Deep Anesthesia Suppresses Ventricular Tachyarrhythmias in Rabbit Model of the Acquired Long QT Syndrome

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Abstract

Background: Anesthesia sometimes suppresses ventricular tachyarrhythmias (VT) resistant to conventional pharmacological treatment.

Methods and Results: To know (1) whether deep anesthesia inhibits abnormal repolarization-related VT and (2) if α2-adrenoceptor (AR) agonistic action is associated with the antiarrhythmic effect of anesthetics, the incidence of VT in a rabbit model of acquired long QT syndrome using different anesthetic regimen was assessed. In Study 1 (n=30), 15 rabbits were lightly anesthetized with ketamine (123±46 mg/kg) and an α2-AR agonist, xylazine (9.4±3.0 mg/kg), while combination of these anesthetics at high doses were used in the other 15 rabbits (343±78 mg/kg and 38.9±3.0 mg/kg). Administration of α1-AR stimulant, methoxamine and nifekalant (lkr blocker) caused VT in all lightly anesthetized rabbits. In contrast, VT was observed only in 1 of the 15 deeply anesthetized rabbits (P<0.01). In Study 2 (n=15), 10 rabbits were anesthetized with high-dose ketamine and low-dose xylazine. In the other 5 rabbits, low-dose ketamine and high-dose xylazine were used. QTc interval in the latter was longer than that of the former (399±56 ms vs. 494±57 ms, P<0.01). Although no VT appeared in high/lows-low-rabbits, VT occurred in 3 out of 5 low/high-rabbits (P<0.05).

Conclusions: These results suggest that (1) deep anesthesia suppresses abnormal repolarization-related VT and (2) antiarrhythmic effect of anesthesia on this type of VT is not dependent on α2-AR agonistic action. (Circ J 2011; 75: 89–93)

Key Words: Anesthesia; Ketamine; Ventricular tachyarrhythmia; Xylazine

INTRODUCTION

It is empirically known that anesthesia has an inhibitory effect on serious ventricular tachyarrhythmias (VT) refractory to conventional antiarrhythmic pharmacological treatment.1–4 However, either the mechanism with which anesthesia facilitates the suppression of VT or arrhythmogenic substrate prone to respond to anesthesia is not clearly defined. Also, a few clinical reports presented patients with long QT syndrome (LQTS) and it was shown episodes of torsade de pointes developed during general anesthesia.5,6

The widely used animal model of abnormal repolarization-related VT is the α1-adrenoceptor (AR)-stimulated rabbit model in combination with lkr blocking agent.8,9 Some anesthetic agents have α2-AR stimulating action.10–12 Because α2-AR stimulation alleviates cardiovascular and electrophysiological changes caused by the α1-stimulation and attenuates L-type Ca2+ current, it is conceivable that α2-AR agonist has a more prominent effect on VT.13

This study was designed to test whether deep anesthesia suppresses abnormal repolarization-related VT, and whether α2-AR stimulating action of anesthetic agents is associated with their antiarrhythmic effect, if it exists.

METHODS

Animal Preparation

The principles of laboratory animal care (NIH publication No 8623, revised 1985) were followed. Forty-five male Japanese white rabbits (2.5–3.5 kg) were anesthetized with intramuscular administration of ketamine and xylazine. Combination of ketamine and xylazine is a commonly used anesthetic regimen in laboratory animals. Ketamine is a short-acting anesthetic and analgesic agent.14–16 Xylazine has sedative and muscle-relaxing properties, and is used to alleviate unfavorable effects of ketamine such as tremor and muscle rigidity.17,18

Rabbits were ventilated with room air through an artificial
respirator (model 6025, Ugo Basile, Italy) via a tracheal cannula. Arterial blood pressure was monitored using a left femoral artery cannula attached to a Statham pressure transducer (Amplifier AP621G, Nihon Kohden, Tokyo, Japan). Body temperature was maintained at about 37°C with an electrical blanket. Arterial blood gases and electrolytes were measured by a portable clinical analyzer (i-STAT 200A, i-STAT Corporation, Princeton, NJ, USA). Tidal volume and respiratory rate were adjusted to maintain arterial blood gases and pH within physiological range. Two surface electrocardiograms were continuously monitored; they were stored in a personal computer together with arterial blood pressure for subsequent analysis (PowerLab 8-channel System, ADInstruments Pty Ltd, Australia).

According to an in vivo animal model of torsades de pointes established by Carlsson et al., we administered nifekalant chloride concomitantly with methoxamine, an AR 1-stimulant. Nifekalant has been reported to block the delayed rectifier (Ikr), the inward rectifier (Ikr), and the transient outward (Ito) K+ channels. We used nifekalant because this is the only one class III agent readily obtainable for intravenous administration in Japan. In our previous study, monophasic action potential recording on the ventricular surface revealed that early afterdepolarization is actually the mechanism of VT in this animal model.

**Experimental Protocol**

**Study 1** Comparison between low-dose combination and high-dose combination of anesthetics (n=30). The protocol of this part is schematically shown in Figure 1. Fifteen rabbits were assigned to the low-dose anesthetic group, and were lightly anesthetized with intramural 35 mg/kg ketamine and 2 mg/kg xylazine. Additional doses (ketamine 15 mg/kg, xylazine 1 mg/kg) were given if necessary to maintain appropriate anesthesia. The remaining 15 rabbits, high-dose anesthetic group, were anesthetized with a combination of 105 mg/kg-ketamine and 6 mg/kg-xylazine. Additional doses of ketamine and xylazine in this group were set at 30 mg/kg and 2 mg/kg, respectively.

After a 10-min period of stabilization, methoxamine was intravenously administered at a rate of 70 nmol · kg⁻¹ · min⁻¹. Ten min infusion of methoxamine was followed by the administration of nifekalant chloride (0.2 mg · kg⁻¹ · min⁻¹). Then, both agents were continuously given until VT induction or for 20 min.

**Study 2** Comparison between combination of high-dose ketamine and low-dose xylazine and that of low-dose ketamine and high-dose xylazine (n=15). This part was designed to know either ketamine or xylazine, which is characterized by α₂-agonistic action, has more prominent effect on VT in this model. The experimental procedures and initial dose of each anesthetic were the same as in Study 1, but combinations of low-dose and high-dose anesthetics were adopted. Ten rabbits were anesthetized with high-dose ketamine and low-dose xylazine (high/low rabbits), while the remaining 5 rabbits were given low-dose ketamine and high-dose xylazine. Additional doses of ketamine and xylazine in this group were set at 30 mg/kg and 2 mg/kg, respectively.

After a 10-min period of stabilization, methoxamine was intravenously administered at a rate of 70 nmol·kg⁻¹·min⁻¹. Ten min infusion of methoxamine was followed by the administration of nifekalant chloride (0.2 mg·kg⁻¹·min⁻¹). Then, both agents were continuously given until VT induction or for 20 min.

**Definitions and Measurements**

VT was defined as the episode of 6 or more consecutive
ventricular beats. Heart rates and QT intervals were obtained from the measurements of 3 consecutive RR intervals or those of 3 beats in either lead with more prominent T waves, respectively. The QT interval was corrected according to the Bazett formula. The measurements of variables in the baseline state were made prior to the administration of methoxamine. Measurements during the treatment with each agent were performed in 5 min from the onset of administration of nifekalant. After this period, frequent premature ventricular contractions or VT interfered with the measurements of electrocardiographic variables in control rabbits.

Figure 2. Demonstrable recordings of electrocardiogram (ECG) and blood pressure in Study 1. Panel A indicates polymorphic ventricular tachyarrhythmias (VT) observed after 10 min of infusion of nifekalant in a rabbit of control group. VT rarely occurred in deeply anesthetized rabbits, while sporadic premature ventricular contractions were seen in some rabbits (Panel B).

Statistics
Results were expressed as mean±SD. Significance of differences in the parameters between the groups was tested by unpaired t-test. The inter-group difference of the incidence of VT was tested using Fisher’s exact test. Probability values less than 0.05 were considered to indicate significance.

Results

Study 1
Total doses of ketamine and xylazine in low-dose group were 123±46 mg/kg and 9.4±3.0 mg/kg, respectively. They
were 343±78 mg/kg and 38.9±3.0 mg/kg in the high-dose group. Metabolic, hemodynamic, and electrocardiographic variables are shown in Table. Intergroup difference was significant only in QTc after the treatment with methoxamine and nifekalant (P<0.01).

Demonstrable recordings are shown in Figure 3. Incidences of VT are given in Figure 3. VT occurred in all 15 rabbits anesthetized with low-dose anesthetics. In contrast, VT was observed only in one of the 15 rabbits (6.7%, P<0.01 vs. low-dose).

Study 2
Accumulated amounts of ketamine and xylazine were 330±57 mg/kg and 14.2±2.8 mg/kg in high/low-rabbits. They were 129±36 mg/kg and 38.9±11.7 mg/kg in low/high-rabbits. Metabolic variables and systolic blood pressure did not differ between the 2 groups (157±18 mmHg vs. 162±14 mmHg, NS). Heart rate in the low/high group was lower than that in high/low group (126±12/min vs. 80±14/min, P<0.01). QTc interval in the latter was longer than that of the former (399±56 ms vs. 494±57 ms, P<0.01). No VT was induced in high/low-rabbits. However, VT occurred in 3 of 5 rabbits in the low/high-rabbits (P<0.05 vs. high/low-rabbits).

Discussion
Observations of the Present Study
Major findings of the present study were that (1) deep anesthesia inhibited VT in the animal model of acquired QT prolongation, (2) xylazine, despite the α2-agonistic action, failed to show marked antiarrhythmic action.

Anesthesia and VT
Anesthesia has been known to be a choice for recurrent episodes of VT/VF. Both ischemic VT and abnormal ventricular repolarization-related VT were suppressed by anesthesia in certain experimental conditions. Observations in the present study also showed that anesthesia is effective to treat VT related with abnormal ventricular repolarization, and that this favorable effect of anesthesia is dependent on its depth, or in other words on the doses of anesthetic agents.

In an earlier study by Vincze et al., pentobarbital has shown marked effect on VT in the rabbit model of acquired LQTS. In contrast, neither propofol or α-chloralose failed to show appreciable antiarrhythmic action. Shimizu et al reported that pentobarbital reduces transmural dispersion of repolarization both in control and under conditions of congenital and acquired LQTS, and attributed its antiarrhythmic action to this mechanism. Because α1-AR stimulant contributes to the genesis of VT in the animal model, modification of sympathetic or parasympathetic activity might explain the antiarrhythmic action of anesthesia. However, no earlier study has confirmed this view. Also, because blood pressure and heart rate in the 2 groups with different depth of anesthesia were similar in Study 1, differences in autonomic state does not seem to be responsible for the decrease in the incidence of VT in rabbits with deep anesthesia.

However, QTc in the high-dose group was markedly shorter than that of the low-dose group. Furthermore, in study 2, prolongation of QTc interval was attenuated by high-dose ketamine, but not by high-dose xylazine. These observations suggest that if alleviated prolongation of ventricular repolarization by deep anesthesia is related with antiarrhythmic action, this action is not caused via α2-agonistic action of xylazine.

Ketamine barely modulates cardiac potassium channels. Antiarrhythmic effect of ketamine is not explained by its direct modification of ventricular repolarization. Farkas et al considered that bradycardia due to reflex activation of cardiac vagal nerve activity is necessary to induce VT in the present rabbit model. When heart rate is low, diminished accumulation of slowly activating delayed rectifier potassium current (IKs) prolongs action potential duration. In fact, in rabbits anesthetized with low-dose ketamine and high-dose xylazine in Study 2, heart rate was relatively low and QTc interval was longer than that seen in high/low-rabbits. Ketamine increases sympathetic discharge and reduces vagal discharge to the heart. Although it is beyond the scope of the present study to quantitatively clarify how modification of autonomic tones and electrophysiologic variables by anesthesia was reflected on the incidence of VT, the difference in the incidence of VT between the 2 groups in Study 2 might
be partly attributable to the difference in heart rate.
Ketamine does not seem to be a reasonable choice to treat VT in ischemic hearts, because they often are suppressed by β-blocking agents. Instead, when changes in QT interval in Study 1 and Study 2 are compared, it is likely that ketamine contributed to attenuate QT prolongation by administration of methoxamine and nifekalant. Ketamine might be a possible choice to treat reentrant VT associated with LQTS.

Conclusions

Deep anesthesia is effective to treat abnormal repolarization-related VT. This antiarrhythmic action of anesthesia is not explained by α2-AR antagonistic action of anesthetics. When one intends to evaluate antiarrhythmic action of a certain pharmacological intervention, one should be careful to choose the anesthetics and the depth of anesthesia. Clinically, when physicians attempt to treat recurrent episodes of torsades de pointes in LQTS patients by sedative or anesthetic agents, depth of anesthesia should be taken into consideration.

References