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Nicardipine inhibits amrinone-enhanced contractility in fatigued diaphragm

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Abstract: The purpose of this study was to examine the effect of amrinone, a bipyridine derivative, with and without nicardipine, a calcium channel blocker, on the contractility of fatigued diaphragm in dogs. Twenty dogs were divided into two groups of ten each: amrinone group (group A) and combined amrinone and nicardipine group (group AN). Diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation at a frequency of 20 Hz applied for 30 min. Diaphragmatic contractility was assessed from changes in transdiaphragmatic pressure (P_{di}). In group A, after producing fatigue, amrinone (0.75 mg·kg^{-1} loading dose plus 10 μg·kg^{-1}·min^{-1} maintenance dose) was administered iv. In group AN, nicardipine 5 μg·kg^{-1}·min^{-1} was infused iv simultaneously with amrinone during this period. After diaphragmatic fatigue, P_{di} at low-frequency (10–30 Hz) stimulation decreased compared with the prefatigue values ($P < 0.05$), whereas no change in P_{di} was observed at high-frequency (50–100 Hz) stimulation. The P_{di} at each stimulus were increased compared with the fatigued values ($P < 0.05$) by administering amrinone, and returned to these values after this agent was discontinued. The P_{di} values at any frequency of stimulation did not change when amrinone was administered with nicardipine. Our results suggest that amrinone may enhance contractility in fatigued diaphragm via its effect on transmembrane calcium movement.

Key words: Diaphragmatic fatigue, Amrinone, Nicardipine

Introduction

Amrinone, a bipyridine derivative, has been known to have both inotropic and vasodilator actions and to improve hemodynamics in patients with congestive heart failure [1]. Recently, we demonstrated that amrinone improves the contractility of fatigued diaphragm in dogs [2], but the exact mechanism of this inotropic action is not known. Aubier et al. [3] have demonstrated that potentiation of diaphragmatic contractility by aminophylline is abolished with a continuous infusion of verapamil. We have also shown that enhancement of diaphragmatic contractility by dobutamine is abolished by the simultaneous infusion of nicardipine [4]. Thus, calcium channel blockers such as verapamil and nicardipine inhibit the beneficial effects of these pharmacological agents on diaphragmatic contractility. The purpose of this study was to clarify the mechanism responsible for amrinone increasing the contractility of fatigued diaphragm. We hypothesized that the contractile response to this agent would be abolished in the presence of a calcium channel blocker (e.g., nicardipine). If so, the positive inotropic effect of this agent on diaphragmatic contractility would be attributed to an alteration in calcium metabolism.

Materials and methods

Approval for the study was obtained from the Institutional Animal Care and Use Committee of Tokyo Medical and Dental University School of Medicine. Twenty healthy mongrel dogs wighing between 10 and 15 kg were used. Animal preparation for the study was similar to that described previously [2]. Briefly, anesthesia was maintained with pentobarbital 2 mg·kg^{-1}·h iv. No muscle relaxant was used. The animal's trachea was intubated with a cuffed tracheal tube, and ventilation was controlled with a mixture of oxygen and air (FiO_2 = 0.4) to maintain over 100 torr of arterial O_2 tension (Pao_2), 35–40 torr of arterial CO_2 tension ($Paco_2$), and a pH of 7.35–7.45. A Swan-Ganz catheter was advanced via the right external jugular vein into the pulmonary artery to measure cardiac output by the thermodilution technique. Transdiaphragmatic pressure (P_{di}) was mea-

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sured by means of two thin-walled latex balloons; one positioned in the stomach, the other in the middle third of the esophagus. The balloons were connected to a differential pressure transducer (Pressure Head, Tokyo Keiki, Japan) and amplifier (Type 1212, Nihondenki San-ei, Tokyo, Japan). The phrenic nerves were exposed bilaterally at the neck, and the stimulating electrodes were placed around them. Supramaximal electrical test stimuli of 0.1-ms duration were applied for 2s at frequencies of 10, 20, 30, 50, and 100Hz with an electrical stimulator (Electronic Stimulator 3F37, Nihondenki San-ei). Diaphragmatic contractility was evaluated by measuring the maximal P_{di} after airway occlusion at functional residual capacity (FRC). The electrical activity of the diaphragm was measured with needle electrodes inserted percutaneously into the upper abdominal area, and was rectified with a permeable integrator (Type 1310, Nihondenki San-ei) with a time constant of 0.1s. This was regarded as the integrated electrical activity of the diaphragm (E_{di}).

The dogs were randomly divided into two groups: an amrinone group (group A, $n = 10$) and a combined amrinone and nicardipine group (group AN, $n = 10$). After measuring the prefatigue values of P_{di}, E_{di}, and hemodynamic variables which included heart rate (HR), mean arterial pressure (MAP), right atrial pressure (RAP), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and cardiac output (Qt), diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation applied for 30min at a frequency of 20Hz (low-frequency fatigue), with a complete cycle of 4s and a duty cycle of 0.5 [5]. In group A, amrinone (0.75mg·kg^{-1} loading dose plus 10μg·kg^{-1}·min^{-1} maintenance dose) iv [2] was administered continuously with an electrical infusion pump (Terumo, Tokyo, Japan) for 30min after 30min of fatigue-producing stimulation. At 30min after the onset of amrinone infusion and 60min after the cessation of amrinone administration, P_{di}, E_{di}, and hemodynamic variables were measured, and Qt was evaluated by the thermodilution method. In group AN, nicardipine 5μg·kg^{-1}·min^{-1} iv [4] was infused continuously during amrinone administration after diaphragmatic fatigue, and the same measurements were performed in group AN as those in group A.

All values were expressed as mean ± SD. Statistical analysis consisted of analysis of variance (ANOVA) for repeated measurements, and Duncan's multiple comparison was used for determining different mean values. Subsequent intergroup comparisons were made with Student's *t*-test. A P value of <0.05 was considered significant.

Results

The hemodynamic results in the two groups are summarized in Table 1. There were no differences in hemodynamic variables (baseline) during the prefatigue period between the two groups. With an infusion of either amrinone (group A) or combined amrinone and nicardipine (group AN), increases in HR and Qt ($P < 0.05$), and decreases in MAP, MPAP, and PCWP ($P < 0.05$) were observed compared with the prefatigue values.

Table 1. Hemodynamic data and changes

Variables	Group	Prefatigue	Fatigue	Amrinone: Amrinone + nicardipine	Post-amrinone (group A): Post-amrinone + nicardipine (group AN)
HR (bpm)	A	144 ± 10	145 ± 10	150 ± 9[a,b]	142 ± 14
	AN	143 ± 12	142 ± 14	152 ± 10[a,b]	143 ± 12
MAP (mmHg)	A	120 ± 12	119 ± 12	106 ± 8[a,b]	117 ± 8
	AN	119 ± 10	119 ± 13	94 ± 8[a,b,c]	119 ± 12
RAP (mmHg)	A	5 ± 2	5 ± 2	5 ± 2	5 ± 2
	AN	5 ± 1	5 ± 2	5 ± 1	5 ± 2
MPAP (mmHg)	A	12 ± 2	12 ± 1	10 ± 2[a,b]	12 ± 2
	AN	12 ± 1	12 ± 2	10 ± 2[a,b]	12 ± 2
PCWP (mmHg)	A	8 ± 2	8 ± 2	6 ± 2[a,b]	8 ± 2
	AN	8 ± 1	8 ± 2	6 ± 2[a,b]	8 ± 2
Qt (l·min^{-1})	A	2.4 ± 0.7	2.2 ± 0.6	2.8 ± 0.8[a,b]	2.2 ± 0.6
	N	2.3 ± 0.9	2.3 ± 0.9	3.0 ± 0.9[a,b]	2.4 ± 0.9

HR, heart rate; MAP, mean arterial pressure; RAP, right atrial pressure; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; Qt, cardiac output; A, amrinone; AN, amrinone + nicardipine.
[a] $P < 0.05$ *vs* Prefatigue.
[b] $P < 0.05$ *vs* Fatigue.
[c] $P < 0.05$ group A *vs* group AN.
All values are expressed as mean ± SD.

Table 2. Changes in P_{di} (cmH_2O) from prefatigue values

Frequency	Group	Prefatigue	Fatigue	Amrinone: Amrinone + nicardipine	Post-amrinone (group A): Post-amrinone + nicardipine (group AN)
10 Hz	A	10.5 ± 1.6	7.8 ± 1.3[a]	11.4 ± 1.6[a,b]	7.8 ± 1.0[a]
	AN	10.4 ± 1.6	7.6 ± 1.4[a]	7.8 ± 1.5[a,c]	7.6 ± 1.5[a]
20 Hz	A	15.5 ± 3.0	11.6 ± 2.3[a]	17.0 ± 2.9[a,b]	11.7 ± 1.9[a]
	AN	15.3 ± 2.1	11.4 ± 1.8[a]	11.7 ± 1.7[a,c]	11.7 ± 1.6[a]
30 Hz	A	17.1 ± 3.3	14.6 ± 2.5[a]	18.6 ± 3.5[a,b]	14.4 ± 3.2[a]
	AN	17.1 ± 2.1	14.2 ± 1.9[a]	14.1 ± 1.9[a,c]	14.4 ± 2.0[a]
50 Hz	A	20.2 ± 2.7	19.8 ± 2.9	21.6 ± 2.1[a,b]	19.8 ± 2.8[a]
	AN	20.2 ± 2.8	19.8 ± 2.8	19.7 ± 2.9[c]	19.8 ± 2.5[a]
100 Hz	A	20.6 ± 2.6	20.4 ± 2.3	21.9 ± 2.5[a,b]	20.4 ± 2.6[a]
	AN	20.5 ± 2.8	20.2 ± 3.1	20.2 ± 3.2[c]	20.2 ± 3.1[a]

P_{di}, transdiaphragmatic pressure; A, amrinone; AN, amrinone + nicardipine.
[a] $P < 0.05$ *vs* Prefatigue.
[b] $P < 0.05$ *vs* Fatigue.
[c] $P < 0.05$ group A *vs* group AN.
All values are expressed as mean ± SD.

After the cessation of infusion, these values returned to the baseline values.

The P_{di} values (cmH_2O) at different stages are shown in Table 2. In both groups, after producing fatigue, P_{di} at low-frequency (10–30 Hz) stimuli decreased from the prefatigue values ($P < 0.05$), whereas P_{di} at high-frequency (50–100 Hz) stimuli did not change. In group A, P_{di} at each frequency stimulation increased compared with the fatigue values ($P < 0.05$) during amrinone infusion. After the cessation of infusion, P_{di} returned to the fatigue values. In group AN, after administering combined amrinone and nicardipine, no P_{di} values showed any change compared with the fatigue values ($P < 0.05$). No change in E_{di} was observed throughout the study in either group.

Discussion

The major findings of this study were as follows: (a) amrinone increased the contractility (as assessed by P_{di}) of fatigued diaphragm without any change in E_{di}, and (b) the positive inotropic effect of amrinone was abolished by a simultaneous administration of nicardipine.

Low-frequency fatigue is of particular clinical importance because the spontaneous, natural rate of phrenic nerve discharge is believed to lie mainly in the low-frequency range (5–30 Hz) [6]. We had therefore, previously studied the effect of amrinone, a type III phosphodiesterase inhibitor, on the diaphragmatic fatigue induced by 20-Hz stimulation (i.e., low-frequency fatigue). It has been demonstrated that this inotropic agent improves the contractility of fatigued diaphragm [2], but the precise mechanism of the improvement of contractility in fatigued diaphragm is not clear. In cardiac muscle, this agent is thought to augment cardiac contractility by selectively inhibiting type III phosphodiesterase and accumulating cyclic AMP intracellularly, which in turn induces the activation of calcium transport from the sarcoplasmic reticulum [7]. On the basis of our results showing that contractility of fatigued diaphragm in group AN was not augmented by administering amrinone with nicardipine, which enhanced diaphragmatic fatigue due to the inhibition of calcium release from the sarcoplasmic reticulum and calcium transport [8], we postulate that the enhancement of diaphragmatic contractility by amrinone administration may be closely related to the alteration of transmembrane calcium transport in fatigued diaphragm.

It is possible that an increase in blood flow to the diaphragm during amrinone administration may contribute to the improvement of contractility in fatigued diaphragm, because an increase in Qt may lead to augmentation in the diaphragmatic blood flow [9]. In this study, however, Qt increased with an infusion of combined amrinone and nicardipine without improvement of contractility in fatigued diaphragm. Improvement of such contractility after amrinone administration probably cannot be ascribed to an increase in diaphragmatic blood flow.

In conclusion, our results suggest that amrinone enhances the contractile properties of the diaphragm by altering the transmembrane movement of calcium, and that the calcium antagonist, nicardipine, inhibits the beneficial effect of this pharmacological agent on diaphragmatic function.

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