologic marker for estimating the proximity to digitalis toxicity as manifested by ventricular tachycardia.

Prior efforts to assess the degree of digitalization involved either (i) the electrical induction of a repetitive ventricular response using a ventricular endocardial stimulating electrode, or (ii) measurements of serum glycoside concentrations. The former method can be done as a single determination and involves an invasive procedure. Serum digitalis levels are related to dose, distribution space, and renal function. The serum concentration of glycoside, however, may not mirror the drug concentration in myocardial tissue (6, 7). Myocardial sensitivity to digitalis drug at any one glycoside level can be markedly altered by metabolic and intrinsic myocardial factors (8, 9). Furthermore, measurement of a blood glycoside level may not provide the clinician with certain evidence as to whether it constitutes a therapeutic or a potentially toxic concentration.

The use of a synchronized thump to the chest wall, a noninvasive mechanical method, may permit the physician repeated assessment of the state of digitalization. The appearance of a repetitive ventricular response after delivery of a chest thump at the end of the T-wave on the surface electrocardiogram avoids the vulnerable period; furthermore it constitutes the optimal point in the cardiac cycle for eliciting repetitive responses identifying the presence of impending digitalis intoxication. Before patients are tested, additional questions need to be examined; namely, whether the presence of cardiac insufficiency, but without digitalization, permits elicitation of RVR and whether this phenonemon can be induced when such animals have been on oral maintenance glycoside medication. This preliminary report provides an approach which needs further evaluation both in appropriate animal models as well as at the bedside before it can be suggested for clinical application.

Summary. An external mechanical cardiac thump was used to induce a repetitive ventricular response (RVR) in dogs receiving acetyl strophanthidin (AS), a rapidly acting glycoside. The presence of RVR prior to and after termination of AS-induced ventricular tachycardia was confirmed by both mechanical and electrical cardiac testing. Mechanically induced RVR may provide a rapid, noninvasive method for assessing the degree of digitalization.

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