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Effect of phenylephrine on histamine-induced bronchoconstriction in dogs

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Abstract

Purpose. Although an α-adrenoceptor has been suggested to be involved in the mechanism of asthma, the effect of α_1-agonist on the airway is still unclear. In this study we evaluated the effect of phenylephrine on the airway with a direct visualization method using a superfine fiberoptic bronchoscope (SFB).

Methods. Seven mongrel dogs were anesthetized with pentobarbital (30 mg·kg^{-1} IV) and paralyzed by pancuronium (0.2 mg·kg^{-1}·h^{-1}). The trachea was intubated with an endotracheal tube (ID 7 mm) that has a second lumen for insertion of a SFB (OD 2.2 mm) to monitor the bronchial cross-sectional area (BCA) continuously. The tip of a SFB was placed at the level between the second and third bronchial bifurcation. To assess hemodynamics, the direct arterial blood pressure (ABP) and pulmonary arterial pressure (PAP) were monitored via a femoral arterial catheter and Swan-Ganz catheter. Bronchoconstriction was elicited by histamine (10 μg·kg^{-1} + 500 μg·kg^{-1}·h^{-1}). At 30 min after the histamine was started, saline or phenylephrine (1, 10, and 100 μg·kg^{-1}) was given intravenously. The BCA and hemodynamic variables were assessed before (basal) and 30 min after the histamine was started and 5 min after saline and each phenylephrine dose.

Results. Histamine reduced BCA by 40.3 ± 6.3%. Phenylephrine at 10 and 100 μg·kg^{-1} significantly increased the ABP and PAP; and it significantly decreased the BCA, by 6.5 ± 6.9% and 14.2 ± 7.9%, respectively. Plasma epinephrine and norepinephrine were also significantly reduced following phenylephrine 100 μg·kg^{-1} IV.

Conclusion. The dose of phenylephrine that produced vasopressive actions worsened the histamine-induced bronchoconstriction slightly but significantly. Therefore, phenylephrine should be used with caution in asthmatic patients.

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Introduction

Adrenergic regulation can mediate airway reactivity, as α- and β-adrenoceptors exist in the airway [1,2]. It has been reported that an imbalance of β-adrenergic activity may contribute to the airway hyperreactivity associated with asthma [3]. In addition, several reports showed that α-receptor antagonists alleviate asthmatic symptoms [4,5], so α-adrenoceptor may also be involved in the mechanism that produces asthma. Although α_1-agonists such as phenylephrine are commonly used as vasopressors against hypotension during anesthesia [6], these agents might worsen or produce bronchoconstriction in patients with asthma or anaphylactic shock, where histamine is released from the mast cells accounts in part for symptoms of the allergic response [7].

As previously reported [8–12], we have developed a direct visualization method to quantify bronchial caliber using a superfine fiberoptic bronchoscope. We showed that this method can be more specific than conventional indirect methods, such as measuring airway pressure, airway resistance, or dynamic pulmonary compliance, to assess airway caliber. Employing this direct visualization method, we have evaluated the effect of phenylephrine on histamine-induced bronchoconstriction.

Methods

After approval of our University Animal Care Committee, seven mongrel dogs were anesthetized with pentobarbital (30 mg·kg^{-1} IV) and paralyzed by pancuronium infusion at 0.2 mg·kg^{-1}·hr^{-1}. The trachea

was intubated with a special endotracheal tube (ID 7 mm) that has a second lumen for insertion of a superfine fiberoptic bronchoscope (OD 2.2 mm) to monitor the bronchial cross-sectional area continuously. The tip of a superfine fiberoptic bronchoscope was placed at a level between the second and third bronchial bifurcation. The lungs were mechanically ventilated by a volume-controlled respirator (Servo 900C) with oxygen, and the end-tidal CO_2 was maintained at 4.0%–4.5%.

To assess the hemodynamics, direct arterial blood pressure, pulmonary arterial pressure, and central venous pressure were monitored via femoral arterial catheter (20 gauge) and a Swan-Ganz catheter (7.5F; Baxter Health, Tokyo, Japan). The bronchial cross-sectional area (BCA), printed out by videoprinter, was measured with NIH Image (Wayne Rasband, US National Institutes of Health, available from the Internet by anonymous ftp from zippy.nimh.nih.gov or on floppy disk from NTIS, 5285 Port Royal Rd., Springfield, VA 22161, USA, part number PB93-504868).

Bronchoconstriction was elicited with histamine 10 μg·kg^{-1} followed by its continuous infusion at 500 μg·kg^{-1}·hr^{-1} until the end of each experiment. At 30 min after the start of histamine infusion, saline and phenylephrine 1, 10, and 100 μg·kg^{-1} were given intravenously, in this order, at 5-min intervals. Lactate Ringer solution (50 ml·kg^{-1}) was loaded to prevent severe histamine-induced hypotension. The bronchial cross-sectional area and hemodynamic variables were assessed before (basal) and 30 min after the start of histamine infusion and 5 min after each intravenous dose of phenylephrine. Changes in the BCA are expressed as the percent of the basal BCA (% BCA). Arterial blood was collected simultaneously to measure the plasma catecholamine levels by gas chromatography-mass spectrometry (GC-MS) [13]. The assay's coefficient of variation was 8.4% for epinephrine and 11.3% for norepinephrine. All data are represented as the mean ± SEM. Statistical analyses were done by repeated measures ANOVA followed by Fisher's PLSD. $P < 0.05$ was considered significant.

Results

Histamine infusion decreased %BCA to 59.7 ± 6.3%. Phenylephrine at more than 10 μg·kg^{-1} significantly increased the systemic and pulmonary arterial pressures and decreased the %BCA (Table 1), but the central venous pressure did not change. Plasma levels of epinephrine and norepinephrine were also significantly reduced following phenylephrine 100 μg·kg^{-1} IV (Table 1).

Discussion

The present data suggest that vasopressive doses of phenylephrine may worsen bronchoconstriction. α_1-Agonists are commonly used as vasopressors against hypotension during anesthesia [6]. However, if hypotension is caused by drug-induced anaphylaxis, especially in asthmatic patients, phenylephrine may worsen the anaphylaxis-caused bronchospasm.

Barnes et al. [1,2] showed, using an autoradiographic method, that autonomic receptors, including α- and β-adrenoceptors, exist in airway smooth muscles; and the adrenergic activities may regulate airway reactivity. They also reported that the α-adrenoceptors increased and β-adrenoceptors decreased during experimental asthma [14]. Moreover, several other investigators reported that α-agonists produce bronchospasm in asthmatic patients, ponies with airway obstruction, or ascaris-sensitized dogs [15–17]; and α-antagonists have been reported to alleviate asthmatic symptoms [4,5]. These findings suggested that α-adrenoceptor is involved in the mechanism of airway hyperreactivity.

It was also demonstrated that α-receptor-mediated bronchoconstriction was not seen in normal subjects

Table 1. Effects of phenylephrine on bronchial cross-sectional area and hemodynamics

Parameter	H30′	Saline	P1.0	P10	P100
BCA (%)	59.7 ± 6.3	59.2 ± 6.5	59.5 ± 7.4	53.4 ± 6.9*	45.5 ± 7.9**
SABP (mmHg)	113 ± 15	115 ± 18	122 ± 18	147 ± 15*	271 ± 12**
SPAP (mmHg)	28 ± 5	28 ± 5	28 ± 5	30 ± 5	39 ± 6**
E (ng/ml)	4.5 ± 2.0	4.2 ± 1.3	4.6 ± 1.5	3.0 ± 1.3	1.6 ± 0.6**
NE (pg/ml)	332 ± 73	308 ± 69	380 ± 92	328 ± 82	190 ± 32*

BCA, bronchial cross-sectional area; SABP, systolic arterial blood pressure; SPAP, systolic pulmonary arterial pressure; E, epinephrine; NE, norepinephrine; H30′, 30 min after the start of H infusion; P1.0, P10, P100, phenylephrine 1.0, 10, 100 μg·kg^{-1} IV.
*$P < 0.05$, **$P < 0.01$ *vs* H30′.

[15–17]. Barnes et al. reported that the density of α-adrenoceptors in patients with chronic airway obstruction was about 10-fold higher than that of patients with no airway obstruction [2]; therefore a low density of α-adrenoceptors may result in an observation of no α-receptor-mediated bronchoconstriction in the normal airway. In addition, to assess airway caliber, they used indirect methods such as airway resistance or compliance, which have been reported to be relatively insensitive for measuring airway caliber [18]. As previously shown, a new portable direct visualization method to quantify bronchial caliber using a superfine fiberoptic bronchoscope is more specific for assessing airway caliber [8–12], similar to a high-resolution computed tomography (CT) method reported by Brown et al. [18,19]. In the present study, we observed that an α_1-agonist produced bronchoconstriction in normal dogs who have α-adrenoceptors in the airway [20], a finding that underlines the sensitivity of our direct visualization method.

In the present study, phenylephrine significantly reduced plasma catecholamine levels. An imbalance of β-adrenergic activity has been suggested to produce bronchospasm [3]. In addition, as the direct neural supply of the sympathetic system in the lung is limited, circulating catecholamines contribute a sympathetic influence on airway tone [21]. Larsson [22] also reported that allergen-induced bronchospasm was counteracted by elevating circulating epinephrine in patients with allergic asthma. Therefore, decreases in plasma catecholamines following intravenous phenylephrine could contribute to a worsening of histamine-induced bronchoconstriction.

Clinically phenylephrine is given as a 40- to 100-μg IV bolus up to 1 mg to adult patients [6]. In the present study, because phenylephrine at a dose of less than $10\,\mu g \cdot kg^{-1}$ did not produce bronchoconstriction, and even $10\,\mu g \cdot kg^{-1}$ reduced the %BCA by only 6.5 ± 6.9%, the clinical dose of phenylephrine may be used safely in patients with normal airways. The hyperreactive airway has been reported to respond to phenylephrine 100–600 μg IV in a does-dependent fashion in humans [15] and $10\,\mu g \cdot kg^{-1}$ in dogs [17], whereas the normal airway did not respond [15,17]. Moreover, in the present study, vasopressive doses of phenylephrine produced a significant reduction in the %BCA. Therefore, even clinical doses may trigger an asthma attack.

In conclusion, vasopressive doses of phenylephrine slightly but significantly worsened histamine-induced bronchoconstriction in normal dogs. As the hyperreactive airway may be more sensitive to α_1-agonists than the normal airway, phenylephrine should be used cautiously in patients with hyperreactive airways.

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