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Effects of nicardipine on diaphragmatic fatigue in the dog: the relationship between dosage and fatigability

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Abstract: We examined the dose-related effects of nicardipine on the diaphragmatic fatigability in 24 anesthetized, mechanically ventilated dogs. Animals were divided into three groups of eight each: the control group (group C), the nicardipine 3 $\mu g \cdot kg^{-1}$ I.V. group (group N_1) and the nicardipine 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ I.V. group (group N_2). Diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation at a frequency of 20 Hz applied for 30 min. In groups N_1 and N_2, nicardipine was continuoulsy infused intravenously during this fatigue-producing period. Diaphragmatic contractility was assessed by changes in transdiaphragmatic pressure (P_{di}). After induction of diaphragmatic stimulation at low-frequency (20 Hz), P_{di} decreased significantly in all groups compared with the pre-fatigue value ($P < 0.05$), whereas no change was observed in P_{di} at high-frequency (100 Hz) stimulation. The P_{di} at 20 Hz stimulation was significantly lower in groups N_1 and N_2 compared with that in group C ($P < 0.05$). The decrease in P_{di} at 20 Hz stimulation was significantly larger in group N_2 than in group N_1 ($P < 0.05$). The speed of recovery of P_{di} at 20 Hz stimulation was dose dependent. The integrated diaphragmatic electric activity (E_{di}) in each group did not change at any frequency of stimulation throughout the study. Our results demonstrate that nicardipine causes a dose-dependent reduction of the contractility of the fatigued diaphragm.

Key words: Diaphragmatic fatigue, Transdiaphragmatic pressure, Nicardipine

Introduction

Recently, we demonstrated that nicardipine predisposes the diaphragm to fatigue [1]. However, the relationship between the dose of nicardipine and diaphragmatic fatigability has not been reported. The purpose of the present study was to examine this relationship and also to clarify the effects of nicardipine on the recovery of the fatigued diaphragm.

Materials and methods

Institutional approval for the study was obtained from the Animal Care and Use Committee of Tokyo Medical and Dental University School of Medicine. We studied 24 healthy mongrel dogs (10–15 kg) anesthetized with pentobarbital sodium and mechanically ventilated. Animal preparation was similar to that described previously [1]. Briefly, anesthesia was maintained with pentobarbital sodium 2 $mg \cdot kg^{-1} \cdot min^{-1}$ I.V. No muscle relaxants were used. The animals' trachea were intubated, and ventilation was controlled with a mixture of O_2 and air ($F_IO_2 = 0.4$) to maintain Pao_2, $Paco_2$, and pH within normal ranges. A Swan-Ganz catheter was advanced via the right external jugular vein into the pulmonary artery for measuring cardiac output by the thermodilution technique. Transdiaphragmatic pressure (P_{di}) was measured by means of two thin-walled latex balloons; one positioned in the stomach, the other in the middle third of the esophagus. Balloons were connected to a differential pressure transducer (Pressure Head, Tokyo Keiki, Tokyo, Japan) and an amplifier (Type 1212, Nihon Denki San-ei, Tokyo, Japan). Bilateral phrenic nerves were exposed at the neck, and the stimulating electrodes were placed around them. Supramaximal electrical test stimuli of 0.1 ms duration were applied for 2 s at frequencies of 20 or 100 Hz with an electrical stimulator (Electronic Stimulator 3F37, Nihon Denki San-ei). Diaphragmatic contractility was evaluated by measuring the maximal P_{di} after the airway occlusion at functional residual capacity (FRC) level. The electrical activity of the diaphragm was measured with needle electrodes inserted percutaneously into the

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diaphragm from the upper abdominal area, and was rectified and integrated with a leaky integrator (Type 1310, Nihon Denki San-ei) with a time constant of 0.1 s. This was regarded as the integrated diaphragmatic electrical activity (E_{di}). The experimental design is shown schematically in Fig. 1.

The dogs were randomly divided into three groups: the control group (group C, $n = 8$), the nicardipine 3 μg·kg^{-1}·min^{-1} I.V. group (group N_1, $n = 8$) and the 5 μg·kg^{-1}·min^{-1} I.V. nicardipine group (groups N_2, $n = 8$). After the prefatigue measurement of P_{di}, E_{di}, and hemodynamics which included heart rate (HR), mean arterial pressure (MAP), and cardiac output ($\dot{Q}t$), diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation applied for 30 min at a frequency of 20 Hz (low-frequency fatigue), with an entire cycle of 4 s and a duty cycle of 0.5 [2]. Nicardipine was administered intravenously continuously with an electrical infusion pump (Terumo, Tokyo, Japan) during the administration of fatigue-producing stimuli. Infusion of nicardipine was stopped at the end of fatigue-producing stimuli, and P_{di}, E_{di}, and hemodynamics were measured immediately (fatigued period). The same measurements were repeated at 30 min after the end of the fatigue-producing procedure (recovery period). In group C, only maintenance fluid was administered during the fatigue-producing period and the same measurements were performed as those in groups N_1 and N_2.

All values were expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way analysis of variance (ANOVA) and Student's t-test. $P < 0.05$ was considered significant.

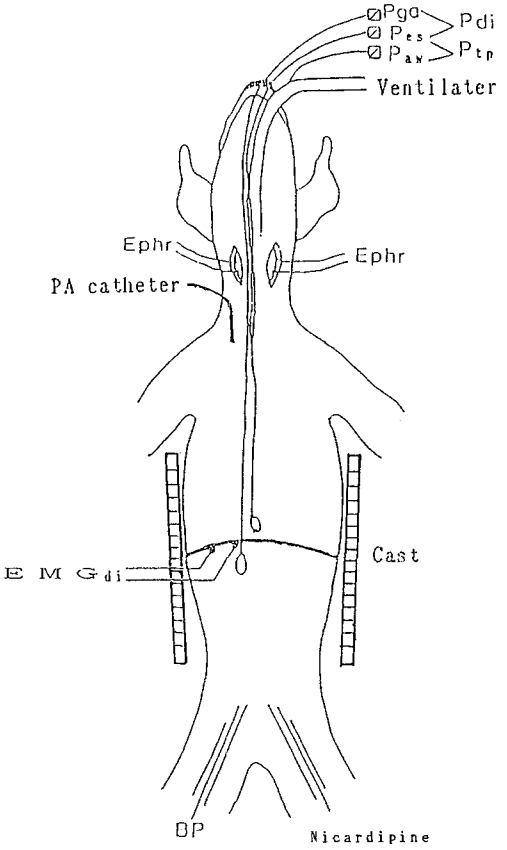

Fig. 1 Animal preparation. P_{ga} gastric presssure; P_{es} esophageal pressure; P_{aw} airway pressure; P_{di} transdiaphragmatic pressure; P_{tp} transpulmonary pressure; E_{phr} phrenic nerve stimulation; EMG_{di} electrical activity of diaphragm; *PA*, pulmonary artery

Results

Hemodynamic results in each group are summarized in Table 1. There were no differences among the three groups in hemodynamic parameters during the prefatigue period. In groups N_1 and N_2, a significant increase in HR and $\dot{Q}t$, and a significant decrease in MAP was observed compared with the prefatigue values during nicardipine infusion. Soon after cessation of administration, these hemodynamics values returned to the prefatigue values. There were significant differences in HR and MAP between groups N_1 and N_2 during the fatigue producing period.

P_{di} values at different stages are shown in Table 2 as percentages of P_{di} obtained at each frequency stimulation during the prefatigue period. In each group, after producing fatigue, P_{di} at 20 Hz stimulation decreased significantly from the prefatigue values, whereas P_{di} at 100 Hz stimulation did not change significantly. P_{di} at 20 Hz stimulation in both the fatigued and recovery periods were significantly lower in groups N_1 and N_2 compared with that in group C. P_{di} at 20 Hz stimulation in group N_2 was significantly lower than that in group N_1.

Table 1. Changes in hemodynamic data

Variable	Group	Prefatigue	Fatigued	Recovery
HR	C	139 ± 7	137 ± 8	137 ± 10
(bpm)	N_1	136 ± 10	143 ± 12[a]	135 ± 11[b]
	N_2	140 ± 9	151 ± 10[a,c,d]	139 ± 8[b]
MAP	C	126 ± 11	126 ± 12	125 ± 11
(mmHg)	N_1	125 ± 12	103 ± 12[a,c]	123 ± 11[b]
	N_2	121 ± 9	88 ± 10[a,b,d]	122 ± 9[b]
$\dot{Q}t$	C	2.0 ± 0.2	2.1 ± 0.2	2.0 ± 0.2
(l·min^{-1})	N_1	2.1 ± 0.1	2.4 ± 0.3[a,c]	2.1 ± 0.1[b]
	N_2	2.0 ± 0.1	2.5 ± 0.2[a,c]	2.1 ± 0.2[b]

Mean ± SD.
HR, heart rate; MAP, mean arterial pressure; $\dot{Q}t$, cardiac output; C, control; N_1, nicardipine 3 μg·kg^{-1}; N_2, nicardipine 5μg·kg^{-1}·min^{-1}
[a] $P < 0.05$ (vs prefatigue); [b] $P < 0.05$ (vs fatigue); [c] $P < 0.05$ (vs group C); [d] $P < 0.05$ (groups N_1 vs N_2).

Table 2. Changes in transdiaphragmatic pressure (%) in the prefatigue, fatigued, and recovery periods

Frequency	Group	Prefatigue	Fatigued	Recovery
20 Hz	C	100.0 ± 0.0	71.9 ± 3.8[a]	74.4 ± 3.3[a]
	N_1	100.0 ± 0.0	65.4 ± 3.5[a,b]	67.3 ± 2.9[a,b]
	N_2	100.0 ± 0.0	59.3 ± 4.7[a,b,c]	60.5 ± 3.9[a,b,c]
100 Hz	C	100.0 ± 0.0	98.9 ± 3.9	99.9 ± 3.4
	N_1	100.0 ± 0.0	98.6 ± 4.2	99.8 ± 4.9
	N_2	100.0 ± 0.0	98.5 ± 4.2	99.6 ± 4.0

Mean ± SD.
[a] $P < 0.05$ (*vs* prefatigue); [b] $P < 0.05$ (*vs* group C); [c] $P < 0.05$ (group N_1 *vs* N_2).

The speed of recovery of P_{di} at 20 Hz stimulation was dose dependent. Especially in groups N_1 and N_2, P_{di} values did not improve markedly during the 30-min recovery phase.

No significant changes in E_{di} were observed throughout the study in any gruop.

Discussion

The major findings of the present study are as follows: (1) after the fatigue-producing procedure, P_{di} at 20 Hz stimulation was significantly lower in groups N_1 and N_2 compared with group C, (2) the decrease in P_{di} at 20 Hz stimulation was significantly larger in group N_2 than that in group N_1, and (3) the speed of recovery of P_{di} at 20 Hz stimulation became relatively slower in a dose-dependent manner.

It is well known that low-frequency fatigue is of particular clinical importance because the spontaneous, natural rate of phrenic nerve discharge is believed to be mainly in the low-frequency range (5–30 Hz) [3]. Therefore, the effects of nicardipine on the diaphragmatic fatigue induced by 20 Hz stimulation (low-frequency fatigue) was examined in this study.

Our present results demonstrated that P_{di} at 20 Hz stimulation in group N_2 (nicardipine 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was significantly lower than that in group C, which was in agreement with our previous study [1]. The present study also demonstrated that P_{di} at 20 Hz stimulation in groups N_2 was significantly lower than that in group N_1 (nicardipine 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Thus, administration of nicardipine augments fatigability of the diaphragm in a dose-dependent manner.

Although the exact mechanism of increased diaphragmatic fatigue following nicardipine infusion remains unclear, it has been suggested that this agent may inhibit calcium release from the sacroplasmic reticulum and calcium transport across the cell membrane [1]. This inhibition may be closely related to the mechanism of the production of diaphragmatic fatigue [2,4].

Diaphragmatic fatigue can also occur when the energy demands of the muscle exceed the available energy supply [5]. It has been suggested that diaphragmatic blood flow changes in accordance with $\dot{Q}t$ [6]. In the present study, we did not measure the blood flow to the diaphragm, but we measured the hemodynamics during and after nicardipine administration. The increase in $\dot{Q}t$ observed with infusion of nicardipine in the present study may have increased the diaphragmatic blood flow. As was described previously [1], however, it is possible that nicardipine causes global vasodilation of the respiratory muscles. Although $\dot{Q}t$ increased with nicardipine, this was not necessarily indicative of an increase in diaphragmatic blood flow. Therefore, the direct measurement of blood flow to the diaphragm during nicardipine administration would be useful.

The present results also show that the speed of recovery from fatigue of the diaphragm was delayed in a dose-dependent manner. In groups N_1 and N_2, the contractility of the fatigued diaphragm had not significantly improved 30 min after the cessation of nicardipine administration. These results suggest that an infusion of this agent has a potent effect on the recovery from diaphragmatic fatigue.

In conclusion, our results suggest that nicardipine dose-dependently reduces the contractility of fatigued diaphragms, and that this agent may also have an adverse effect on a fatigued diaphragm even after the cessation of administration.

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