J Anesth (1995) 9:343–347

Journal of
Anesthesia

The dose–response relationship of amrinone in increasing the contractility of fatigued diaphragm in dogs

YOSHITAKA FUJII[1] and HIDENORI TOYOOKA[2]

[1] Department of Anesthesiology, Toride Kyodo General Hospital, 2-1-1 Hongo, Toride, Ibaraki, 302 Japan
[2] Department of Anesthesiology and Critical Care Medicine, Tokyo Medical and Dental University School of Medicine, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113 Japan

Abstract: We studied the dose-related effects of amrinone on the contractility of a fatigued diaphragm in 16 anesthetized, mechanically ventilated dogs. The animals were divided into two groups: the control group (Group C, $n = 8$) and the amrinone group (Group A, $n = 8$). Diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation at a frequency of 20 Hz applied for 30 min. The contractility of the diaphragm was assessed from changes in transdiaphragmatic pressure (P_{di}). After inducing fatigue, P_{di} at low-frequency (20 Hz) stimulation decreased significantly compared with the pre-fatigue values ($P < 0.05$), whereas no change was observed at high-frequency (100 Hz) stimulation. In Group A, after producing fatigue, P_{di} at 20 Hz stimulation increased significantly with a bolus injection (0.75 mg·kg^{-1}) followed by continuous infusion of amrinone (2.5, 5 and then 10 μg·kg^{-1}·min^{-1}) IV ($P < 0.05$). P_{di} at 100 Hz stimulation increased significantly with an administration of amrinone (10 μg·kg^{-1}·min^{-1}) IV ($P < 0.05$). There was a significant positive correlation between P_{di} at both stimuli and amrinone dose ($P < 0.01$). In Group C, the speed of recovery of P_{di} at 20 Hz stimulation was relatively slower. The integrated electric activity of the diaphragam (E_{di}) in each group did not change at any frequency of stimulation throughout the experiment. We conclude that amrinone exerts a dose-dependent enhancement of the contractility of a fatigued diaphragm in dogs.

Key words: Amrinone, Diaphragmatic fatigue, Transdiaphragmatic pressure

Introduction

Studies have shown that theophylline, β_2 agonists, digoxin, dopamine, and dobutamine may improve the contractility of a fatigued diaphragm [1–5]. Recently, we have also demonstrated that amrinone has a potent positive effect on the contraction of a fatigued diaphragm [6]. However, to our knowledge, the dose-related effects of amrinone on the strength of contraction in the fatigued diaphragm have not been reported. The purpose of the present study was to determine the dose-dependent effects of amrinone on experimentally induced diaphragmatic fatigue.

Address correspondence to: Y. Fujii
Received for publication on October 19, 1994; accepted on May 31, 1995

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 18 healthy mongrel dogs (10–15 kg) anesthetized with pentobarbital sodium and mechanically ventilated. Animal preparation was similar to that described previously [6].

Briefly, anesthesia was maintained with pentobarbital (2 mg·kg^{-1}·h^{-1} IV). No muscle relaxants were used. The animal's trachea was intubated, and ventilation was controlled with an oxygen-and-air gas mixture (FiO_2 = 0.3–0.4) 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 to measure 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. The balloons were connected to a differential pressure transducer (Pressure Head, Tokyo Keiki, Tokyo, Japan) and an 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 2 s at frequencies of 20 and 100 Hz with an electrical stimulator (Electronic Stimulator 3F37, Nihondenki

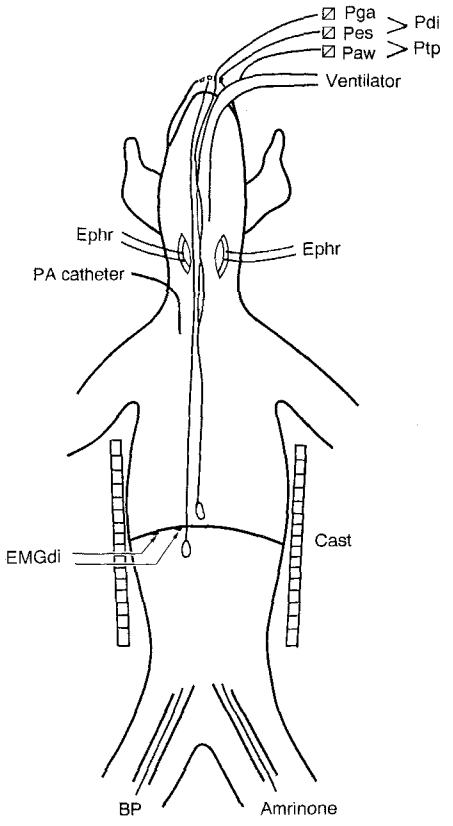

Fig. 1. Animal preparation. P_{ga}, gastric pressure; P_{es}, esophageal pressure; P_{aw}, airway pressure; P_{di}, transdiaphragmatic pressure; P_{tp}, transpulmonary pressure; E_{phr}, phrenic nerve stimulation; EMG_{di}, electrical activity of diaphragm; *PA*, pulmonary artery

San-ei). The contractility of the diaphragm was evaluated by measuring the maximal P_{di} generated by test stimuli after airway occlusion at functional residual capacity (FRC) level. The electrical activity of the diaphragm was measured with needle electrodes inserted percutaneously into the diaphragm from the upper abdominal area, and was rectified and integrated with a leaky integrator (Type 1310, Nihondenki San-ei) with a time constant of 0.1 s. This was regarded as the integrated electrical activity of the diaphragm (E_{di}). The experimental design is shown schematically in Fig. 1.

The dogs were randomly divided into two groups: the control group (Group C, $n = 8$) and the amrinone group (Group A, $n = 8$). After the pre-fatigue measurements of P_{di}, E_{di}, and hemodynamic variables which included heart rate (HR), mean arterial pressure (MAP), and cardiac output (Q_t), diaphragmatic fatigue was induced by intermittent supramaximal bilateral electrophrenic stimulation applied for 30 min at a frequency of 20 Hz, an entire cycle of 4 s and a duty cycle of 0.5 (i.e. low-frequency fatigue) [7]. In Group A, after producing fatigue, a bolus injection (0.75 mg·kg^{-1}) followed by continuous infusion of amrinone (2.5 μg·kg^{-1}·min^{-1}) IV were administered with an electrical infusion pump (Terumo, Tokyo, Japan) for 10 min. Then administration of 5 and then 10 μg·kg^{-1}·min^{-1} amrinone (in this order) IV for 10 min was performed. P_{di}, E_{di}, and hemodynamic parameters were measured every 10 min after the onset of amrinone infusion. In Group C, only maintenance fluid was administered, and the same measurements were performed as in Group A.

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 statistically significant. Paired P_{di}–amrinone dose determinations were fitted to both exponential and linear regression analyses to determine the best fit for the relationship. Because both analyses yielded almost identical correlation coefficients, linear regression analysis was used for comparisons.

Results

Hemodynamic results in both groups are summarized in Table 1. There were no significant differences between the two groups in hemodynamic parameters during the pre-fatigue period. In Group A, with an infusion of 5 and 10 μg·kg^{-1}·min^{-1} amrinone, significant increases in HR and Q_t ($P < 0.05$), and a significant decrease in MAP ($P < 0.05$) were observed compared with the pre-fatigue values. There were significant differences in these parameters between the two groups during amrinone (5 and 10 μg·kg^{-1}·min^{-1}) administration ($P < 0.05$).

All P_{di} values are shown in Table 2. No significant differences in P_{di} at either stimulus were observed during the pre-fatigue period. In each group, after producing fatigue, P_{di} at 20 Hz stimulation decreased significantly from the pre-fatigue values ($P < 0.05$), whereas P_{di} at 100 Hz stimulation did not change significantly. In Group A, P_{di} at 20 Hz stimulation increased significantly compared with the fatigued values during amrinone (2.5, 5 and 10 μg·kg^{-1}·min^{-1}) administration ($P < 0.05$). P_{di} at 100 Hz stimulation increased significantly with administration of amrinone (10 μg·kg^{-1}·min^{-1}) ($P < 0.05$). In Group C, the speed of recovery of P_{di} at 20 Hz stimulation was relatively slower.

There was a significant positive correlation between P_{di} at both stimuli and amrinone dose (Figs. 2 and 3), and the regression equations were: P_{di} at 20 Hz stimulation (cmH_2O) = 0.69 × amrinone (μg·kg^{-1}·min^{-1}) + 12.10 ($r = 0.65$, $n = 32$, $P < 0.01$); P_{di} at 100 Hz stimulation (cmH_2O) = 0.33 × amrinone (μg·kg^{-1}·min^{-1}) + 19.98 ($r = 0.50$, $n = 32$, $P < 0.01$).

No significant change in E_{di} was observed throughout the experiment in either group.

Table 1. Hemodynamic data and changes

Variable	Group	Pre-fatigue	Fatigued	Recovery time (Group C) or amrinone dose (Group A)		
				10 min 2.5 μg·kg^{-1}·min^{-1}	20 min 5 μg·kg^{-1}·min^{-1}	30 min 10 μg·kg^{-1}·min^{-1}
HR (bpm)	C	148 ± 7	148 ± 5	147 ± 8	147 ± 6	145 ± 8
	A	146 ± 9	146 ± 8	149 ± 9	155 ± 8[abc]	160 ± 7[abc]
MAP (mmHg)	C	123 ± 9	128 ± 7	124 ± 9	126 ± 8	126 ± 10
	A	125 ± 10	126 ± 9	120 ± 10	115 ± 9[abc]	108 ± 8[abc]
Q_t (l·min^{-1})	C	2.1 ± 0.4	2.1 ± 0.5	2.0 ± 0.5	2.1 ± 0.4	2.1 ± 0.5
	A	2.0 ± 0.3	2.0 ± 0.4	2.2 ± 0.3	2.5 ± 0.2[abc]	3.0 ± 0.5[abc]

All data are mean ± SD.
HR heart rate; MAP, mean arterial pressure; Q_t cardiac output; C, control; A, amrinone.
[a] $P < 0.05$ (*vs* pre-fatigue); [b] $P < 0.05$ (*vs* fatigued); [c] $P < 0.05$ (*vs* group C).

Table 2. Changes in P_{di} (cmH_2O) from pre-fatigue values

Frequency	Group	Pre-fatigue	Fatigued	Recovery time (Group C) or amrinone dose (Group A)		
				10 min 2.5 μg·kg^{-1}·min^{-1}	20 min 5 μg·kg^{-1}·min^{-1}	30 min 10 μg·kg^{-1}·min^{-1}
20 Hz	C	15.5 ± 2.8	12.0 ± 3.1[a]	11.9 ± 3.0[a]	12.0 ± 2.8[a]	11.9 ± 3.4[a]
	A	15.3 ± 3.0	11.9 ± 2.9[a]	14.3 ± 2.5[bc]	15.4 ± 3.1[bc]	19.0 ± 4.2[abc]
100 Hz	C	20.2 ± 2.7	19.9 ± 2.5	20.0 ± 2.3	20.1 ± 2.1	20.1 ± 2.3
	A	20.3 ± 2.3	19.9 ± 2.2	20.8 ± 2.3	21.6 ± 2.3	23.3 ± 2.3[abc]

All data are mean ± SD.
P_{di}, transdiaphragmatic pressure.
[a] $P < 0.05$ (*vs* pre-fatigue); [b] $P < 0.05$ (*vs* fatigued); [c] $P < 0.05$ (*vs* group C).

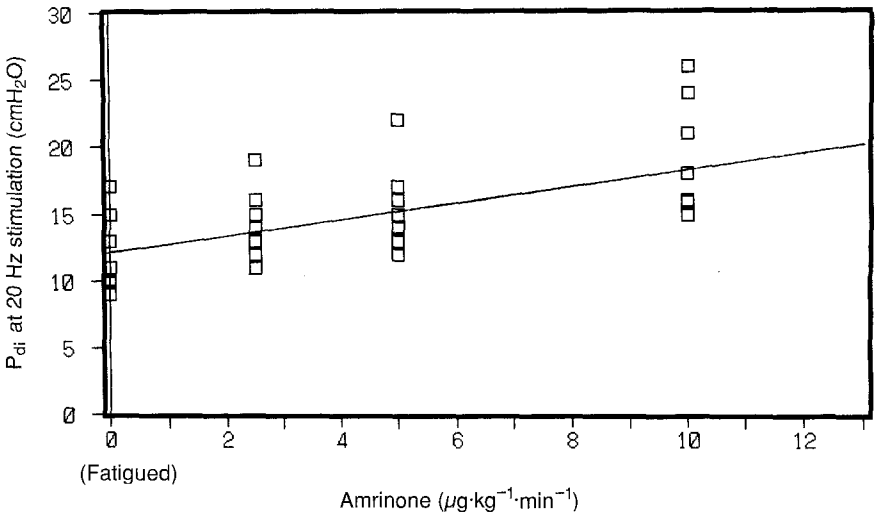

Fig. 2. P_{di} at 20 Hz stimulation varied with amrinone dose. P_{di}, transdiaphragmatic pressure. P_{di} (cmH_2O) = 0.69 × amrinone (μg·kg^{-1}·min^{-1}) + 12.10 (r = 0.65, n = 32, $P < 0.01$)

Discussion

The major finding of the present study was that administration of amrinone increased P_{di} of a fatigued diaphragm in a dose-dependent manner.

It is 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) [8]. Therefore, the effects of amrinone on contractility were examined in

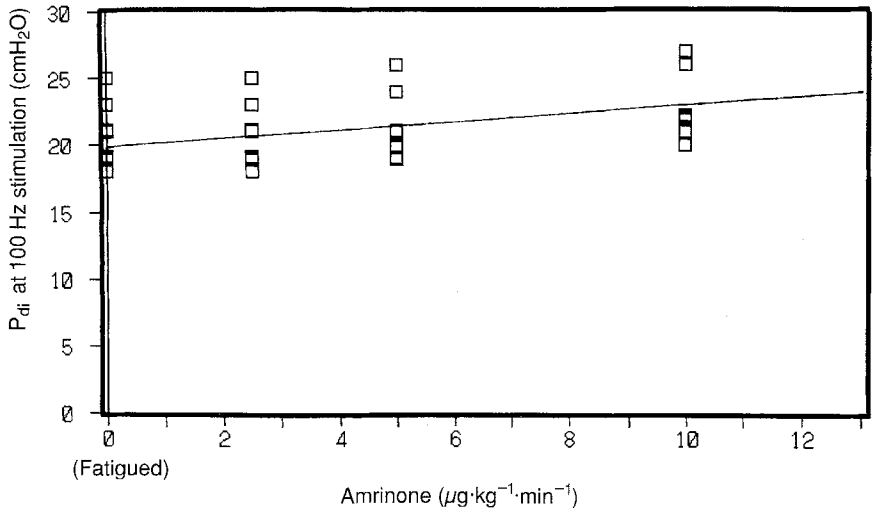

Fig. 3. P_{di} at 100 Hz stimulation varied with amrinone dose. P_{di}, transdiaphragmatic pressure. P_{di} (cmH_2O) = 0.33 × amrinone ($\mu g \cdot kg^{-1} \cdot min^{-1}$) + 19.98 ($r$ = 0.50, n = 32, $P < 0.01$)

the fatigued diaphragm experimentally induced by 20 Hz stimulation.

The results of the present study showed that P_{di} at 20 Hz stimulation decreased significantly after producing fatigue ($P < 0.05$), whereas P_{di} at 100 Hz stimulation and E_{di} at any frequency stimulation did not change in Group C, in which amrinone was not administered. This was in agreement with our previous study [6].

The results in Group A demonstrated that P_{di} at 20 Hz stimulation increased significantly compared with the fatigued values ($P < 0.05$) with an infusion of amrinone ($>2.5 \mu g \cdot kg^{-1} \cdot min^{-1}$), while P_{di} at 100 Hz stimulation increased significantly during $10 \mu g \cdot kg^{-1} \cdot min^{-1}$ amrinone administration ($P < 0.05$). Therefore, it is suggested that the high dose ($>10 \mu g \cdot kg^{-1} \cdot min^{-1}$) of amrinone increases the contractility of a fatigued diaphragm at both stimuli, but the low dose ($<10 \mu g \cdot kg^{-1} \cdot min^{-1}$) of this agent enhances fatigued diaphragmatic contraction only at 20 Hz stimulation. However, on the basis of our findings that a relationship between P_{di} at both stimuli and amrinone dose was significantly positively different ($P < 0.01$), amrinone may improve the contractility of a fatigued diaphragm in a dose-dependent manner.

Although the precise mechanism of improvement of the contractility in a fatigued diaphragm with an infusion of amrinone remains unclear, it has been suggested that this bipyridine derivative may have either a direct positive effect on diaphragmatic contractility, or an indirect effect on it through the increase in blood flow to the diaphragm [6].

Low-frequency fatigue is closely related to the impairment of excitation–contraction coupling [9]. This impairment is supposed to result from the alteration in movement of Ca^{2+} from the sacroplasmic reticulum [7]. It is possible that amrinone may improve the impediment of Ca^{2+} influx in the fatigued diaphragm [6]. Therefore, the significant difference in the contractility between the two groups during amrinone infusion ($P < 0.05$) may be related to the difference in the influx of Ca^{2+} caused by administering amrinone.

The increase in blood flow to the diaphragm is known to be one of the major factors in improvement of the contractility of a fatigued diaphragm [4]. In the present study, the diaphragmatic blood flow was not measured. However, our previous study showed that Q_t was an important factor in the regulation of blood flow to the diaphragm [10]. The increase in Q_t observed in the present study may have led to an increase in diaphragmatic blood flow with an infusion of amrinone. The present study demonstrated that Q_t increased significantly with an infusion of amrinone ($P < 0.05$), and Q_t in Group A was significantly larger than that in Group C ($P < 0.05$). Therefore, the significant difference in the strength of contraction between the two groups during amrinone infusion ($P < 0.05$) may also be attributable to the difference in Q_t which is related to diaphragmatic blood flow.

In conclusion, our results suggest that amrinone improves the contractility of a fatigued diaphragm, and this agent exerts a dose-dependent enhancement of its strength of contraction.

Acknowledgments. The authors are very grateful to Prof. K. Amaha for his valuable comments, and to Mr. K. Yokoyama for his expert technical assistance.

References

1. Murciano D, Aubier M, Lecocguic Y, Pariente R (1984) Effects of theophylline on diaphragmatic strength and fatigue in patients with chronic obstructive pulmonary disease. N Engl J Med 311:349–353

2. Howell S, Roussos C (1987) Isoproterenol and aminophylline improve contractility of fatigued canine diaphragm. Am Rev Respir Dis 129:118–124
3. Aubier M, Murciano D, Viires N, Lebargy F, Curran Y, Seta J-P, Pariente R (1987) Effects of digoxin on diaphragmatic strength generation in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am Rev Respir Dis 135:544–548
4. Aubier M, Murciano D, Menu Y, Boczkowski, Boczkowski J, Mal H, Pariente R (1989) Dopamine effects on diaphragmatic strength during acute respiratory failure in chronic obstructive pulmonary disease. Ann Intern Med 110:17–23
5. Fujii Y, Toyooka H, Ebata T, Amaha K (1993) Contractility of fatigued diaphragm is improved by dobutamine. Can J Anaesth 40:453–458
6. Fujii Y, Toyooka H, Amaha K (1995) Amrinone improves contractility of fatigued diaphragm in dogs. Can J Anaesth 42: 80–86
7. Aubier M, Farkas G, DeTroyer A, Mozes R, Roussos C (1981) Detection of diaphragmatic fatigue in man by phrenic nerve stimulation. J Appl Physiol 50:538–544
8. Roussos C, Macklem PT (1982) The respiratory muscles. N Engl J Med 307:786–797
9. Moxham J, Wiles CM, Newham D, Edwards RHT (1981) Contractile function and fatigue of the respiratory muscles in man. In: Human muscle fatigue: Physiological mechanics. Ciba Foundation Symposium, London. Pitman Medical 82:197–205
10. Fujii Y, Toyooka H, Amaha K (1991) Diaphragmatic fatigue and its recovery are influenced by cardiac output. J Anesth 5:17–23