Repetitive Ventricular Response (RVR) in the Digitalized Heart of Various Mammalian Species[1] (34895)

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(Introduced by F. J. Stare)

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A method for estimating the degree of digitalization by electrical stimulation of the myocardium was presented by Lown *et al.* in 1967 (1). Threshold stimuli delivered directly to the endocardium in diastole evoked repetitive ventricular responses (RVR) in dogs digitalized with acetyl strophanthidin or ouabain. RVR occurred after infusion of about 50% of the digitalis dose necessary to produce ventricular tachycardia (VT) [toxic dose] (2). In view of the known differences in digitalis sensitivity among various animals (3–6), it was uncertain whether this phenomenon was unique to the dog. A comparative study of the RVR phenomenon in different mammalian species was, therefore, undertaken.

Material and Methods. This study involved experiments on three dogs, three monkeys, three cats, three rabbits, and two goats. Each animal was anesthetized with intravenous pentobarbital according to a dose schedule ranging from 15 mg/kg in the monkey to about 70 mg/kg in the cat. The monkeys were, in addition, premedicated with intramuscular phencyclidine 0.045 mg/kg. Except for the monkeys, all the animals were ventilated with a Harvard respiratory pump, dogs and goats via a cuffed endotracheal tube, cats and rabbits from a tracheostomy tube.

Endocardial stimulation of the heart was carried out with a unipolar electode catheter[2] or with a Teflon-coated 00 surgalloy multistrand wire. Each was inserted through the external or internal jugular vein and passed to the apex of the right ventricle. A subcutaneous needle placed over the sternum served as an indifferent electrode. Energy for stimulation was derived from a Lown Cardioverter[3] in which the test pulse was delivered from a 16-mF oil-filled capacitor discharge through an inductor of 100 mH and 20 ohms internal resistance. This produced a monophasic discharge with a half-power duration of 2.5 msec. Energies from 1 μJ to 400 J were available by varying the voltage on the capacitor. The discharge was synchronized to the R wave of the surface electrocardiogram (ECG) and timed in the cardiac cycle through an adjustable delay, permitting variation from 10 to 400 msec ($\pm$ 3 msec). The energy level was set at three times the mid-diastolic cathodal threshold for a single propagated response and did not exceed 3 μJ in any of the animals (mean 2.2 μJ $\pm$ 0.94 SD).

Intravenous digitalization was accomplished with acetyl strophanthidin (AS)[4] 100 μg/ml through the left external or internal jugular vein or femoral vein. The drug was infused by means of a Harvard constant-infusion pump, model 600/900. The infusion rate for animals weighing above 10 kg (dogs and goats) was 1.23 ml/min, while smaller animals (monkeys, cats, rabbits) were given 0.247 ml/min. The toxic endpoint was defined by the occurrence of four consecutive ventricular premature beats, at which point the infusion of AS was stopped.

Prior to AS administration, the entire dias-

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[2] United States Catheter Instrument, C-51.

[3] American Optical Company.

[4] Obtained through the courtesy of Dr. G. C. Chiu, Eli Lilly Co., Indianapolis, Indiana.

tole was tested at 10 msec intervals to determine the presence of RVR in the control state. Within 1 min after beginning of the AS infusion, the presence of RVR was determined by discharging test stimuli at the downslope of the T wave, since previous work had shown this to be the most consistent part of the cardiac cycle for inducing RVR (2). Immediately upon recovery from AS-provoked ventricular tachycardia, the entire diastolic interval was tested to map the limits of the cardiac cycle from which RVR could be elicited. The regression of the RVR zone with recovery from digitalization was followed. Duration of RVR was defined as the time, after recovery from ventricular tachycardia, during which electrically evoked repetitive responses could be induced from the downslope base of the T wave with three times threshold energy.

One hour after the disappearance of RVR, all animals except for one goat were digitalized with ouabain. Dogs, two rabbits, and one goat were given 0.025 mg/kg. Smaller animals, including one rabbit, received 0.0125 mg/kg. If ventricular tachycardia (VT) did not develop within 20 min, a second ouabain dose was administered. For dogs this amounted to 0.1 mg of ouabain, while all other species were given 25% of the initial dose. Even with this second dose, VT did not always occur. RVR was detected in all animals, however, and its time course was followed after the administration of the glycoside.

Results. In each of the 14 animals, derived from five species, RVR was demonstrable during and after digitalization with both acetyl strophanthidin and ouabain (Fig. 1). In none of the animals could RVR be produced with discharges three times threshold prior to digitalization. During infusion of acetyl strophanthidin, RVR emerged first as a fusion beat, then as a wide ventricular ectopic beat, and with more drug administration, as a salvo of multiple ventricular tachycardia extrasystoles. Upon subsidence of drug-induced ventricular tachycardia, low-energy discharges once again resulted in RVR. The RVR zone at its maximum encompassed most of electrical diastole, but regressed rapidly with time until finally it could be evoked only from the point of junction of the downslope of the T wave and the ST segment.

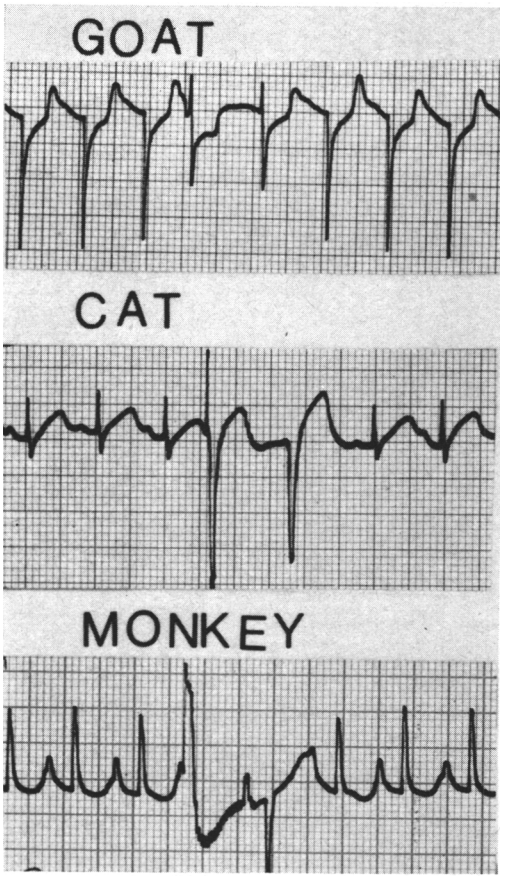

FIG. 1. Repetitive ventricular response (RVR) in different animal species after recovery from acetyl strophanthidin-induced ventricular tachycardia. Low energy electric pulses delivered near the base of the T wave evokes in sequence: a ventricular premature beat (VPB) with an ensuing pause, followed by a second VPB. The second VPB or RVR beat may or may not resemble the electrically induced extrasystole.

Table I summarizes some details of the time course of RVR and ventricular tachycardia in the different animal species. The mean dose of acetyl strophanthidin needed to produce ventricular tachycardia among the different species varied from 36.5 μg/kg in the goat to 77.2 μg/kg in the cat. A wide scatter was observed in the duration of AS-induced ventricular tachycardia, ranging

TABLE I. Results of Acetyl Strophanthidin (AS) in five Mammalian Species.

	Dose of AS (μg/kg)[a]	RVR (%)[b]	Duration of VT (min)	Duration of RVR (min)
Dogs	64.4, 45.4, 62.0 (57)	85, 76.5, 80 (80.5)	14, 23.5, 20.3 (19.3)	15, 20, 14 (16.6)
Monkeys	65.7, 66.2, 30.8 (54)	80, 67, 84 (77)	21, 12, 8.6 (13.9)	12, 37, 36 (28.3)
Cats	51.7, 100, 80 (77.2)	68, 67.4, 43.5 (59.4)	19.2, 10.4, 10.3 (13.3)	5.2, 7.2, 14.5 (8.9)
Rabbits	37.8, 54, 137.5 (76.4)	77, 80, 16 (57.3)	2.2, 2.2, 1.0 (1.6)	2.0, 2.0, 17 (7)
Goats	44.8, 27.6 (36.5)	71, 89 (80)	5, 7.9, (6.4)	14, 32 (23)

[a] Data in parentheses represent means.

[b] RVR (%) = time to first appearance of RVR/time to first appearance of VT $\times$ 100.

from about 2.0 to 19.0 min. There appeared to be no relation between the toxic dose, duration of the ventricular tachycardia, and duration of RVR. The zone in diastole from which RVR could be evoked was maximal just after the disappearance of ventricular tachycardia. When expressed as a percentage of the prevailing R-R interval, this zone of maximum RVR had a mean value ranging from 11.8% in monkeys to 30.5% in goats.

Oubain was administered to 13 animals. In all but one dog, RVR occurred within 1 to 6 min after the initial dose of the drug; in the single exception it appeared only after additional increments of drug. The mode of onset and extension of the zone for RVR during diastole with increasing ouabain effect was analogous to the findings after acetyl strophanthidin administration. In all species but the dog the RVR phenomenon persisted for a longer duration than the duration of the ouabain-induced ventricular tachycardia.

Discussion. When an electric discharge is delivered in early diastole to the digitalized heart, there occurs a dual and at times multiple response. In the nondigitalized animal, a single stimulus results in but a single immediate depolarization. The present study demonstrates that the phenomenon of repetitive entricular responses (RVR), originally described in dogs (1, 2), is also present in the several other mammalian species tested. In dogs, the morphology of RVR resembles closely the configuration of the QRS complex of the arrhythmia ensuing from an overdose of digitalis glycoside. This was also true in monkeys, cats, rabbits, and goats. The similarity in onset and offset in all species studied suggests that RVR is a general phenomenon in the digitalized mammalian heart.

The time course of recovery from digitalis toxicity, as judged by the duration of ventricular tachycardia or RVR, varied in the different species studied. A number of factors are known to influence the uptake of digitalis. Among these are the serum potassium concentration, specific type of glycoside employed, rate of administration, and heart rate (7–11). Because these variables were not kept constant among the different animals studied, it is not possible to draw any conclusion about comparative species sensitivity to the two cardiotonic agents employed. However, RVR was consistently first manifest at 57–85% toxic dose of acetyl strophanthidin, and it persisted after overt toxic manifestations had disappeared. These findings suggest that electrical testing for digitalis toxicity may find useful clinical application in man.

Summary. Fourteen animals of five mammalian species (monkeys, dogs, rabbits, cats, and goats) were digitalized with acetyl strophanthidin and ouabain to an end-point of ventricular tachycardia. RVR was present in all animals before onset and after recovery from digitalis-induced intoxication. The appearance and development of RVR was analogous in all animals studied.

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