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Dobutamine increases diaphragmatic contractility in dogs

The effects of dobutamine on diaphragmatic contractility were studied in 24 dogs anaesthetized with secobarbital and receiving mechanical lung ventilation. The phrenic nerves were stimulated supramaximally for two seconds with electrodes placed around the fifth and sixth cervical roots when the airway was closed at the level of FRC. The stimulating frequency ranged from 10 to 100 Hz. Transdiaphragmatic pressure gradient (Pdi) generated by the electrophrenic stimulation was used as an index of diaphragmatic contractility. The electrical activity of the diaphragm during the stimulation (Edi) was also measured with needle electrodes inserted in the right hemidiaphragm percutaneously. During an infusion of dobutamine ($10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 20 min), Pdi increased by $15 \pm 2.1\%$ of control value at 20 Hz stimulation ($P < 0.01$), and by $13 \pm 1.2\%$ at 100 Hz stimulation ($P < 0.01$). The Edi was not altered by dobutamine infusion. This enhancement of Pdi by dobutamine was abolished by simultaneous infusion of nicardipine, a Ca-channel blocker, but was not affected by prostaglandin E_1 . These results suggest that dobutamine has a stimulating effect on canine diaphragmatic contraction, and this action may be related to the increased inward movement of extracellular calcium.

Les effets de la dobutamine sur la contractilité diaphragmatique ont été étudiés sur 24 chiens anesthésiés avec du séobarbital et ventilés artificiellement. Alors que les voies aériennes étaient obstruées en position de capacité résiduelle fonctionnelle, les nerfs phréniques recevaient un stimulus supramaximal durant deux secondes au moyen d'électrodes entourant les cinquièmes et

sixièmes racines cervicales. La fréquence de stimulation s'étalait de 10 à 100 Hz. Le gradient de pression transdiaphragmatique (Pdi) généré par la stimulation électrophrénique était utilisé comme indice de contractilité diaphragmatique. L'activité électrique du diaphragme durant la stimulation (Edi) était aussi mesurée et cela au moyen d'électrodes insérées au niveau de l'hémidiaphragme droit par voie percutanée. Durant une perfusion de dobutamine ($10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ durant 20 min), le Pdi a augmenté de $15 \pm 2,1\%$ de sa valeur initiale pour une stimulation à 20 Hz ($P < 0,01$), et de $13 \pm 1,2\%$ pour une stimulation à 100 Hz ($P < 0,01$). Le Edi n'était pas modifié par la perfusion de dobutamine. Cette amélioration du Pdi par la dobutamine était abolie lors de l'administration concomitante de nicardipine, un bloqueur de canaux calciques, mais elle n'était pas affectée par la prostaglandine E_1 . Ces résultats suggèrent que la dobutamine possède un effet stimulant sur la contraction diaphragmatique chez le chien, et cette action peut être reliée à une rentrée accrue du calcium extracellulaire.

Key words

HEART: dobutamine, nicardipine;
HORMONES: prostaglandin E_1 ;
MUSCLE SKELETAL: diaphragm;
SYMPATHETIC NERVOUS SYSTEM: pharmacology,
dobutamine.

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Respiratory muscle dysfunction has recently been regarded to play an important role in the pathogenesis of respiratory failure by leading to ventilatory pump failure.^{1,2} In clinical practice, ventilatory failure seen in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD),³ neuromuscular disease, malnutrition⁴ and circulatory shock⁵ is related to respiratory muscle dysfunction. To treat these patients, several pharmacological agents have been used in an attempt to improve the contractility and endurance of respiratory muscles, especially the diaphragm. So far, methylxanthine compounds and sympathomimetic amines have been reported to have positive inotropic effects on the diaphragm. Methylxanthine compounds, such as caffeine⁶ and theophylline⁷⁻⁹ possess a direct potentiating effect on diaphragmatic contractility. The effects of sympathomimetic amines are more controversial.

The β_2 sympathomimetics such as isoproterenol,¹⁰ terbutaline¹¹ and fenoterol,¹² are known to have an inotropic effect on fatigued diaphragm in dogs, while having no effect on fresh diaphragm. Dopamine at the dose of $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, which is expected to have mainly β_1 adrenergic effect, increased transdiaphragmatic pressure (Pdi) in patients with COPD during acute respira-

tory failure.¹³ As an explanation for the mechanisms of these drugs, β_2 stimulants are thought to increase the contractility of the fast-contracting fibres which are susceptible to the process of fatigue, while β_1 stimulants are considered to act by increasing the diaphragmatic blood flow and the energy supply to the muscles.

However, salbutamol, a selective β_2 -adrenergic agonist, does not exert a remarkable inotropic effect even on fatigued diaphragm,¹⁴ and there still remains much to be investigated to clarify the mechanisms of action of these drugs. In this present study, we investigated the effects of dobutamine, another sympathomimetic amine possessing β_1 adrenergic effects, on diaphragmatic contractility in anaesthetized dogs. In addition, we evaluated the effects of two kinds of vasodilating agents, prostaglandin E_1 (PGE_1) and nicardipine, on diaphragmatic contractility when they are combined with dobutamine, in order to find the mechanism of dobutamine on the diaphragm.

Methods

With institutional review board approval, in 24 mongrel dogs weighing 10 to 18 kg, anaesthesia was induced with $20 \text{ mg} \cdot \text{kg}^{-1}$ of ketamine *im* and maintained with $4 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ of secobarbital *iv* during the course of experiment. The tracheas were intubated with a cuffed tracheal tube and the lungs were mechanically ventilated with air and oxygen to keep PaO_2 around 100 mmHg and PaCO_2 between 35 and 40 mmHg. Metabolic acidosis, if any, was corrected with *iv* sodium bicarbonate. The right femoral artery was cannulated to monitor blood pressure and to obtain blood samples for arterial blood gas analysis and electrolyte measurement. The right femoral vein was cannulated for the administration of dobutamine, PGE_1 or nicardipine, and the left femoral vein for the administration of secobarbital and fluid ($10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ of Ringer's lactate solution). A Swan-Ganz catheter was inserted via the right external jugular vein for cardiac output measurement. Rectal temperature was monitored continuously and maintained at $37 \pm 1^\circ \text{C}$.

The phrenic nerves were exposed bilaterally in the neck and stimulating electrodes were placed around the fifth and sixth roots. Two thin-walled latex balloons were positioned in the stomach and in the middle third of the oesophagus to measure gastric (Pga) and oesophageal pressure (Peso), respectively. Balloons were connected to a differential pressure transducer to obtain Pdi (= Pga - Peso). Supramaximal stimuli (10–15 volts) of 0.1 ms duration lasting 2 sec were applied to the phrenic nerves at frequencies of 10, 20, 50 and 100 Hz. Diaphragmatic contractility was evaluated by measuring the maximal Pdi generated in response to electro-phrenic stimulation with the airway closed at FRC level while mechanical ventilation was stopped. An abdominal binder was closely placed

FIGURE 1 Schematic diagram of the experimental protocol. Interventions DOB: dobutamine infusion at $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. PGE_1 : prostaglandin E_1 infusion at 0.5 to $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. NIC: nicardipine infusion at 1 to $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Measurements (1) control, (2) after DOB, (3) after DOB/ PGE_1 , or DOB/NIC, (4) post- PGE_1 , or post-NIC, (5) post-DOB.

around the abdomen and lower rib cage to avoid distension of the abdomen during stimulation. Transpulmonary pressure, the difference between airway and oesophageal pressures, was kept constant when the airway was closed at FRC to maintain the same lung volume. The electrical activity of the diaphragm was measured with needle electrodes inserted percutaneously into the right hemidiaphragm 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 sec. This was regarded as the integrated diaphragmatic electrical activity (Edi).

As a pilot study, we measured the changes in Pdi and Edi in response to 1 to $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of dobutamine, $1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of PGE_1 and $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of nicardipine respectively.

In the present study, after the baseline measurements of Pdi, Edi and haemodynamics which included mean arterial pressure (MAP) and cardiac output (CO), a dobutamine infusion was started at the dose of $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The second set of measurements was done 20 min after the initiation of dobutamine infusion. Thereafter the animals were randomly assigned to two groups to receive either infusions of PGE_1 (defined as PGE_1 group, $n = 12$), or nicardipine (defined as NIC group, $n = 12$), while the dobutamine infusion was continued at the same rate. The dosages of these vasodilators were adjusted to decrease MAP to around 100 mmHg. After the target MAP was obtained, the third set of measurements was performed. Subsequently the measurements were repeated, once at 20 min after the infusion of PGE_1 or nicardipine was stopped, and again at 20 min after the dobutamine infusion was stopped. Intervals between each measurement took approximately 30 min, and therefore the whole experiment lasted about 120 min (Figure 1).

TABLE I Haemodynamic data (mean $\pm$ SEM)

Variable	Group	Control	DOB	DOB/PGE ₁ DOB/NIC	Post-PGE ₁ Post-NIC	Post-DOB
MAP	PGE ₁	117 $\pm$ 6	141 $\pm$ 8 ^a	94 $\pm$ 6 ^a	136 $\pm$ 7 ^a	112 $\pm$ 3
	NIC	110 $\pm$ 7	135 $\pm$ 8 ^a	98 $\pm$ 7	103 $\pm$ 9 ^b	109 $\pm$ 5
CO	PGE ₁	2.3 $\pm$ 0.3	4.5 $\pm$ 0.6 ^a	4.2 $\pm$ 0.5 ^a	5.5 $\pm$ 0.7 ^a	2.8 $\pm$ 0.5
	NIC	2.4 $\pm$ 0.2	4.6 $\pm$ 0.5 ^a	5.6 $\pm$ 0.6 ^a	6.3 $\pm$ 0.8 ^a	3.4 $\pm$ 0.3

All values are expressed as mean $\pm$ SEM.

MAP: mean arterial pressure (mmHg). CO: cardiac output (L $\cdot$ min⁻¹). DOB: dobutamine. PGE₁: prostaglandin E₁, NIC: nicardipine.

^aSignificantly different from control ($P < 0.05$).

^bSignificantly different from PGE₁ group ($P < 0.01$).

All values given are means $\pm$ SEM. The values for Pdi were expressed as % changes of the baseline for each frequency of stimulation. Statistical analysis was performed by analysis of variance (ANOVA) for repeated measurements, and Duncan's multiple comparison was used for determining significantly different mean values. Student's *t* test was used for comparisons between the two groups. P values < 0.05 were considered to be statistically significant.

Results

Effects of dobutamine, PGE₁, and nicardipine on haemodynamics

The dobutamine infusion at 10 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ resulted in an increase in MAP and CO in both PGE₁ and NIC groups ($P < 0.05$). With the infusion of either PGE₁ or nicardipine together with dobutamine, MAP was decreased to approximately the same level in both groups. The dosages of these vasodilating agents to achieve MAP around 100 mmHg were 0.5 to 1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for PGE₁, and 1 to 5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for nicardipine. The CO did not change significantly by the infusion of PGE₁ or nicardipine. Soon after the PGE₁ infusion was stopped, MAP returned to the pre-PGE₁ level; however the lowered MAP caused by nicardipine remained even 20 min after the cessation of nicardipine infusion. The MAP and CO in both groups returned to the control level 20 min after dobutamine infusion was stopped (Table I).

Effects of dobutamine, PGE₁, and nicardipine on diaphragmatic contractility

In the pilot study, we confirmed that dobutamine at the dose of 1 to 10 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ showed an increase in Pdi in a dose dependent manner, but PGE₁ or nicardipine alone did not influence Pdi.

In the present experiment, Pdi increased with dobutamine infusion ($P < 0.05$). These changes were observed at each frequency of stimulation. Since no vasodilators were given at this time, changes in Pdi during dobutamine

FIGURE 2 Typical recordings of changes in Pdi (20 Hz and 100 Hz) in response to dobutamine, dobutamine + prostaglandin E₁, dobutamine + nicardipine. Pdi: transdiaphragmatic pressure.

infusion were calculated together for the two groups. Consequently, Pdi increased by $15 \pm 2.1\%$ of control value for 20 Hz stimulation ($P < 0.01$), and by $13 \pm 1.2\%$ for 100 Hz stimulation ($P < 0.01$). However, there was no change in Edi. During the infusion of PGE₁ together with dobutamine, Pdi did not show any significant change. On the other hand, nicardipine infusion combined with dobutamine lowered Pdi to pre-dobutamine level, and Pdi during the infusions of these vasodilators differed between the groups (Table II) ($P < 0.05$). Typical recordings of Pdi (20 and 100 Hz) are shown in Figure 2. After the infusion of the vasodilating agents was stopped, Pdi returned towards the values during dobutamine infusion. Twenty minutes after the cessation of dobutamine infusion, Pdi returned to the control level. Edi did not show any remarkable changes throughout the experiment.

Discussion

The main findings of this study are; (1) 10 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ dobutamine, the dose used in clinical practice, increased contractility of the canine diaphragm, (2) the potentiating action of dobutamine on canine diaphragm

TABLE II Changes in Pdi (%) in response to DOB, PGE₁ and NIC (mean $\pm$ SEM)

Frequency	Group	Control	DOB	DOB/PGE ₁ DOB/NIC	Post-PGE ₁ Post-NIC	Post-DOB
10 Hz	PGE ₁	100 $\pm$ 0.0	116 $\pm$ 2.9 ^a	116 $\pm$ 2.8 ^a	115 $\pm$ 2.9 ^a	104 $\pm$ 2.2 ^b
	NIC	100 $\pm$ 0.0	122 $\pm$ 3.7 ^a	92 $\pm$ 4.2 ^{b,c}	112 $\pm$ 5.7	96 $\pm$ 3.3 ^b
20 Hz	PGE ₁	100 $\pm$ 0.0	116 $\pm$ 3.7 ^a	115 $\pm$ 3.9 ^a	116 $\pm$ 3.8 ^a	103 $\pm$ 2.6 ^b
	NIC	100 $\pm$ 0.0	114 $\pm$ 2.3 ^a	97 $\pm$ 3.9 ^{b,c}	112 $\pm$ 5.6	99 $\pm$ 4.7 ^b
50 Hz	PGE ₁	100 $\pm$ 0.0	112 $\pm$ 1.7 ^a	111 $\pm$ 1.8 ^a	111 $\pm$ 1.9 ^a	98 $\pm$ 2.4 ^b
	NIC	100 $\pm$ 0.0	116 $\pm$ 3.4	99 $\pm$ 5.7	111 $\pm$ 7.0	100 $\pm$ 6.3
100 Hz	PGE ₁	100 $\pm$ 0.0	112 $\pm$ 2.0 ^a	110 $\pm$ 2.2 ^a	110 $\pm$ 2.2 ^a	100 $\pm$ 2.4 ^b
	NIC	100 $\pm$ 0.0	113 $\pm$ 1.3 ^a	97 $\pm$ 4.6 ^{b,c}	107 $\pm$ 4.9	96 $\pm$ 4.5 ^b

DOB: dobutamine. PGE₁: prostaglandin E₁. NIC: nicardipine. Pdi: transdiaphragmatic pressure.

^aSignificantly different from control ($P < 0.05$).

^bSignificantly different from DOB ($P < 0.05$).

^cSignificantly different from PGE₁ group ($P < 0.05$).

was reversed by the simultaneous infusion of nicardipine, but was not influenced by the infusion of PGE₁, (3) the decrease in MAP with nicardipine and PGE₁ were similar.

We observed that Pdi was increased by the administration of dobutamine without any change in Edi. This implies that contractility of the muscle was increased by dobutamine in response to the same amount of neural stimulation. The Pdi can also be dependent on the initial length of the muscle fibres and a major determinant of the length of the diaphragm is lung volume. Therefore, we stimulated the phrenic nerves with the airway closed at FRC level, and tried to keep the transpulmonary pressure constant at FRC level throughout the experiment. On the basis of our observations that the drugs administered did not change the initial lung volume and that Edi did not change throughout the whole experiment, the changes in Pdi are considered to reflect the changes in contractility of the diaphragm.

The effects of sympathomimetic amines on skeletal muscle have been studied extensively. The direct effect of these amines on skeletal muscle is considered to be mediated via β_2 receptors, and their effect is largely dependent on the type of fibres involved: slow-contracting muscles show a decrease in tension and duration of maximum twitch responses, while fast-contracting muscles respond with an increase in tension and duration.¹⁵ Therefore, the net effect of these amines on skeletal muscle contractility depends on the distribution of these muscle fibres. In regard to their actions on respiratory muscles, there have been several studies of the effect of β_2 sympathomimetic amines on the canine diaphragm. Isoproterenol,¹⁰ terbutaline¹¹ and fenoterol¹² increased Pdi of fatigued diaphragm, but did not affect Pdi of nonfatigued diaphragm. Since the canine diaphragm is composed of almost equal amounts of both slow- and fast-

contracting fibres,¹⁶ the effects of β_2 sympathomimetic amines on muscle fibres may have counteracted each other, resulting in no change in Pdi for nonfatigued diaphragm. However, in the fatigued diaphragm, their actions on fast-contracting fibres, which are more susceptible to the process of fatigue and decrease in contractility, may have been unmasked, resulting in an increase in contractility as a whole.

In the present study, dobutamine in a dose of 10 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, which possesses mainly β_1 adrenergic action,¹⁷ showed a potentiating effect on canine diaphragmatic contractility. This effect of dobutamine could have been mediated either by the direct action of the drug on the diaphragm or by increasing blood flow to the diaphragm. However, β_1 sympathomimetic amines do not seem to affect the contractility of diaphragm directly. Aubier *et al.* administered dopamine (10 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) to the patients with COPD during acute respiratory failure and found that the Pdi in response to electro-phrenic stimulation increased by 30%. At the same time, they evaluated diaphragmatic blood flow and found a concomitant increase in diaphragmatic blood flow. Therefore, they suggested that the increase in diaphragmatic contractility was the result of increased diaphragmatic blood flow.¹³

We did not measure diaphragmatic blood flow in the present study. Instead, we investigated the changes in systemic haemodynamic variables in response to dobutamine, PGE₁ and nicardipine. The increased CO with dobutamine did not change with either of these vasodilators, but the elevated MAP produced by dobutamine was decreased by these vasodilators to similar levels. There were no differences in CO and MAP between the two groups while these vasodilators were infused during dobutamine infusion. From our previous study, diaphragmatic blood flow changes in parallel with changes in CO.¹⁸ It has been

reported that diaphragmatic blood flow is maintained constant with MAP above 70 mmHg.¹⁹ There is also another report stating that diaphragmatic blood flow is dependent on MAP.²⁰ In any case, under the conditions where CO and MAP are maintained at approximately the same level, a difference in diaphragmatic blood flow is not likely to occur while these two different vasodilators are given. Besides, it is also unlikely that PGE₁ or nicardipine would act on phrenic arteries in a different manner. Therefore, we postulate that the effect of dobutamine on diaphragm is not due to changes in blood flow to the diaphragm.

Digoxin was shown to augment diaphragmatic contractility in dogs²¹ and in patients with COPD.²² Digoxin is known to have an inotropic effect on the myocardium but not on skeletal muscle.²³ Digitalis inhibits Na⁺-K⁺-ATPase at the cell membrane level, which will augment cell entry of calcium. This influx of calcium will then increase the contractile strength of the myocardium. However, movement of extracellular calcium across the cell membrane during the action potential plays a minor role in determining contractile strength in skeletal muscle, with all the needed calcium being liberated from the sarcoplasmic reticulum. However, extracellular calcium has been shown to be necessary for diaphragmatic contraction but not for contraction of other skeletal muscle such as hindlimb muscle.²⁴ This finding suggests that the diaphragm behaves more like cardiac muscle. We postulate that dobutamine exerted a positive inotropic action on the diaphragm in the same manner as digoxin, and that may explain why nicardipine inhibited the effect of dobutamine. Inhibited calcium influx caused by nicardipine may have decreased diaphragmatic contractility. In the pilot study we did not observe a negative inotropic effect of nicardipine alone on diaphragm. However, with a larger dose than was used in the pilot study, nicardipine might, like verapamil,⁹ have reduced diaphragmatic contractility.

In summary, dobutamine infusion of 10 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ increased diaphragmatic contractility in dogs and this effect was abolished by the simultaneous infusion of nicardipine but not of PGE₁. These results suggest that the mechanism of dobutamine may be related to increased influx of calcium ion. To apply the results of the present study to clinical situations, the effects of dobutamine administration on fatigued diaphragm as well as in patients with diaphragmatic dysfunction should be investigated.

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