REVIEWS

Atrial Fibrillation: A New Explanation of the Old Phenomenon

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We propose a new mechanism of atrial fibrillation basing on the results of 30 series of acute experiments on anesthetized cats. In brief, combination of two or more arrhythmogenic factors shortens the interval between the inward and outward ionic currents in cardiomyocytes to a critical value. Under these conditions repolarization of cardiomyocyte membrane reaches the excitation threshold before complete inactivation of the depolarizing currents. This inevitably results in autoexcitation of myocytes (or extrasystole), that in turn promotes repolarization. Once occurred, autoexcitation turns into self-triggering activity resembling tachyarrhythmia paroxysm.

Key Words: *vagus nerve*; *chronotropic effect*; *effective refractory period*; *neurogenic atrial fibrillation*

Tachyarrhythmias, *e.g.* paroxysmal atrial fibrillation, are an important problem of cardiology. Their treatment and research require taking considerable intellectual and material investments. Two alternative hypotheses are usually used for explaining the basic mechanisms of tachyarrhythmia: the re-entry phenomenon (self-excitatory waves circulating in the myocardium) and polyfocal trigger automatism of the contractile myocardium [4,6,26,27]. Each of these hypotheses had a number of limitations. Thus, according to the reentry hypothesis, all events develop in a plane. But the myocardium represents a three-dimensional conductor, which excludes monoplanar circulation of the excitatory waves. As for another hypothesis, it remains unclear what conditions are required for transformation of normal excitation into self-triggered activity of contractile myocytes. Thus, experimental and practical medicine has no reliable criteria for evaluation of the efficacy of antiarrhythmic preparations and uses various empirical models (for example, aconitine-, ouabain-, adrenaline-, potassium chloride-, barium chloride-induced arrhythmia, *etc*.) never occurring under natural conditions. In light of this, extrapolation of experimental data to clinical practice often provides erroneous results. Moreover, some antiarrhythmic preparations exhibit paradoxical proarrhythmogenic properties [6].

We proposed a new explanation for the mechanism of cardiac tachyarrhythmia and confirmed it experimentally. In brief, all natural arrhythmogenic factors represent regulatory stimuli modulating the duration of action potential and effective refractory period (ERP) in myocytes . This is achieved via prolongation/shortening of inward currents and delayed/accelerated onset of outward currents. The key role in this mechanism is disproportional changes in the opposite currents. Thus, arrhythmogenic lengthening of ERP is associated with predominance of prolonged inward currents (sympathetic stimulation, treatment with adrenoceptor agonists, or calcium ions). By contrast, arrhythmogenic shortening of ERP (extrasystole, high-frequency stimulation, stimulation of parasympathetic nerves, treatment with cholinergic receptor agonists or cholinesterase inhibitors) is associated with earlier onset of inward currents. Thus, all arrhythmogenic factors dose-dependently reduce the interval between the inward and outward currents. However, functional

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organization of the myocardium is characterized by high reliability, so that none of the above-mentioned factors alone can induce tachyarrhythmia paroxysm. Functional stability of the myocardium is confirmed in various physiological and pharmacological experiments (*e.g.*, vagus-induced cardiac arrest, rhythm transformation during high-frequency stimulation of the heart, calcium-induced contraction of isolated myocardium, *etc*.). At the same time, combination of two or more arrhythmogenic factors can reduce the interval between the inward (depolarization) and outward (repolarization) ionic currents to a critical level (which is incompatible with normal excitation) and breach the antiarrhythmic defense of the myocardium. Under these conditions, repolarization potential reaches the excitation threshold when inactivation of voltage-dependent inward currents is not completed (*i.e.* is still reversible). This inevitably leads to reactivation of inward currents and autoexcitation of the contractile myocardium, *i.e.* early extrasystole. This early extrasystole produces an additional arrhythmogenic effect by accelerating repolarization. In the presence of the initial arrhythmogenic factor, the excitation process in the myocardium becomes self-activating (or paroxysmal). In this case, each excitation is a result of critical superposition of the background arrhythmogenic factors and extrasystole.

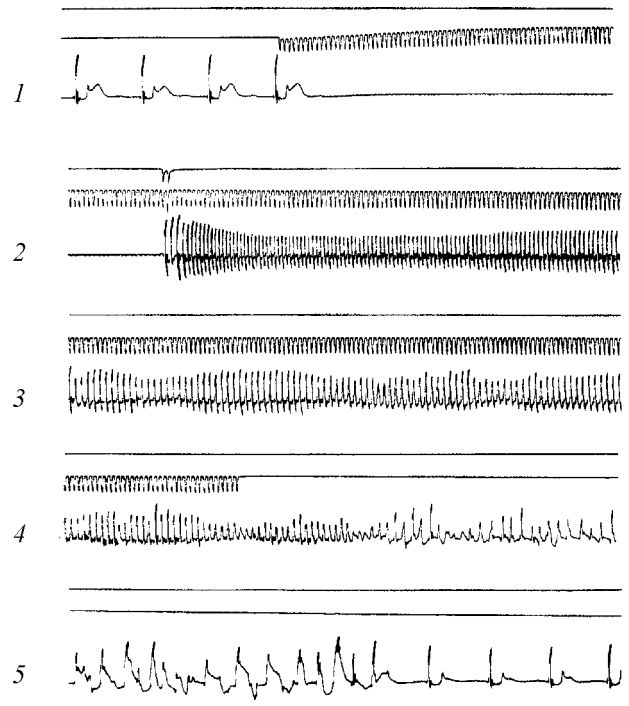

Fig. 1. A method of induction of neurogenic atrial fibrillation (NAF) [17]. Each fragment contains (from top to bottom): atrial stimulation mark; stimulation of the vagus nerve; intra-atrial electrocardiogram (maximum peak *P*). Records corresponding to the start of NAF (*1-2*), minute 4 of NAF (*3*), and cessation of NAF after termination of vagal stimulation on minute 6 (*4-5*, continuous recording).

This hypothesis was confirmed in experiments with controlled neurogenic atrial fibrillation (NAF) reproducible in 100% healthy cats. The animals were anesthetized with chloralose and nembutal (75+15 mg/kg, intraperitoneally) and artificially ventilated. In order to induce NAF, the right vagus nerve was exposed and cut on the neck. The peripheral end of the vagus nerve was pinned on bipolar needle electrodes (distance between tips 2 mm) and covered with wax-mineral oil grease. Two bipolar platinum probes (for myocardial stimulation and ECG recording) were introduced intravenously into the right atrium. NAF paroxysm was evoked with a pair of electrical pulses (5 msec, 4 thresholds, interval 20-40 msec) delivered to the right atrium against the background of cardiac arrest induced by vagal stimulation (2 msec, 40 Hz, 6 thresholds, Fig. 1). Fibrillation can be stopped and restarted by termination and resumption of the vagal stimulation.

The key element of this model is a short interval (50 msec) between the two electrical pulses (atrial ERP in the absence of vagal stimulation is 110-150 msec). Hence, vagal stimulation sharply accelerates the onset of repolarization in myocytes, while extrasystole induced by the second pulse sharply accelerates this process and induces autoexcitation of the myocardium. The latter also represents an extrasystole and triggers the next excitation and so on, i.e. a paroxysm of atrial fibrillation develops.

In order to confirm our hypothesis, we carried out a series of experiments on cats under conditions of whole-body hypothermia [8]. The duration of cardiac cycle, the tonic chronotropic effect (CE) of a single vagal stimulation (evaluated by the duration of cardiac cycle, in msec), ERP of the right atrium, and duration of NAF were measured during cooling (every 2°C). The duration of NAF at 37, 35, 33, 31, 29, and 27°C was 222±23, 216±25, 139±21, 97±19, 73±18, and 32±7 sec, respectively (for the last four points the differences from the control were significant, $p<0.05$). Our experiments showed that the antiarrhythmic effect of hypothermia is associated with temperature-dependent lengthening of ERP (*i.e.* delayed onset of repolarization) at the same chronotropic influence of the vagus nerve. In other words, arrhythmogenic effect of the vagus nerve evaluated by the ratio CE/ERP (in arb. units) decreased during cooling and was 0.79, 0.58, 0.49, 0.36, 0.30, and 0.26 at 37, 35, 33, 31, 29, and 27°C, respectively.

Another argument in favor of our hypothesis was obtained in experiments with antiarrhythmic preparations. In 10 experimental series we studied the antiarrhythmic effects of procainamide, lidocaine, allapinine, ethmosine, ethacizine, and methacizine (class I, by E. M. Vaughan-Williams); propranolol (class II);

amiodarone and nibentan (class III); and verapamil (class IV) during NAF [7-9,12,13,15,21]. All test drugs exhibited pronounced antiarrhythmic activity and reduced the duration of NAF to 75-12% of its initial length. Nibentan, procainamide, lidocaine, propranolol, and amiodarone produced also a bathmotropic effect (prolonged ERP or slightly increased excitation threshold), while verapamil, conversely, decreased the excitation threshold to 71%.

At the same time, it was established that all antiarrhythmic drugs, except propranolol, exhibit cholinolytic properties. The observed antiarrhythmic effect of these preparations strongly correlated with their neurotropic (*i.e.* inhibition of cholinergic acceleration of repolarization), but not cardiotropic activity.

The antiarrhythmic effect of propranolol is also due uncoupling of the inward and outward currents in myocytes due to delayed rhythm-dependent repolarization and blockade of sympathetic potentiation of inward currents.

Thus, our findings suggest that all antiarrhythmic drugs possess pronounced cholinolytic and/or adrenolytic activity. This fact is of fundamental importance, because the major factors leading to autoexcitation of the contractile myocardium under natural conditions are sympathetic and/or parasympathetic hyperactivation. This conclusion provide the possibility of improving the efficacy of antiarrhythmic therapy in animal models or in humans, because the contribution of neurogenic and cardiotoxic factors is taken into account. It also promotes efficient search of antiarrhythmic drugs on the basis of their cholinolytic and/or adrenolytic effects.

In 9 experimental series, we also studied the antiarrhythmic effect of opioid peptide metenkephalin [11], local anesthetics (dicaine, leocaine, and TZ-50-2) [7,16], antidepressant befol [2], non-glycoside cardiotonic preparation suphan [2], antioxidant mexidol [10], and antihistaminic preparations, H_1-receptor inhibitors dimebon and phencarol [1].

All test preparations possessed antiarrhythmic activity against NAF, which correlated with their cholinolytic, but not cardiotropic properties. Cholinolytic effect of some drugs was demonstrated for the first time.

It was assumed that gangionic blockers possess maximum antiarrhythmic activity, because they inhibit both sympathetic and parasympathetic influences on the heart. We found that pentamine had no effect on atrial myocardium in cats, but reduced the duration of NAF to 6% [23], *i.e.* produced a more potent effect than some conventional antiarrhythmics.

In 4 experimental series on NAF model we studied the antiarrhythmic effects of adrenoceptor agonists isadrine and epinephrine, cholinreceptor agonist pilocarpine, and cholinesterase inhibitor neostigmine [14]. As expected, all these substances significantly prolonged NAF. This can be explained by prolongation of inward currents in myocytes (epinephrine and isadrine) or acceleration of repolarization processes (pilocarpine and neostigmine). Neostigmine produced the most pronounced arrhythmogenic effect and increased NAF duration to 120 min (i.e. to the end of observation). Epinephrine produced a biphasic effect: it prolonged NAF to 195% of the initial value in low doses (0.1 μg/kg) and shortened NAF to 18% in high doses (2 μg/kg or higher); vagal CE decreased to 38%. These findings suggest that epinephrine produces a dual effect on NAF. On the one hand, epinephrine-induced prolongation of the inward currents potentiated NAF. On the other hand, epinephrine suppresses vagal influences on myocyte repolarization, thus producing a pronounced antiarrhythmic effect.

Significant potentiation of NAF was also observed after injection of aconitine or ouabain [22], which prolonged inward currents in myocytes.

As was mentioned above, adrenergic factors produce opposite effects on NAF. In two special series we compared the vagotropic effects of stimulation of various branches of the right stellate ganglion on NAF [24]. It was found that stimulation (2 msec, 20 Hz, 2 thresholds) of the ansa subclavia (Vieussens' loop) 3-fold prolonged NAF, while similar stimulation of the caudal cardiac nerve (*n. cardiacus cervicalis iferior*) 9-fold shortened it. Thus, sympathovagal interaction and the development of NAF largely depend on vagotropic sympatho-sympathetic balance, because some sympathetic nerves potentiate, while others inhibit vagal effects on the heart [20].

This strong correlation between atrial fibrillation and arrhythmogenic effects of extracardial nerves prompts us to carry out special experiments, where we demonstrated a direct effect of antiarrhythmic drugs on not only myocardial, but also nervous tissue [18]. Experiments were carried out on neurons of *Lymnaea stagnalis* gastropod mollusc. Ionic mechanisms in these cells are similar to those observed in other species [5]. Perfusion with physiological saline containing ethmosine and ethacizine in various concentrations induced a dose-dependent inhibition of Na, Ca, and K currents, which confirmed the presence of a neurotropic component in the antiarrhythmic effects of these drugs [3].

All the discussed results encouraged us to propose a new classification of antiarrhythmic factors and pharmacological agents considering their cardiotropic and neurotropic activities. According to this classification all antiarrhythmic factors can be divided into three major classes depending on their ability to inhibit cholinergic (C), adrenergic (A), or both cholinergic and adrenergic (CA) influences on the heart. Each class is

further subdivided into subclasses according to specific myotropic activity of factors:

I — factors, which block Na^+ and Ca^{2+} influxes in myocytes;

E — factors, which block or delay K^+ and Cl^- effluxes in myocytes;

IE — factors, which affect both the inward and outward currents in myocytes;

0 — factors exhibiting no myotropic effects.

The value of each antiarrhythmic property can be indicated by the uppercase or lowercase letters (for example, HA, hA, Ha, or ha).

According to this classification, procainamide is $H:i_{Na}E_K$ factor. This means that it possess pronounced cholinolytic activity, slightly affects sodium inward current and significantly increases the latency of repolarization in myocytes. Antiarrhythmic portraits of such factors as propranolol, metacine, pentamine, and hypothermia are expressed as follows: $A:i_{Ca}e_K$, H:0, HA:0, hA:$+i_{Ca}E_K$, where $+i_{Ca}$ means moderate prolongation of Ca^{2+} influx.

On our opinion, our considerations can be also applicable to other types of cardiac arrhythmias, such as single and grouped extrasystole, and ventricular tachyarrhythmia and fibrillation.

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