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ORIGINAL ARTICLE

Effect of lidocaine on swine lingual and pulmonary arteries

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Abstract
Purpose Lidocaine has a biphasic action on smooth muscle of peripheral blood vessels, with vasoconstriction at low concentrations and vasodilation at higher concentrations. Many in vivo studies have demonstrated the effects of lidocaine on aortic or coronary arteries in several animals, but there are few reports about the effect on peripheral vessels. This study was designed to investigate the direct effects of lidocaine on peripheral vessels, namely swine lingual and pulmonary arterial rings.
Methods Swine lingual artery and pulmonary artery segments, about 2–3 mm in diameter, were cut into 3-mm-long rings, and the lumen surface was gently rubbed to remove the endothelium. Isometric tension was measured using a displacement transducer and recorded. After a stable constriction was developed with 5 μM noradrenaline, 5 μM noradrenaline containing lidocaine (0.5, 1.0, 10, 20, 50 or 100 μg/ml) was perfused for 5 min, and then all drug perfusion was stopped. The strength of any isometric tension during an experiment was normalized to the strength of the isometric tension immediately before lidocaine perfusion, and expressed as a percentage.
Results Lidocaine elicited a concentration-dependent biphasic response of lingual and pulmonary arterial rings. The lidocaine concentration at 1 μg/ml caused mild contraction. Dilation occurred at 10 μg/ml and increased with increasing dose.
Conclusions Lidocaine-induced vasoconstriction of swine lingual and pulmonary smooth muscle may occur at low concentration when lidocaine is infiltrated into the oral submucosa or administered intravenously for the treatment of ventricular arrhythmia.

Keywords Lidocaine · Contraction · Isometric tension · Smooth muscle · Swine artery

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Introduction

Lidocaine is one of the most widely used local anesthetic agents and is administered in various surgical operations in the treatment of life-threatening ventricular arrhythmia and for suppression of airway reflexes associated with tracheal intubation or tracheal suction.

Lidocaine occasionally induces adverse events in the cardiovascular system when it is administered for epidural block, bronchial plexus block, or major lower limb block [1, 2]. However, the effects of lidocaine on hemodynamics are not well known and there are also a few reports of adverse cardiovascular events following local anesthesia with lidocaine. In addition, local anesthetics have a biphasic action on smooth muscle of peripheral vessels, with vasoconstriction at low concentrations, and vasodilation at higher concentrations [3–7]. The mechanism of these biphasic effects on vascular function is not fully understood. Although many in vivo studies have demonstrated the effects of lidocaine on aortic or coronary arteries in several animals, there are few reports about its effect on other peripheral vessels.

For dentists, lidocaine is usually used as a local anesthetic in dental treatment, and in oral and maxillofacial

surgery. However, there are few reports of the effects of lidocaine on craniofacial arteries, such as the lingual artery, which is a pivotal vessel for oral function. Effects of drugs on this artery may have implications in the clinical treatment of pathological circulation in the tongue [8]. The pulmonary artery is also relatively unexplored though it is a prominent artery that nourishes the lungs. Pulmonary vasoconstriction plays a central role in pulmonary arterial hypertension, which can be fatal, with a progressive elevation of pulmonary arterial resistance and pressure [9]. However, there are only a few reports of the effects of lidocaine on the pulmonary artery [10, 11]. The diversity of effects of lidocaine on smooth muscle precludes guessing the effects of lidocaine on any particular smooth muscle.

Although the effects of lidocaine on aortic or coronary arteries have been reported in several animals, its effects on craniofacial and pulmonary arteries have not been demonstrated. The present study was designed to further investigate the direct effects of lidocaine on these vessels in vitro using swine lingual and pulmonary arterial rings.

Materials and methods

This study was approved by the Institutional Review Committee on the Ethics of Animal Experiments of Iwate Medical University. All experiments were conducted in accordance with the Institutional Animals Care and Use Committee guidelines.

Reagents and solutions

l-noradrenaline bitartrate monohydrate (NA) was purchased from Alexis Corp. (Lausen, Switzerland). The other chemicals were obtained from Wako Pure Chemical Industries (Osaka, Japan).

In all experiments, air-equilibrated Hank's balanced salt solution (HBSS) [8] was used to maintain the arteries under resting conditions. HBSS consisted of 137 mM NaCl, 5.4 mM KCl, 0.8 mM $MgSO_4$, 1.26 mM $CaCl_2$, 0.34 mM Na_2HPO_4, 0.44 mM KH_2PO_4, 4.2 mM $NaHCO_3$, and 5.55 mM glucose (pH 7.34). The concentration of Na^+ and K^+ in the resting condition was 141.78 and 5.84 mM, respectively. All other salt solutions (SSs) used as perfusate were formulated by modifying HBSS. SS containing 100 mM KCl (100 KSS) was prepared by substituting the respective concentration of KCl for the equivalent concentration NaCl in HBSS. Each SS containing noradrenaline (NA) and lidocaine alone or in combination was prepared by adding the component agents into the respective base SS immediately before use.

Artery ring preparation and isometric tension measurement

Fresh tongues and lungs were obtained from six swine at a local abattoir. A segment of the lingual artery in the proximal region of the tongue, and a third of the pulmonary artery was dissected out. After the adventitia was removed, lingual artery segments about 2 mm in diameter, and pulmonary artery segments about 2–3 mm in diameter, were cut into 3-mm-long rings, and the lumen surface was rubbed gently against the thin arm of stainless-steel tweezers to remove the endothelium. It was confirmed that 3 μM acetylcholine-induced relaxation of the artery rings disappeared after this procedure. The artery rings were kept in HBSS at 5 °C until being used for measurement.

An artery ring was held by two tungsten needles in a perfusion chamber (volume of perfusate was 3 ml). One needle was fastened to a displacement transducer (Type UL-2GR, Minebea Co., Fujisawa, Japan) and the other to a micromanipulator. Perfusate, adjusted to 37 °C, flowed at a rate of 1.6 ml/min using a peristaltic pump (SMP-23, Tokyo Rikakikai Co., Tokyo, Japan). Since the strength of contraction did not change when the resting tone was 3–7 mN, artery rings were extended to give a resting tone of about 4 mN and immediately tested for contractility with two 2.5-min perfusions with 100 KSS separated by a 10-min HBSS perfusion. After a 30-min HBSS perfusion, artery rings were perfused with 5 μM NA. When a stable constricted plateau was obtained with 5 μM NA, 5 μM NA plus lidocaine (0.5, 1.0, 10, 20, 50, or 100 μg/ml) was perfused. Each concentration was perfused for 5 min, followed again by HBSS perfusion. Isometric tension was measured with the displacement transducer, and signals detected were amplified with a carrier amplifier (CSD-815 Digital indicator, Minebea Co., Fujisawa, Japan) and recorded with a Powerlab 16/30T data acquisition system (Australia AD Instruments). The isometric tension during an experiment was normalized to the isometric tension immediately before lidocaine perfusion, and expressed as a percentage.

Data analysis

Dilation was determined by measuring the cumulative reduction in induced tone in the arterial segments and expressed as a percentage of the contraction induced by 5 μM NA. A value of 0 % indicated the initial resting tension (5 mN), and a value of 100 % indicated the isometric tension generated by exposure to 5 μM NA. Values greater than 100 % indicated that vasoconstriction had occurred in response to lidocaine. Values are presented as mean ± SEM. Statistical analysis was performed using SPSS, version 11.0 (SPSS, Chicago, IL, USA). The Shapiro–Wilk test was used for normality and Bartlett's test for homogeneity of variance. Repeat measure analysis of variance (ANOVA)

followed by Bonferroni's post-test was performed. Differences were considered significant at $p < 0.05$.

Results

Typical traces of the changes in isometric tension in response to 5 μM NA only (without lidocaine) for 60 min on lingual and pulmonary arteries are shown in Fig. 1.

Lidocaine produced a relaxation of swine lingual and pulmonary arterial rings. A typical trace of the changes in isometric tension in response to increasing lidocaine concentration (0.5–100 μg) is shown in Figs. 2 and 3. Dose–response curves are shown in Fig. 4. Lidocaine elicited a concentration-dependent biphasic response of lingual and pulmonary arterial rings. The lidocaine concentration at 1 μg/ml caused mild contraction in lingual and pulmonary artery rings, indicated by an increase in isometric tension

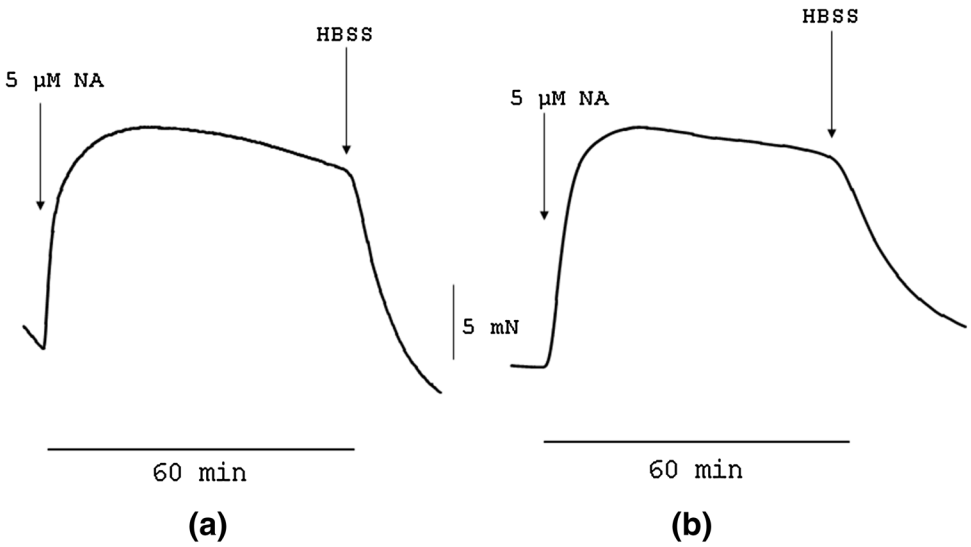

Fig. 1 Typical traces of changes in isometric tension in response to 5 μM noradrenaline (NA) only (without lidocaine) for 60 min on lingual and pulmonary arteries. **a** Lingual artery. **b** Pulmonary artery

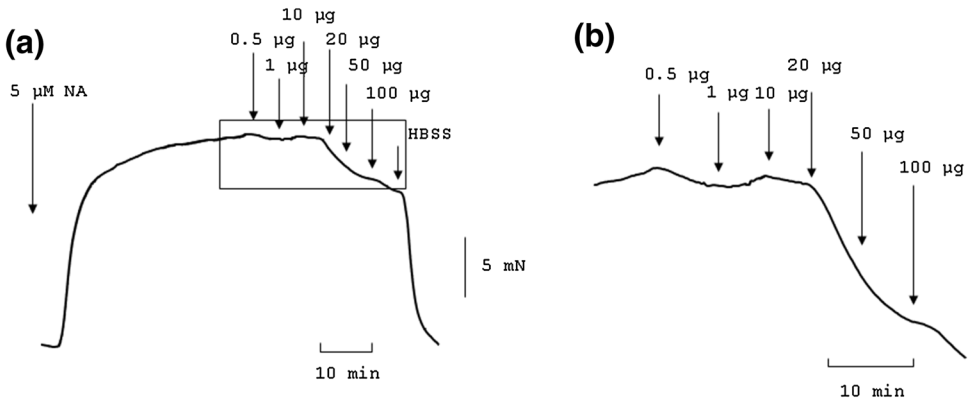

Fig. 2 A typical trace showing the effects of lidocaine on lingual artery ring contraction induced with 5 μM NA. **a** Recording of the lidocaine-induced contraction. **b** Enlarged view of the indicated portion of Fig. 2a

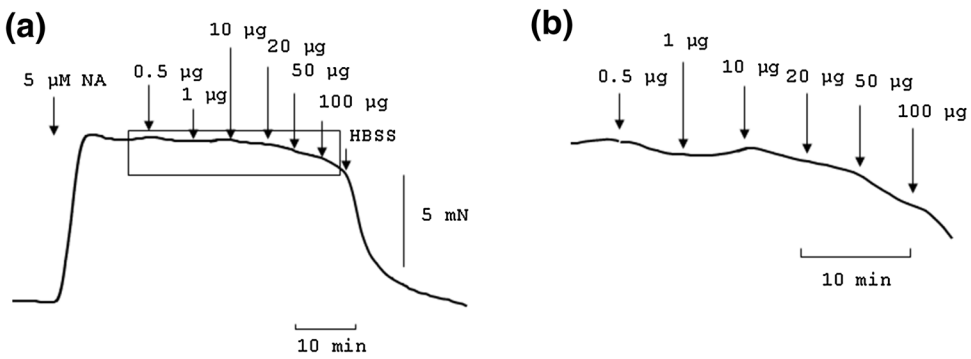

Fig. 3 A typical trace showing the effects of lidocaine on pulmonary artery ring contraction induced with 5 μM NA. **a** Recording of the lidocaine-induced contraction. **b** Enlarged view of the indicated portion of Fig. 3a

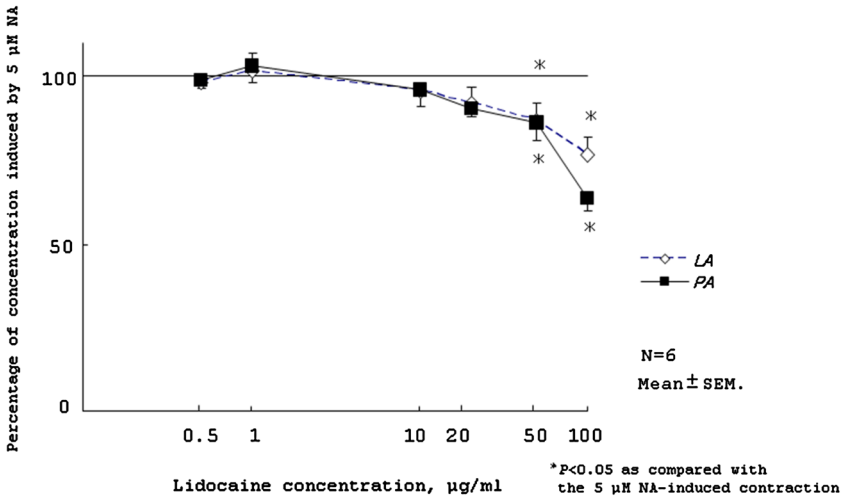

Fig. 4 Lidocaine dose-related vasorelaxation of lingual and pulmonary artery rings. Endothelium-denuded lingual and pulmonary artery rings were challenged with cumulative doses of lidocaine. Tension was measured as isometric force transduction, and expressed as a percentage of the 5 μM NA-induced tension. *LA* lingual artery, *PA* pulmonary artery

Table 1 Effect of lidocaine on lingual and pulmonary arteries (percent of 5 μM NA-induced contraction)

Lidocaine (μg/ml)	Contraction	
	Lingual artery ($n = 6$) (%)	Pulmonary artery ($n = 6$) (%)
0.5	99.5 ± 0.54	99.8 ± 1.0
1	104.4 ± 0.9	105.8 ± 1.9
10	98.3 ± 0.5	98.8 ± 2.1
20	94.7 ± 1.9	93.1 ± 1.2
50	89.4 ± 3.6*	88.8 ± 2.2*
100	79.1 ± 3.0*	66.2 ± 3.4*

*$P < 0.05$ as compared with the 5 μM NA-induced contraction

104.4 ± 0.9 % of the contraction induced by 5 μM NA in lingual artery rings and 105.8 ± 1.9 % in pulmonary artery rings. Dilation occurred at 10 μg/ml (98.3 ± 0.5 % of the contraction induced by 5 μM NA in lingual artery rings and 98.8 ± 2.1 % in pulmonary artery rings), and increased with an increase in concentration (at 100 μg/ml: 79.1 ± 3.0 % of the contraction induced by 5 μM NA in the lingual rings and 66.2 ± 3.4 % in the pulmonary rings) in Table 1.

Discussion

Our study demonstrated that lidocaine affects the NA-induced contraction of swine lingual and pulmonary arterial endothelium-denuded rings in a biphasic manner. Further contraction occurred at 1 μg/ml, followed by dose-dependent dilation at higher concentrations from 10 to 100 μg/ml.

Many studies [3–7] have demonstrated that amino-amide local anesthetic agents exhibit biphasic vascular effects to varying extents, with vasoconstriction at low concentrations and a decrease in contraction or even vasodilation at high concentrations in aortic or coronary arterial rings in several animals, but there have been few studies in craniofacial arterial rings, such as lingual artery rings. The biphasic vascular effect is a common characteristic of amino-amide local anesthetic agents that has been well examined in vivo and in vitro [3–7, 9, 10]. However, previous studies have demonstrated that the biphasic activity may occur mainly in aortic or coronary arterial rings and there are few reports of this effect in other peripheral vessels. Based on the results of our study, in lingual and pulmonary artery rings, a biphasic contraction-dilation may occur at low and high lidocaine concentrations, respectively.

Perlmutter [4] reported that in epicardial porcine coronary arteries, increasing the lidocaine concentration from 3 to 10 μg/ml caused mild vasoconstriction. Our data demonstrated that in swine lingual and pulmonary arterial rings, increasing the lidocaine concentration at 1 μg/ml caused mild contraction. This study suggested that in swine lingual and pulmonary arterial rings, lidocaine-induced contraction may occur at lower concentrations than in swine coronary arteries.

The circulating levels of lidocaine after dental injections have been investigated. The serum concentration of lidocaine was evaluated when 40 or 80 mg lidocaine with or without 1:80,000 adrenaline was infiltrated into the mucosa [11]. For 40 and 80 mg lidocaine without adrenaline, the mean maximum serum concentration was 0.35 μg/ml after infiltration and 0.93 μg/ml. For 40 and 80 mg lidocaine in combination with 1:80,000 adrenaline, the mean maximum serum concentration was 0.22 μg/ml after infiltration and 0.56 μg/ml [11].

It is thought that the concentration of lidocaine encountered in the clinical setting is approximately 50 % protein bound and the rest free in plasma. If approximately 50 % of lidocaine is bound to plasma proteins, we would assume

that only the 50 % free in plasma would affect vascular muscle directly. In this study, the lidocaine concentration at 1 μg/ml caused mild vasoconstriction in swine lingual and pulmonary arterial rings. The volume and lidocaine concentration of a dental cartridge are 1.8 ml and 2 %, respectively, and one dental cartridge contains 36 mg of lidocaine with 12.5 μg/ml adrenaline. If we consider the free plasma lidocaine, when dentists infiltrate 4–6 dental lidocaine cartridges with adrenaline into the oral mucosa, lidocaine-induced vasoconstriction may occur in the orofacial and pulmonary arteries. Considering the current results, lidocaine-induced vasoconstriction may occur after infiltration of 4–6 dental lidocaine cartridges. An increase in the plasma concentration of lidocaine would increase the concentration of free plasma lidocaine. Therefore, we think it is possible that lidocaine-induced vasoconstriction may occur in orofacial and pulmonary arteries when less than 4–6 lidocaine cartridges are infiltrated into the oral mucosa. In dental treatment, we usually use one or two 2 % lidocaine with adrenaline cartridges, but occasionally use 4–6 for minor surgery or extraction. During general anesthesia for oral maxillofacial surgery, 1 % lidocaine containing 1:100.000 adrenaline is often used over 10 ml at a time.

Depending on the vascularity of the injection site, vasoconstriction induced by the local anesthetic itself in combination with adrenaline may reduce the absorption of local anesthetics into the systemic circulation. This would lead to prolonged exposure of nerves to local anesthetics and reduce plasma levels of local anesthetics, suggesting that the duration of local analgesia is correlated with the magnitude of local-anesthetic-induced vasoconstriction or adrenaline-induced vasoconstriction [12].

Medical doctors and dental anesthetists occasionally administer lidocaine intravenously for the treatment of ventricular arrhythmia and to suppress airway reflexes associated with tracheal intubation. Intravenous lidocaine is usually administered at 0.5 or 1.0 mg/kg, or approximately 30–60 mg. When 40 and 80 mg lidocaine were administered intravenously, the mean maximum concentration was 0.73 at 2.3 min and 2.29 μg/ml at 2.1 min [11].

To suppress airway reflexes, lidocaine in 8 % solution is sprayed rapidly into the trachea using a lidocaine pump. The volume of one application is 0.1 ml (8 mg lidocaine). Lidocaine is usually sprayed 3–5 times, giving a concentration of 24–40 mg. When 40 or 80 mg lidocaine was sprayed onto the intraoral mucosa with an 8 % lidocaine pump, the mean maximum plasma concentrations were 0.16 and 0.26 μg/ml, respectively [11]. Therefore, this study suggested that if lidocaine was administered intravenously for the treatment of ventricular arrhythmia, lidocaine-induced vasoconstriction may occur in orofacial and pulmonary arteries, and if sprayed to suppress airway reflexes associated with tracheal intubation, it may not occur normally. We suggest that, given the concentrations of lidocaine in the clinical situation, lidocaine may induce vasoconstriction at these low levels.

We did not investigate the mechanism(s) of smooth muscle constriction and dilation by lidocaine in this study. There is a report that investigated the effect of mepivacaine, an amino-amide-linked local anesthetic like lidocaine, in the isolated rat aorta. Sung [12] reported that verapamil and calcium-free Krebs solution attenuated mepivacaine-induced contraction of the endothelium-denuded aorta. Thus, calcium influx via voltage-operated calcium channel (VOCC) activation by low concentrations of mepivacaine may trigger the initial contraction, while a high concentration of mepivacaine had an inhibitory effect on the VOCCs in vascular smooth muscle. From that study, we consider that the mechanisms of smooth muscle constriction and dilation by lidocaine may be associated with concentration-dependent activation or inhibition of VOCCs.

In conclusion, lidocaine-induced vasoconstriction of swine lingual and pulmonary smooth muscle may occur at a low concentration when lidocaine is infiltrated into the oral submucosa, or administered intravenously for the treatment of ventricular arrhythmia.

Conflict of interest The authors have no potential conflicts of interest to disclose.

Ethical approval The study was approved by the Institutional Review Committee on the Ethics of Animal Experiments of Iwate Medical University. All experiments were conducted in accordance with the Institutional Animals Care and Use Committee guidelines (Ethical number is 26-010).

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