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Effects of dobutamine on the fatigued diaphragm: A comparison with dopamine

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Abstract: We examined the effects of dopamine (DOA) 10 μg·kg^{-1}·min^{-1} I.V. and dobutamine (DOB) 10 μg·kg^{-1}·min^{-1} I.V. on the contractility of the fatigued diaphragm in 26 anesthetized, mechanically ventilated dogs. Animals were divided into two groups of 13 each: the DOA and DOB groups. 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}). After diaphragmatic fatigue, P_{di} at low-frequency (20 Hz) stimulation decreased significantly compared with the prefatigue value ($P < 0.05$), whereas no change in P_{di} was observed at high-frequency (100 Hz) stimulation. In the fatigued diaphragm, P_{di} at both stimuli increased with an infusion of either DOA ($P < 0.05$) or DOB ($P < 0.05$). The increase of P_{di} at 20 Hz stimulation was significantly larger in the DOB group compared with that of the DOA group ($P < 0.05$). In each group, P_{di} at both stimuli decreased after the cessation of administration. The integrated diaphragmatic electric activity (E_{di}) in the two groups did not change at any frequency of stimulation throughout the study. We conclude that DOB in comparison with DOA is more effective in improving the contractility of the fatigued diaphragm.

Key words: Diaphragmatic fatigue, Transdiaphragmatic pressure, Dopamine, Dobutamine

Introduction

Recently, Aubier et al. have demonstrated that diaphragmatic contractility in patients with chronic obstructive pulmonary disease is augmented by administering dopamine (DOA) [1]. We showed previously that dobutamine (DOB) has a potent positive effect on the contractility of the fatigued diaphragm in dogs [2]. However, to our knowledge, the effects of DOB in comparison with DOA on the contractility of the fatigued diaphragm have not been reported. The purpose of the present study was to compare the effects of DOA and DOB on the contractility of the fatigued diaphragm.

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Materials and methods

Institutional approval for the experiment was obtained from the Animal Care and Use Committee of Tokyo Medical and Dental University School of Medicine. We studied 26 healthy mongrel dogs (10–15 kg) anesthetized with pentobarbital sodium and mechanically ventilated. Animal preparation was similar to that described previously [2].

Briefly, anesthesia was maintained with pentobarbital sodium 2 mg·kg^{-1}·hr^{-1} I.V. No muscle relaxants were used. Ventilation was controlled with an oxygen and air gas mixture ($F_IO_2 = 0.3–0.4$) 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 for cardiac output measurement 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, Nihondenki 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 and 100 Hz with an electrical stimulator (Electronic Stimulator 3F37, Nihondenki San-ei). Diaphragmatic contractility was evaluated by measuring the maximal P_{di} generated by test stimuli after airway occlusion at

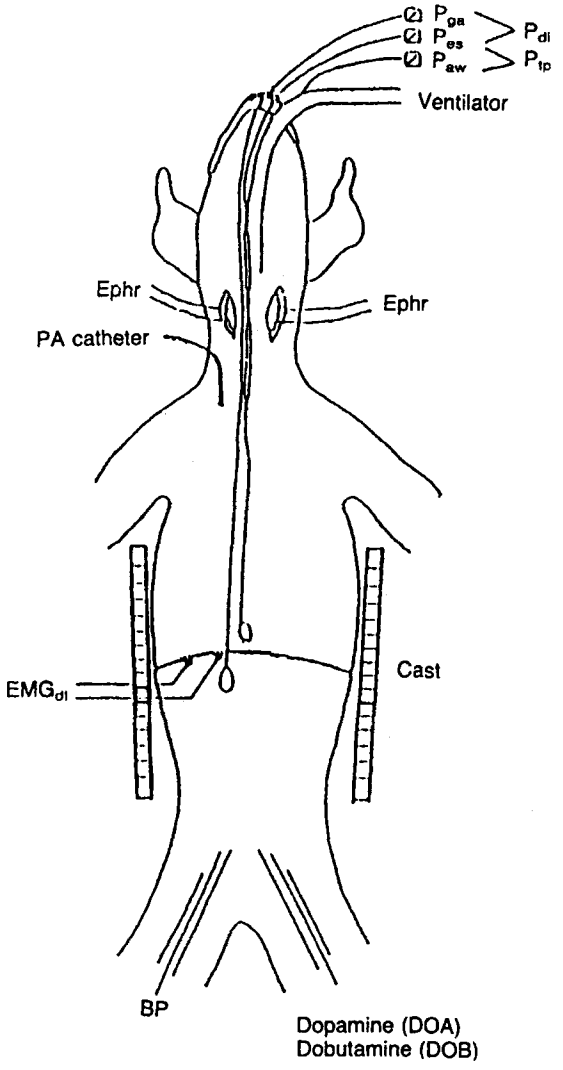

Fig. 1. Animal preparation. P_{ga}, gastric pressure; P_{es}, esophageal pressure; P_{aw}, airway pressure; P_{di}, transdiaphragmatic pressure; P_{tp}, transpulmonary pressure; E_{phr}, phrenic nerve stimulation; EMG_{di}, electrical activity of diaphragm; *PA*, pulmonary artery

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 diaphragmatic electrical activity (E_{di}). The experimental design is schematically shown in Fig. 1.

The dogs were divided into two groups of 13 each: the DOA and DOB groups. After prefatigue measurements of P_{di}, E_{di}, and hemodynamics 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 ($\dot{Q}t$), diaphragmatic fatigue (low-frequency 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 [3]. In the DOA group, DOA 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ I.V. was administered continuously with an electrical infusion pump (Terumo, Tokyo Japan) for 30 min after producing fatigue. Similarly, in the DOB group, DOB 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ I.V. was infused continuously after diaphragmatic fatigue. At 60 min after administration (30 min after the cessation of infusion), P_{di}, E_{di}, and hemodynamics were measured.

All values were expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way analysis of variance and Student's *t*-test, with a probability of less than 0.05 considered statistically significant.

Results

Hemodynamic results in the two groups are summarized in Table 1. There were no differences between the two groups in hemodynamic parameters during the prefatigue period. With an infusion of either DOA or DOB, HR, MAP, and $\dot{Q}t$ increased significantly compared with prefatigue values ($P < 0.05$). After cessation of administration, these values returned to prefatigue values.

All P_{di} values are shown in Table 2 as percentages of P_{di} obtained at each frequency stimulation during the prefatigue period. In both groups, after producing fatigue, P_{di} at 20 Hz stimulation decreased significantly from prefatigue values ($P < 0.05$), whereas P_{di} at 100 Hz stimulation did not show any significant change. In the DOA group, P_{di} at both stimuli increased significantly with DOA infusion in comparison with fatigue values ($P < 0.05$). In the DOB group, DOB administration also produced a significant increase in P_{di} at both stimuli compared with fatigue values. The increase of P_{di} at 20 Hz stimulation in the DOB group was significantly larger compared with that of DOA group ($P < 0.05$). In both groups, P_{di} at both stimuli decreased after the cessation of administration, although the change was not statistically significant.

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

Discussion

The major findings of the present study were as follows: (1) administration of either DOA or DOB significantly increased P_{di} of the fatigued diaphragm ($P < 0.05$), and

Table 1. Hemodynamic data and changes

Variable	Group	Prefatigue	Fatigue	During DOA/DOB administration	Post-DOA/DOB administration
HR	DOA	143 ± 17	144 ± 18	189 ± 15[a,b]	142 ± 15
(bpm)	DOB	148 ± 18	151 ± 16	186 ± 17[a,b]	149 ± 20
MAP	DOA	106 ± 19	104 ± 19	130 ± 20[a,b]	105 ± 18
(mmHg)	DOB	110 ± 17	111 ± 16	127 ± 12[a,b]	113 ± 19
RAP	DOA	5 ± 1	5 ± 1	5 ± 1	5 ± 1
(mmHg)	DOB	5 ± 1	5 ± 1	5 ± 2	5 ± 1
MPAP	DOA	12 ± 3	12 ± 2	13 ± 3	12 ± 3
(mmHg)	DOB	12 ± 3	12 ± 3	13 ± 3	12 ± 3
PCWP	DOA	8 ± 2	8 ± 2	8 ± 2	8 ± 2
(mmHg)	DOB	8 ± 1	8 ± 2	8 ± 1	8 ± 1
$\dot{Q}t$	DOA	1.7 ± 0.4	1.7 ± 0.4	2.2 ± 0.6[a,b]	1.7 ± 0.4
($l \cdot min^{-1}$)	DOB	1.7 ± 0.4	1.7 ± 0.3	2.7 ± 0.5[a,b,c]	1.7 ± 0.3

All values are expressed as mean ± SD. DOA, dopamine; DOB, dobutamine; HR, heart rate; MAP, mean arterial pressure; RAP, right arterial pressure; MPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; $\dot{Q}t$, cardiac output.
[a] $P < 0.05$ (*s* prefatigue); [b] $P < 0.05$ (*s* fatigue); [c] $P < 0.05$ (DOA *s* DOB group).

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

Frequency	Group	Prefatigue	Fatigue	During DOA/DOB administration	Post-DOA/DOB administration
20 Hz	DOA	100.0 ± 0.0	74.1 ± 3.9[a]	100.1 ± 6.9[b]	94.2 ± 3.7[a,b]
	DOB	100.0 ± 0.0	75.7 ± 3.8[a]	114.7 ± 5.5[a,b,c]	97.0 ± 4.2[a,b]
100 Hz	DOA	100.0 ± 0.0	98.8 ± 2.2	104.1 ± 5.6[a,b]	99.4 ± 1.6
	DOB	100.0 ± 0.0	98.9 ± 2.1	107.2 ± 4.3[a,b]	100.2 ± 2.1

All values are expressed as mean ± SD. P_{di}, transdiaphramatic pressure; DOA, dopamine; DOB, dobutamine.
[a] $P < 0.05$ (*s* prefatigue); [b] $P < 0.05$ (*s* fatigue); [c] $P < 0.05$ (DOA *s* DOB group).

(2) the increase of P_{di} was significantly larger with infusion of DOB compared with DOA ($P < 0.05$).

It is known that low-frequency fatigue is of clinical importance because the spontaneous, natural rate of phrenic nerve discharge is believed to be mainly in the range of low frequency (5–30 Hz) [4]. Therefore, we studied the effects of DOA and DOB on diaphragmatic fatigue induced by 20 Hz stimulation (low-frequency fatigue).

The results of the present study showed that P_{di} was increased in the DOA group by administering DOA in the fatigued diaphragm, which was in agreement with a previous study by Aubier et al. [1]. Our results in the DOB group demonstrated that administration of DOB also increased P_{di} of the fatigued diaphragm. This was in accordance with our previous study [2].

Although the precise mechanism of improvement of diaphragmatic fatigue following the administration of either DOA or DOB remains unclear, it has been suggested that these sympathomimetic amines may have direct positive effects on diaphragmatic contractility and may increase the blood flow and energy supply to the diaphragm [1,2]. In the present study, we did not measure blood flow to the diaphragm [1,2]. In the present study, we did not measure blood flow to the diaphragm. However, our previous study demonstrated that $\dot{Q}t$ was an important factor in the regulation of blood flow to the diaphragm [5]. The increase in $\dot{Q}t$ observed in the present study during infusion of either DOA or DOB may have led to an increase in diaphragmatic blood flow. In addition, P_{di} decreased as $\dot{Q}t$ returned to the prefatigue value after the cessation of infusion. These results suggest that an increase in diaphragmatic blood flow is one of the major mechanisms by which the contractility of the fatigued diaphragm is improved by administration of these agents.

The present study also showed that administration of DOB in comparison with DOA significantly increased the contractility of the fatigued diaphragm ($P < 0.05$). This may be explained by the significant difference in $\dot{Q}t$ between the two groups during administration of DOA and DOB ($P < 0.05$).

It has been demonstrated that low-frequency fatigue is closely related to the impairment of excitation-contraction coupling [6]. This impairment is thought to be the result of changes in the movement of Ca^{2+} from the sarcoplasmic reticulum [3]. In our previous study, it

was demonstrated that DOB improves the inhibition of Ca^{2+} influx in the fatigued diaphragm [2]. Therefore, the significant difference in the contractility between the two groups during the infusion of these agents ($P < 0.05$) may also be related to the influx of Ca^{2+} improved by administering DOB.

In conclusion, our results suggest that the contractility of the fatigued diaphragm is improved by administration of either DOB or DOA, but the positive inotropic effect of DOB is significantly greater than that of DOA at the same dose. This may be because these agents augment cardiac output, as well as diaphragmatic blood flow, to different degrees.

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