Study of Pathogenesis of Ventricular Arrhythmia in Experimental Rats by Separation of Sinus and Ventricular Substitutional Rhythms

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Pathogenesis of cardiac arrhythmia was determined by EEC changes after ATP-induced complete atrioventricular block. The re-entry mechanism underlays extrasystoles with equal coupling intervals with complexes of ventricular substitution rhythms, which transformed into paroxysmal tachycardia with equal *R—R* intervals, ventricular flutter, and ventricular fibrillation. Ectopic automaticity was characterized by extrasystole unrelated to the complexes of substitutional rhythms, which was transformed into accelerated idioventricular rhythm and asystole. During trigger activity, the extrasystoles were associated with complexes of basic rhythm and transformed themselves into torsades de pointes and ventricular fibrillation.

Key Words: *cardiac arrhythmias; ionic channels; experimental cardiac arrhythmia models*

Numerous electrophysiological voltage clamp studies with assessment of intracellular concentrations of Na^+, K^+, and Ca^{2+} ions showed that cardiac arrhythmias (CA) originate from intracellular ionic imbalance and result from three major pathogenic mechanisms: circulation of the excitation wave (reentry), ectopic automaticity, and trigger activity of myocardial cells [1,3,4,6]. In clinical practice, it is practically impossible to differentiate these arrhythmogenic mechanisms [8], so the antiarrhythmic therapy still has no scientific basis [4,9].

Our aim was to use a pharmacological test as a simple method to identify the pathogenic mechanisms underlying various CA in experimental animals.

MATERIALS AND METHODS

The possibility to identify pathogenesis of CA in animals was examined on aconitine and calcium chloride models of arrhythmia. Experiments were carried out on random-bred albino male and female rats (n=54) weighing 150-220 g. The rats were intraperitoneally narcotized with nembutal (40 mg/kg). ECG was recorded from extremities in standard lead II. Group 1 rats (control, n=7) were intravenously injected with 0.5% ATP (1 mg/kg) over 1 sec. ECG was continuously recorded until regular sinus rhythm recovery (1.0-1.5 min). In group 2 rats (n=20), CA was induced by intravenous injection of aconitine (30 μg/kg). After recording ventricular CA, ATP was injected intravenously and ECG was continuously recorded. After 10 min, if ventricular CA persisted, ATP was repeatedly injected in the same dose for evaluation of possible alterations in CA pathogenesis. In group 3 rats (n=12), aconitine dose was increased to 40 μg/kg. In group 4 rats (n=15) the arrhythmogenic agent was $CaCl_2$ (10% solution), which was infused intravenously over 2 sec in a dose of 220 mg/kg. Three rats of this group were given additional intravenous injection of ATP to produce atrioventricular (AV) block.

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RESULTS

Within 1.5-2 sec after infusion of ATP solution, all group 1 rats demonstrated complete AV block with nodal (n=5) or regular idioventricular (n=2) rhythm, which was not accompanied by CA. In rats with aconitine-induced CA, the pathogenesis of CA depended on the dose of aconitine. In group 2 rats receiving 30 μg/kg aconitine, extrasystolic CA was observed on 2.5-4 min after infusion of the toxin. In 11 rats extrasystoles appeared and disappeared within 1.5-2 min postinjection, but became stable on minutes 6-7. In all rats of this group, bolus injection of ATP resulted in infrequent nodal rhythm (50-80 min^{-1}) and extrasystolic bigeminy with equal coupling intervals. In 16 rats, extrasystole transformed into monotopic ventricular paroxysmal tachycardia with equal *R—R* intervals. In 12 of these rats episodes of ventricular flutter and fibrillation-appeared, in 11 rats ventricular flutter eventuated in asystole. Evidently, the pathogenic basis of CA in group 2 rats was re-entry of the excitation wave. Repeated injection of ATP on minute 10 resulted in torsades de pointes in 2 rats, which later transformed into ventricular fibrillation; to minute 20 postinjection 18 rats died.

In group 3 rats, the extrasystolic bigeminy was observed in 0.5-2 min after aconitine injection. At first, it did not differ from that observed in group 2 rats. However, after bolus injection of ATP and appearance of AV block with nodal and idioventricular rhythm, 7 rats demonstrated paroxysms of tachycardia of torsades de pointes type characterized by high frequency of ventricular contractions (700-900 min^{-1}), various *R—R* intervals, and *QRS* complexes of varying amplitude, shape, and pola-

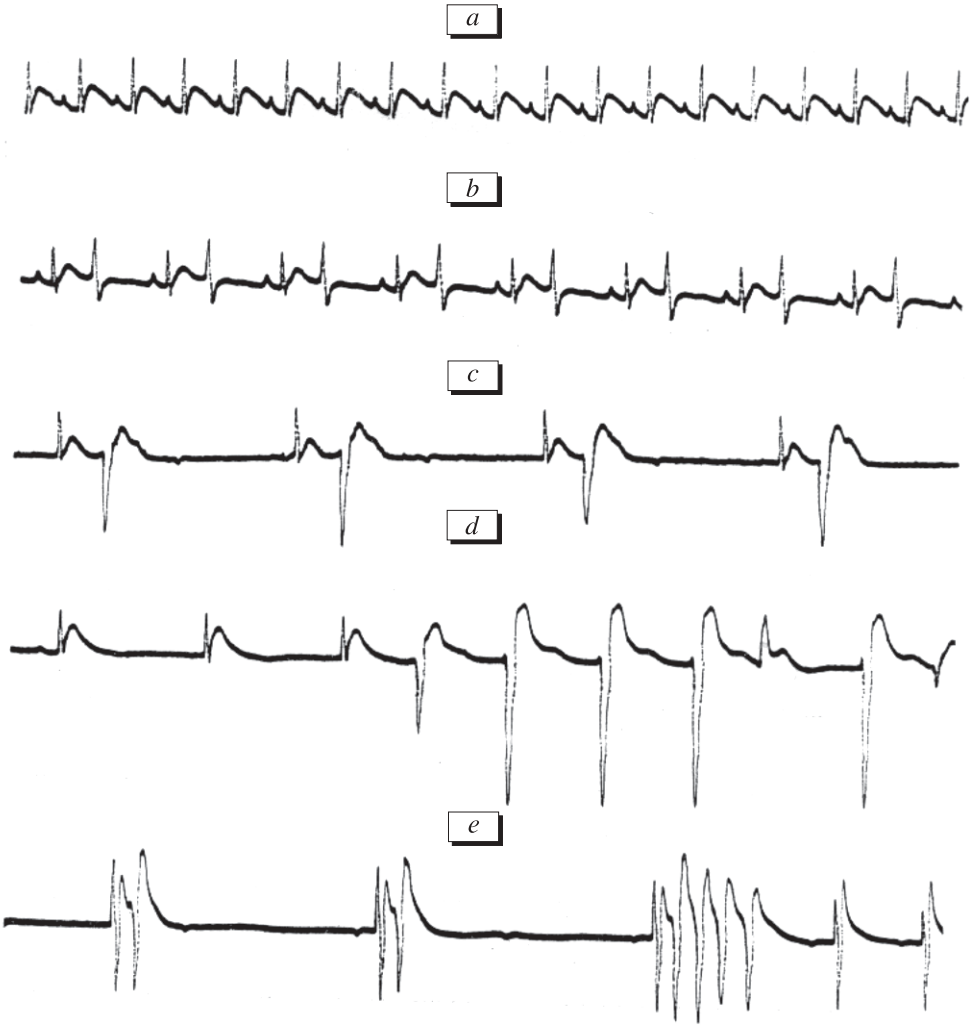

Fig. 1. Changes of ECG during ATP-induced complete atrioventricular (AV) block in rats with various pathogenic mechanisms of arrhythmogenesis. *a*) ECG in the standard lead II prior to injection of aconitine; *b*) extrasystolic bigeminy in 3 min after injection of aconitine; *c*) complete AV block with nodal rhythm after infusion of ATP; *d*) complete AV block with nodal rhythm; *e*) transformation of ventricular bigeminy into of torsades de pointes tachycardia during trigger activity.

rity. In 5 rats, torsades de pointes transformed into ventricular fibrillation. The bi-directional spindle-shape tachycardia of torsades de pointes type results from trigger activity [1,2,4,6,7]. In 5 rats, ATP-induced AV block was followed by extrasystolic bigeminy and monotopic paroxysmal tachycardia.

The results of this study show that moderate activation of Na channels with 30 μg/kg aconitine leads to intracellular imbalance of ion concentrations, which disturbs conduction and provokes reentry CA depending on dysfunction of Na channels. Probably, higher doses of the toxin activate Na channels in such a way, that they trigger Na^+/Ca^{2+} exchange mechanism, so the surplus of Na^+ ions is bartered for extracellular Ca^{2+}. In its turn, accumulation of Ca^{2+} ions in the cells results in trigger activity and torsades de pointes. Prior to infusion of ATP, only 3 rats in the third group demonstrated torsades de pointes. By contrast, 7 rats exhibited this type of tachycardia after ATP-induced AV block.

In group 4 rats, infusion of $CaCl_2$ induced complete AV block in all cases. During 2-2.5 min postinjection, 9 rats demonstrated torsades de pointes episodes against the background idioventricular substitutional rhythm. In 6 rats, tachycardia transformed into a stable form, but then it was replaced by ventricular fibrillation and asystole. Six rats with complete AV block demonstrated only single or clustered extrasystoles. They disappeared after 3-4 min, and the sinus rhythm restored. The pathogenic forms of CA and mortality largely depended on the rate of $CaCl_2$ infusion.

Dissociation of sinus and substitutional ventricular rhythms by AV block reveals typical changes in ECG characteristic of many pathogenic mechanisms of CA genesis. Low-rate nodal or idioventricular rhythm creates optimal conditions for the appearance of latent pacemakers in the ventricular myocardium due to cessation of their inhibition from more frequent sinus impulses.

Comparative analysis of ECG changes in various experimental CA models with due account for the action of arrhythmogenic cardiotoxins [5] reveals certain criteria of the origin and further development of CA. Thus, circulation of excitation wave is characterized by a short pause after AV block. In addition, during monotopic extrasystoles, the latter are associated with complexes of nodal or idioventricular rhythm with equal coupling intervals. These extrasystoles can transform into paroxysmal tachycardia with equal *R-R* intervals or into ventricular flutter and fibrillation terminated by asystole (Fig. 1). The ectopic automaticity is characterized by the absence of short pause after appearance of AV block. The extrasystoles appear spontaneously and irrespectively to the of nodal rhythm complexes. Frequently, they transform into paroxysmal tachycardia with different *R—R* intervals and idioventricular rhythm terminated by ventricular asystole (Fig. 1).

During trigger activity, short-term ventricular asystole was documented, and after the appearance of nodal rhythm, we recorded extrasystoles associated with the complexes of basic rhythm and characterized by the coupling intervals of stable duration. At greater doses of cardiotoxin, the extrasystole transformed into torsades de pointes and ventricular fibrillation (Fig. 1).

Thus, the most reliable diagnostic features were recorded during ectopic automaticity. The absence of temporary connection between the extrasystoles and the complexes of dominating rhythm indicates spontaneous diastolic depolarization. We also revealed transformation of extrasystole into accelerated idioventricular rhythm and asystole instead of ventricular fibrillation.

Differentiation between re-entry and trigger activity is possible only when extrasystolic arrhythmia transforms into paroxysmal tachycardia. The paroxysms of bidirectional spindle-shape tachycardia of torsades de pointes type should be considered as a precise and reliable criterion of trigger activity [2,4,7]. When only extrasystolic CA was recorded on minutes 10-12 postinjection, we increased the dose of arrhythmogenic cardiotoxin to augment paroxysms of torsades de pointes and ventricular flutter. The significant criteria of trigger activity were documented in 90% cases.

We hypothesize that the proposed method for evaluation of the pathogenesis of CA can be used in experimental studies and in the assessment of the efficiency of novel antiarrhythmic drugs during therapy of pathogenic CA.

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