METHODS

Modeling of Tachyarrhythmias in Conscious Animals

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A model for reproduction of sustained tachyarrhythmias in conscious animals is developed. Adequacy of the model and the possibility of using it for screening of antiarrhythmic drugs are demonstrated.

Key Words: *animals; heart; tachyarrhythmia*

Primary screening of potential antiarrhythmics has been performed in various models of arrhythmia (strophanthin, epinephrine, potassium chloride, aconitine, ligation of coronary artery, etc.) [2,3]. It should be noted that these models provide no control over the onset of arrhythmia and its duration, which hampers the screening.

We have developed a method for reproduction of sustained differential (atrial and ventricular) tachyarrhythmias in conscious animals.

To model of atrial and ventricular tachyarrhythmias the phrenic nerve is sutured, respectively, to the sinus node region and to the arrhythmogenic zone of the right ventricle [5]. Our 5-year experience with this model shows that rabbits, dogs, and cats are the most suitable animals.

MATERIALS AND METHODS

Atrial tachyarrhythmias (ATA) were reproduced in Chinchilla rabbits weighing 3.0-4.0 kg under intravenous Nembutal (4 mg/kg) anesthesia with artificial ventilation. The thorax was opened between the 2nd and 3rd or the 3rd and 4th ribs, and the wound was widened with ophthalmic retractors. The phrenic nerve together with the artery was dissected from surrounding tissues with ophthalmic microsurgery instruments. The nerve was stripped off the epineurium in the fixation site and stitched to the sinus node with a knotted suture (Fig. 1, *a*, *b*). Pericardium and thorax were then closed. The operative wound was treated with an antiseptic, pneumotorax was eliminated, and the animal was transferred to spontaneous breathing.

For reproduction of ventricular tachyarrhythmias (VTA) the phrenic nerve was stitched to the arrhythmogenic zone. In the control series and before surgery this zone was identified by elecrostimulation (with practice it is possible to calculate its location, Fig. 1, *c*). The animals were taken in experiment 3-7 days after surgery. All experiments were carried out according to international and Russian Ministry of Health and Russian Academy of Medical Sciences instructions on the use of laboratory animals in scientific research.

Thus, the following conditions should be observed in the proposed model:

- operation is performed with ophthalmic microsurgery instruments under a microscope or magnifying lense;
- the phrenic nerve is dissected under vaseline oil cover together with the artery;
- the nerve is stripped off epineurium and myocardium is stripped off epicardium in the fixation site;
- subepicardial and myocardial hematomas in the arrhythmogenic zone are prevented;
- the phrenic nerve is stitched between visible coronary arteries.

Cardiac rhythm disturbances were diagnosed by the electrocardiogram using standard, enhanced, and

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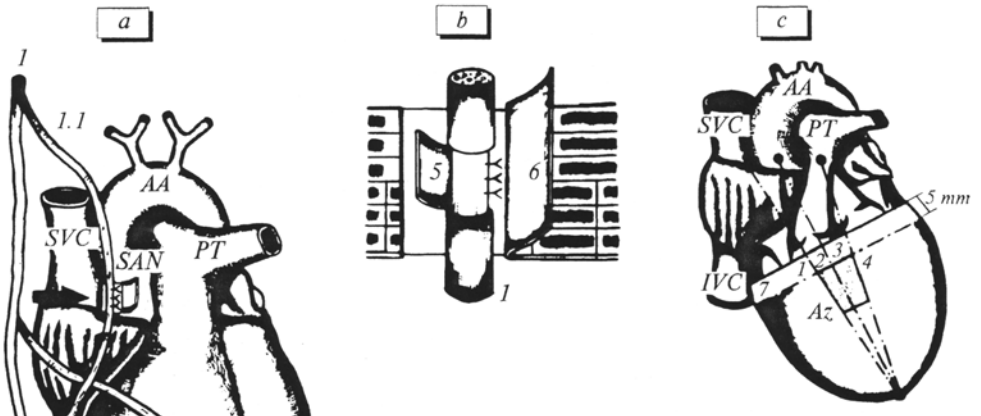

Fig. 1. Snitching of phrenic nerve to the heart. A schematic drawing. *a*) general appearance; *b*) stitching of the phrenic nerve to the myocardium; *c*) identification of the arrhythmogenic zone by calculation (anterior surface of the right ventricle). *1*) phrenic nerve; *1.1*) phrenic nerve is stitched to the sinus node region; *1.2*) phrenic nerve is stitched to arrhythmogenic zone of the right ventricle. *SVC*) superior vena cava; *IVC*) inferior vena cava; *AA*) aortic arch; *SAN*) sinoatrial node; *PT*) pulmonary trunk; *Az*) arrhythmogenic zone on the anterior surface of the right ventricle. Arbitrary lines connecting heart apex with the SVC base (*1*), the middle of aortic base (*2*), the middle of PT (*3*); *7*) horizontal line at the level of atrioventricular valves; *4*) line drawn 5 mm lower and parallel to line *7*; *6*) dissected epicardium; *5*) dissected epineurium of phrenic nerve.

TABLE 1. Effects of Reference Antiarrhythmic Drugs on Electrophysiological Parameters of Heart and Systemic Arterial Pressure in Rabbits with ATA (*M*±*m*, *n*=47)

Parameter	Control (*n*=100)	Aethacizine, 0.5 mg/kg	Verapamil, 5 μg/kg	Strophanthin K, 14 μg/kg
Heart rate, beats/min	265±6.9	244±6.7	253±5.4	248±7.2
Ectopic atrial contractions, %	75±4.8	21±4.8*	34±2.7*	42±6.1*
ECG, msec:				
P—Q	62±4.3	82±5.4*	87±2.3*	71±5.8*
QRS	35±3.5	53±2.3*	34±4.5	33±2.6
The *R* wave in standard leads I, II, III, mV	0.71±0.08	0.62±0.03*	0.75±0.05*	0.84±0.05*
Systemic arterial pressure, mm Hg	115±9.0	110±5.0	105±5.0	132±6.0

Note. Here and in Table 2: preparations were administered as intravenous bolus injection; *p<0.001 compared with the control.

TABLE 2. Effects of Reference Antiarrhythmic Drugs on Electrophysiological Parameters of Heart and Systemic Arterial Pressure in Dogs with VTA (*M*±*m*, *n*=26)

Parameter	Control (*n*=100)	Strophanthin K, 30 μg/kg	Propranolol, 0.2 mg/kg	Bonnecor, 1 mg/kg
Heart rate, beats/min	148±4.5	165±6.3*	134±5.6*	127±3.8*
Ectopic ventricular contractions, %	72±3.9	81±4.2*	50±9.7*	35±10.5*
ECG, msec:				
P—Q	79±8.6	87±3.3	83±5.4	86±8.9
QRS	38±4.1	45±2.6*	44±2.5*	48±3.7*
The *R* wave in standard leads I, II, III, mV	1.23±0.18	1.35±0.06*	1.12±0.08*	1.19±0.07*
Systemic arterial pressure, mm Hg	100±10.5	110±8.5	90±5.5	95±5.0

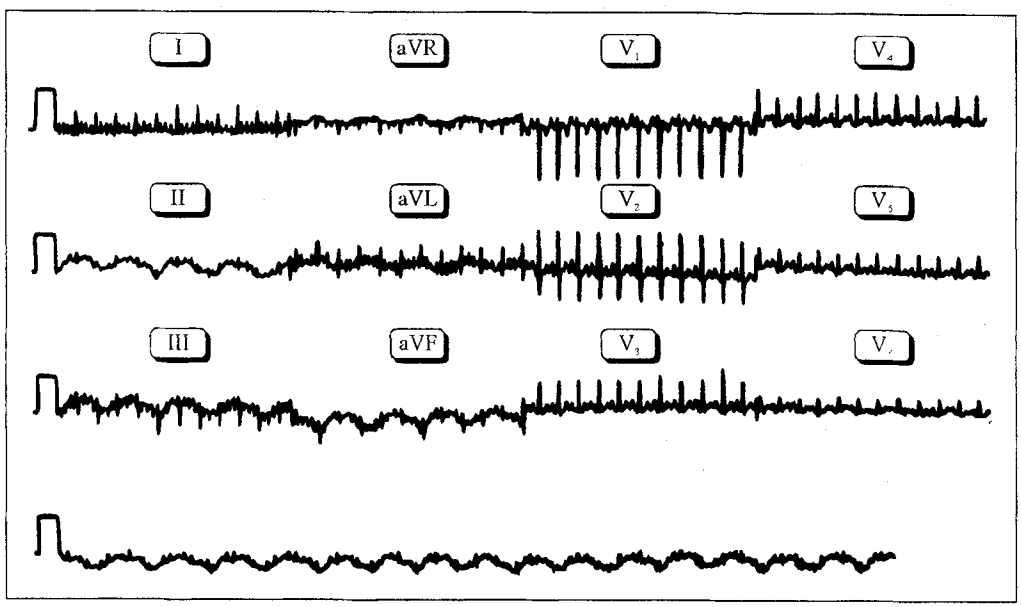

Fig. 2. Electrocardiogram recorded from a rabbit with atrial tachyarrhythmias using 12 leads. I, II, III) standard leads; aVR—aVL—aVF) enhanced leads from extremities; V1-V6) thoracic leads.

thoracic leads in the supine position. The data were processed using Statistika-R and STX-95 software.

RESULTS

Undoubtedly, modeled cardiac arrhythmias, particularly those induced with drugs, differ from those occurring in humans. In addition, antiarrhythmic effects are examined on isolated preparations: cardiomyocytes, papillary muscle, and heart [4,6] with the exception of reperfusion and postinfarction arrhythmias [1,2]. Therefore, new models should be tested for adequacy. For this purpose it is necessary to determine the nature of evoked arrhythmias, their onset and duration, and to examine the effects of reference antiarrhythmics such as ethacizine, propranolol, verapamil, trimecaine, etc. A model is regarded as adequate if antiarrhythmics produce a positive effect, while arrhythmogenic preparations (strophanthin in subtoxic doses) stimulate arrhythmia. Electrocardiograms recorded from conscious animals with modeled ATA (rabbit) and VTA (dog) are shown in Figs. 2 and 3. In control animals, modeled arrhythmias were preserved for at least 6 months without any morphological manifestations of myocardial necroses [7].

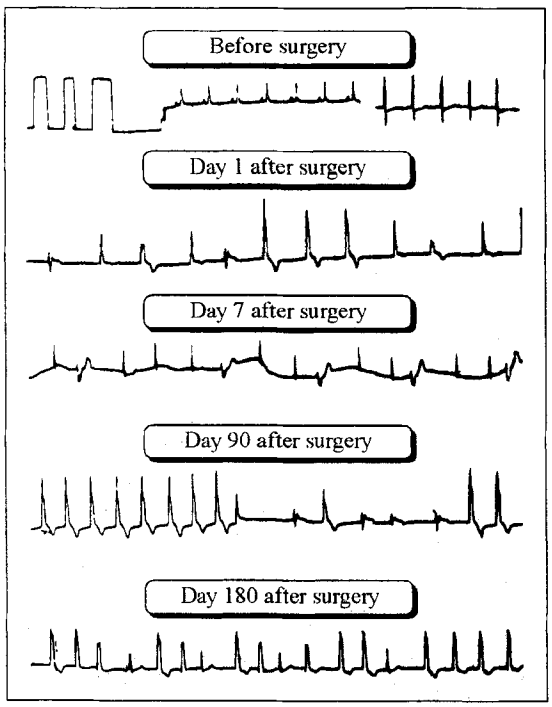

Fig. 3. Electrocardiogram (standard leads) recorded from a dog with ventricular tachyarrhythmias at different terms after surgery.

In contrast to strophanthin (Table 2), antiarrhythmic drugs normalized heart rate, conductivity, and excitability of the myocardium, i.e., produced a positive effect on rhythm disturbances (Table 1).

From these findings it can be concluded that the proposed model is adequate for studies of antiarrhythmic activity of pharmacological preparations. This model has the following advantages: it is not labor-consuming and allows differential reproduction of atrial and ventricular arrhythmias. The operation lasts 30-40 min; postoperative lethality is 20-25%. If pharmacokinetic and pharmacodynamic parameters of studied preparations are taken into consideration, one animal can be used in a number of experiments, which increases the quality and rate of screening.

Thus, the proposed method allows for differential modeling of atrial and ventricular arrhythmias and screening of antiarrhythmogenic preparations.

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