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Dobutamine increases contractility of fatigued diaphragm in dogs: the relationship between dose and diaphragmatic contractility

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Abstract: The dose-related effects of dobutamine (DOB) on the contractility of fatigued diaphragm were studied in 16 anesthetized, mechanically ventilated dogs. The animals were divided into two groups of eight: the control (group C) and the DOB (group D). Diaphragmatic fatigue was induced by intermittent supramaximal electrophrenic stimulation at a frequency of 20 Hz applied for 30 min. Diaphragmatic contractility was assessed from changes in transdiaphragmatic pressure (P_{di}). After the induction of diaphragmatic fatigue, P_{di} at low-frequency (20-Hz) stimulation decreased significantly compared with the prefatigue values ($P < 0.05$), whereas no change in P_{di} was observed at high-frequency (100-Hz) stimulation. In group D, after producing fatigue, P_{di} at 20-Hz stimulation increased significantly with a continuous infusion of DOB (5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) i.v. ($P < 0.05$). The P_{di} at 100-Hz stimulation increased significantly with administration of DOB 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ i.v. ($P < 0.05$). There was a significant correlation between dose of DOB and P_{di} at both stimuli ($P < 0.05$). In group C, the speed of P_{di} recovery at 20-Hz stimulation was relatively slower. The integrated diaphragmatic electric activity (E_{di}) in each group did not change at any frequency of stimulation throughout the study. It is concluded that DOB increases the contractility of fatigued diaphragm in a dose-dependent manner.

Key words: Dobutamine, Diaphragmatic fatigue, Transdiaphragmatic pressure

Introduction

Several studies have demonstrated that methylxanthine compounds, β_2-sympathomimetics, digoxin, dopamine, and amrinone may improve the contractility of fatigued diaphragm [1–5]. Recently, we have also shown that dobutamine (DOB) has a potent positive effect on the strength of contraction in fatigued diaphragm [6]. However, to our knowledge, the dose-related effects of DOB on fatigued diaphragm have not been reported. Therefore, the present study was performed to determine the relationship between dose of DOB and contractility in experimentally fatigued diaphragm.

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Materials and methods

Institutional approval for the study was obtained from the Animal Care and Use Committee of the Tokyo Medical and Dental University School of Medicine. We studied 16 healthy mongrel dogs (10–15 kg) anesthetized with pentobarbital and mechanically ventilated. Animal preparation was similar to that described previously [6].

Briefly, anesthesia was maintained with pentobarbital 2 $mg \cdot kg^{-1} \cdot h^{-1}$ i.v. No muscle relaxants were used. The animal's trachea was intubated, and ventilation was controlled with a mixture of oxygen and air ($Fio_2 = 0.4$) to maintain Pao_2, $Paco_2$, and pH within normal ranges. A pulmonary catheter was advanced via the right external jugular vein into the pulmonary artery for the measurement of 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 and 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, Nihondenki San-ei, Tokyo, Japan). Transpulmonary pressure (P_{tp}), the difference between airway and esophageal pressures, was kept constant to maintain the same lung volume before phrenic nerve stimulation. 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 and 100 Hz

with an electrical stimulator (Electric Stimulator 3F37, Nihondenki San-ei). Diaphragmatic contractility was evaluated by measuring the maximal P_{di} generated by test stimuli after airway occlusion at the functional residual capacity (FRC) level. The geometry and muscle fiber length of the diaphragm during contractions were kept constant by placing a plaster cast around the abdomen and the rib cage. 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 permeable integrator (Type 1310, Nihondenki 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 two groups: the control group (group C, $n = 8$) and the DOB group (group D, $n = 8$). After prefatigue measurements of P_{di}, E_{di}, and hemodynamic variables 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, for an entire cycle of 4 s and a duty cycle of 0.5 (i.e., low-frequency fatigue) [7]. In group D, after producing fatigue, continuous administration of DOB was started at 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ i.v. for 10 min with an electrical infusion pump (Terumo, Tokyo, Japan). The dose of DOB was increased stepwise to 5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ i.v. in this order, and an infusion of DOB was performed for 10 min for each dose. At every 10 min after the start of DOB administration, P_{di}, E_{di}, and the above-mentioned hemodynamic variables were measured. In group C, nothing but maintenance fluid (10 $ml \cdot kg^{-1} \cdot h^{-1}$ i.v. of Ringer's lactate solution) was administered, and the same measurements were performed as those in group D.

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

Results

The hemodynamic results in each group are summarized in Table 1. There were no differences between the two groups in hemodynamic variables during the prefatigue period. In group D, with an infusion of DOB ($\geqq$2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ i.v.), significant increases in HR, MAP, and $\dot{Q}t$ were observed compared with the prefatigue values ($P < 0.05$). There were significant differences in these variables between the two groups during DOB administration ($\geqq$2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ i.v.) ($P < 0.05$).

All P_{di} values (cmH_2O) are shown in Table 2. No significant differences in P_{di} at both stimuli were observed during the prefatigue period. In each group, after 30 min of fatigue-producing stimulation, P_{di} at 20-Hz stimulation decreased from the prefatigue values ($P < 0.05$), whereas P_{di} at 100-Hz stimulation did not show any change. In group D, P_{di} at 20-Hz stimulation increased significantly compared with the fatigued values with an infusion of DOB (5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ i.v.) ($P < 0.05$). The P_{di} at 100-Hz stimulation increased significantly with administration of DOB (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ i.v.) ($P < 0.05$). In group C, the speed of recovery of P_{di} at 20-Hz stimulation was relatively slower.

There was a significant correlation between dose of DOB and P_{di} at both stimuli (Figs. 2, 3), and the regres-

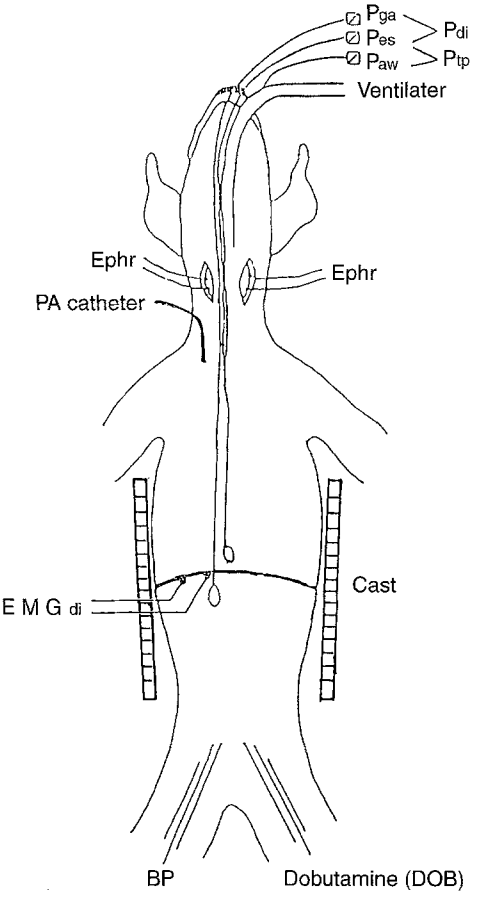

Fig. 1. Animal preparation. P_{ga}, gastric pressure; P_{es}, esophageal pressure; P_{aw}, airway pressure; P_{di}, transdiaphragmatic pressure; P_{tp}, transpulmonary pressure; E_{phr}, phrenic nerve stimulation; EMG_{di}, electrical activity of diaphragm; *PA*, pulmonary artery

Table 1. Hemodynamic changes

Variable	Group	Prefatigue	Fatigued	Recovery 10 min DOB 2 μg·kg^{-1}	20 min 5 μg·kg^{-1}	30 min (Group C) 10 μg·kg^{-1} (Group D)
HR (bpm)	C	138 ± 4	136 ± 7	137 ± 6	136 ± 8	137 ± 5
	D	137 ± 7	136 ± 2	152 ± 6[a,b,c]	168 ± [a,b,c]	182 ± 8[a,b,c]
MAP (mmHg)	C	108 ± 9	108 ± 9	107 ± 9	109 ± 8	107 ± 10
	D	106 ± 10	106 ± 6	116 ± 4[a,b,c]	124 ± 3[a,b,c]	134 ± 4[a,b,c]
$\dot{Q}t$ (l·min^{-1})	C	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.1	2.0 ± 0.1	2.0 ± 0.2
	D	2.0 ± 0.2	2.0 ± 0.3	2.4 ± 0.3[a,b,c]	2.9 ± 0.3[a,b,c]	4.0 ± 0.4[a,b,c]

HR, heart rate; MAP, mean arterial pressure; $\dot{Q}t$, cardiac output; C, control; D, dobutamine; DOB, dobutamine.
[a] $P < 0.05$ *vs* prefatigue.
[b] $P < 0.05$ *vs* fatigued.
[c] $P < 0.05$ *vs* group C.
All values are expressed as mean ± SD.

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

Frequency	Group	Prefatigue	Fatigued	Recovery 10 min DOB 2 μg·kg^{-1}	20 min 5 μg·kg^{-1}	30 min (Group C) 10 μg·kg^{-1} (Group D)
20 Hz	C	15.8 ± 3.8	11.5 ± 3.1[a]	11.4 ± 3.0[a]	11.5 ± 3.8[a]	11.4 ± 3.4[a]
	D	15.9 ± 3.9	11.6 ± 3.2[a]	13.8 ± 3.3	16.9 ± 3.7[b,c]	18.6 ± 3.7[b,c]
100 Hz	C	21.2 ± 3.0	20.7 ± 2.7	20.9 ± 2.5	20.8 ± 3.1	20.9 ± 3.3
	D	21.4 ± 3.1	20.8 ± 3.3	21.6 ± 3.5	22.9 ± 3.6	24.3 ± 3.2[b,c]

P_{di}, transdiaphragmatic pressure; C, control; D, dobutamine; DOB, dobutamine.
[a] $P < 0.05$ *vs* prefatigue.
[b] $P < 0.05$ *vs* fatigued.
[c] $P < 0.05$ *vs* group C.
All values are expressed as mean ± SD.

sion equations were: P_{di} at 20-Hz stimulation (cmH_2O) = 0.62 × DOB(μg·kg^{-1}·min^{-1}) + 12.27 (r = 0.617, n = 32, P = 0.002) and P_{di} at 100-Hz stimulation (cmH_2O) = 0.38 × DOB(μg·kg^{-1}·min^{-1}) + 20.89 (r = 0.381, n = 32, P = 0.032).

No changes in E_{di} were observed throughout the study in either group.

Discussion

The major findings of the present study were as follows: (a) administration of DOB increased the contractility (as assessed by P_{di}) of fatigued diaphragm without any change in E_{di}, and (b) the increase in strength of contraction was dose-dependently related to DOB.

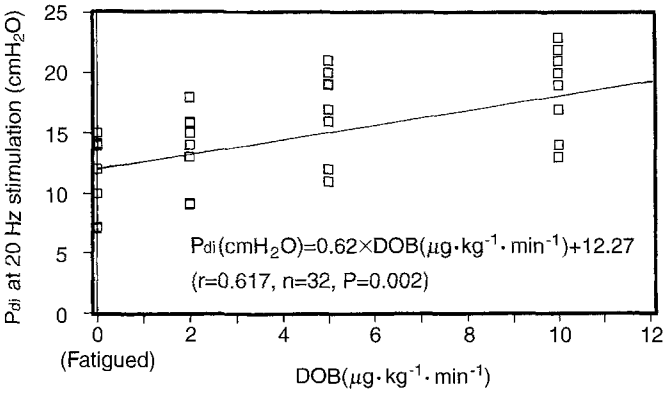

Fig. 2. Relationship between dose of dobutamine (*DOB*) and P_{di} at 20 Hz stimulation. P_{di}, transdiaphragmatic pressure. $P_{di}(cmH_2O)$ = 0.62 × DOB(μg·kg^{-1}·min^{-1}) + 12.27 (r = 0.617, n = 32, P = 0.002)

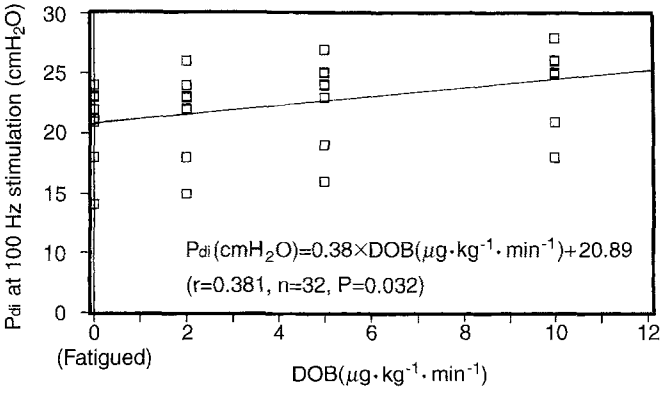

Fig. 3. Relationship between dose of DOB and P_{di} at 100 Hz stimulation. P_{di}, transdiaphragmatic pressure. $P_{di}(cmH_2O)$ = 0.38 × DOB(μg·kg^{-1}·min^{-1}) + 20.89 (r = 0.381, n = 32, P = 0.032)

It is well documented 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 ranges (5–30 Hz) [8]. Therefore, the effect of DOB on contractility was assessed in fatigued diaphragm experimentally induced by low-frequency (20-Hz) stimulation (i.e., low-frequency fatigue).

The results of the present study showed that P_{di} at 20-Hz stimulation decreased after producing fatigue, whereas P_{di} at 100-Hz stimulation and E_{di} at any frequency stimulation did not show any change in group C, in which no DOB was administered. These results were in accordance with our previous study [6].

Our results in group D demonstrated that P_{di} at 20-Hz stimulation increased significantly compared with the fatigued values ($P < 0.05$) with an infusion of DOB (5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ i.v.), while P_{di} at 100-Hz stimulation increased significantly with administration of DOB 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ i.v. ($P < 0.05$). There was a significant correlation between dose of DOB and P_{di} at both stimuli ($P < 0.05$) in the present study. Therefore, it is suggested that DOB increases the contractility of fatigued diaphragm in a dose-dependent manner.

Although the precise mechanism of enhancement of the contractility of fatigued diaphragm after administration of DOB remains unclear, it has been suggested that this sympathomimetic amine may have a direct positive effect on diaphragmatic contractility [6]. It has been demonstrated that low-frequency fatigue is closely related to the impairment of excitation-contraction coupling [9]. This impairment is thought to be the result of changes in the movement of Ca^{2+} from the sarcoplasmic reticulum [7]. As previously demonstrated, it was possible that administration of DOB improved the impediment of Ca^{2+} influx in fatigued diaphragm [6].

It has been proposed that the increase in diaphragmatic blood flow occurring with infusion of DOB may lead to an augmentation of contraction strength in fatigued diaphragm [6]. This may be attributed to the fact that diaphragmatic contractility depends on its energy supply, which in turn is dependent on blood flow [10], and that diaphragmatic blood flow changes in accordance with $\dot{Q}t$ [11]. The present study demonstrated that $\dot{Q}t$ increased significantly with infusion of DOB ($P < 0.05$) and that $\dot{Q}t$ in group D was significantly larger than that in group C ($P < 0.05$). It also showed that P_{di} at both stimuli in group D with an infusion of DOB 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ i.v. was larger compared with those in group C ($P < 0.05$). Therefore, the dose-related effects of DOB on $\dot{Q}t$ may partly explain the dose-related increase of contractility in fatigued diaphragm.

In conclusion, our results suggest that the contractility of fatigued diaphragm is improved by administering DOB, and that this sympathomimetic amine has a dose-related effect on its strength of contraction.

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