Effect of NO-Synthase Inhibitor L-NAME on Occlusion and Reperfusion Arrhythmias in Cats

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On the model of occlusion/reperfusion arrhythmia in cats it was shown that repeated injections of the NO-synthase inhibitor L-NAME decreased the incidence of occlusion arrhythmias (to 40%), eliminated reperfusion-induced ventricular fibrillation, and drastically reduced the latency of occlusion arrhythmias. A single injection of L-NAME (20 mg/kg) immediately before ligation of the coronary artery did not decrease the incidence of occlusion and reperfusion arrhythmias.

Key Words: *ventricular arrhythmias; nitric oxide; NO-synthase inhibitor*

Nitric oxide (NO) is an intercellular transmitter, which affects various cell processes by modulating activity of metal-containing enzymes and formation of oxygen radicals [4]. NO is produced during conversion of arginine into citrulline catalyzed by constitutive and inducible isoforms of NO-synthase (NOS). NO plays an important role in the ischemic pathology of the myocardium. There are experimental data on both protective and cytotoxic effects of NO [6,13]. The role of NO in the genesis of ischemia/reperfusion disturbances of the cardiac rhythm remains unclear, and experimental data are in many respects controversial [9,10,12,13].

Our aim was to study the effect of a nonspecific inhibitor of NOS, Nω-nitro-L-arginine methyl ester (L-NAME) on the development of occlusion and reperfusion arrhythmias in cats.

MATERIALS AND METHODS

Experiments were carried out on 38 mature cats of both sexes weighing 2.5-3.5 kg. The descending branch of the left coronary artery was ligated for 30 min under hexenal narcosis (40 mg/kg) and then the ligature was removed and perfusion was restored.

In the present study we used L-NAME (Sigma), a non-specific inhibitor of NOS, which blocks the constitutive and inducible isoforms of this enzyme. In series I (n=5), L-NAME (20 mg/kg) was infused 10 min prior to applying the ligature. In series II (n=5), the inhibitor was injected intraperitoneally during 3 days (10 mg/kg/day) and intravenously on the 4th day (20 mg/kg) immediately before coronary occlusion.

The control cats were injected with 0.9% NaCl. ECG was recorded during occlusion and 20 min of reperfusion. The data were statistically analyzed using the χ^2 test.

RESULTS

In the control series, ventricular extrasystole and tachycardia developed in all cats after ligating of coronary artery, in some cats fatal ventricular fibrillation was observed. When the coronary blood flow was restored, reperfusion arrhythmias appeared in 100% cats, and ventricular fibrillation in 65% cats (Table 1).

Single injection of L-NAME immediately before ligation of the coronary artery did not change the incidence of arrhythmias and ventricular fibrillation during both during ischemia and reperfusion, which were

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TABLE 1. Effect of L-NAME on the Development of Occlusion and Reperfusion Arrhythmias

Experiment		Number of cats			Latency of arrhythmia after occlusion, min
		total	arrhythmia	ventricular fibrillation	
Occlusion arrhythmias					
Control		28	28 (100)	8 (28)	16.5±1.1
Injection	single	5	5 (100)	0 (0)	10.7±4.9
	repeated	5	2 (40)*	0 (0)*	5±1*
Reperfusion arrhythmias					
Control		20	20 (100)	13 (65)	Arrhythmias started
Injection	single	5	5 (100)	3 (60)	at the moment of
	repeated	5	4 (80)	0 (0)*	commencing reperfusion

Note. *$p<0.05$ compared with the control (χ^2 test). Percent of cats is given in parenthesis.

the same as in control. Repeated injections of NOS inhibitor considerably decreased the incidence of occlusion arrhythmias (to 40%) in comparison with the control and prevented the development of ventricular fibrillation during reperfusion in experimental cats. On the other hand, repeated injections of L-NAME decreased the latency of occlusion arrhythmias more than 3-fold.

The nonspecific NOS inhibitor L-NAME produced a statistically significant effect on the development of arrhythmias only after repeated administration.

The data indicate ambiguity of the L-NAME effect. Repeated injections of this inhibitor decreased the incidence of occlusion ventricular arrhythmias and reperfusion fibrillation, i.e. produced an antiarrhythmic effect. On the other hand, it greatly accelerated the development of occlusion arrhythmias, which can be considered as an arrhythmogenic effect of L-NAME.

This contradiction reflects the general regularity, which corresponds to experimental evidence on participation of NO in myocardial ischemic pathology: NO produces a protective effect during short-term ischemia and a toxic effect during long-term ischemia [11,15].

Such dual effect of NO is well known in pathology of the nervous system. It primarily depends on the amount of synthesized NO and on oxygen availability that plays a dual role: it is a necessary substrate for NO synthesis and metabolite participating in the formation of toxic radicals [3,4].

The antiarrhythmic effect of chronically injected L-NAME is presumably analogous to adaptation of the myocardium to ischemia by repeated ischemia/reperfusion procedures, because the inhibitor periodically decreases the vasodilation capacity of coronary arteries. Taking into consideration that inhibition of NOS abolishes the protective effect of repeated ischemia/reperfusion procedures on the course of ischemic damage [5], other mechanisms of L-NAME antiarrhythmic effect in our experiments should be proposed.

The cardiotropic effect of NOS inhibitors was also observed in the intact heart. Micronecroses and a decrease in coronary blood flow in rats were observed 72 h after injection of a single dose of L-NAME (5 mg/kg) [8]. Long-term (6 weeks) repeated injections of L-NAME (25 mg/kg/day) caused myocardial hypertrophy and sustained elevation of blood pressure [7].

Our model of myocardial ischemia/reperfusion is highly arrhythmogenic. This feature presumably explains the absence of a pronounced arrhythmogenic effect of L-NAME in acute experiments after a single injection of the drug, which mainly agrees with the accepted concept of the protective effect of NO [2].

The arrhythmogenic effect of repeated L-NAME injections is manifested during the first few minutes of ischemia and possibly reflects a direct protective effect of NO during ischemic damage to cardiomyocytes.

Our findings agree with previous data [12,14] on the existence of species-specific peculiarities of cell-cell communication mediated by NO and on the ambiguity of NO effect on cells, in particular under pathological conditions.

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