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Dopamine ameliorates bronchoconstriction induced by histaminergic and cholinergic pathways in rabbits

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ABSTRACT

To clarify the potential of dopamine to alter airway tone in the presence of different bronchoconstrictor stimuli, changes in airway function following dopamine administrations were characterized when the bronchial tone was elevated by stimulating the histaminic or cholinergic pathway. Airway resistance, tissue damping and tissue elastance were measured in anesthetized mechanically ventilated rabbits under baseline conditions, during steady-state bronchoconstriction induced by methacholine or histamine, and following intravenous dopamine (5 and 15 μg/kg/min). Bronchoconstriction induced by methacholine and histamine was significantly ameliorated by dopamine (14.8 ± 2.9% and 14.9 ± 2.9%; $p < 0.05$ for both), with no difference between the mode of stimuli. Dopamine had no effect on the tissue mechanics. These findings indicate that dopamine relaxes the elevated airway smooth muscle tone without affecting the lung periphery, and this effect is independent of the mode of constrictor stimuli. This profile of dopamine suggests its ability to treat effectively cholinergic and histaminergic bronchoconstriction, besides its positive inotropic effects on the myocardial contractility.

1. Introduction

Bronchoconstriction is a major adverse event occurring both during general anesthesia and critical care (Habre et al., 2017; Hirshman and Bergman, 1990; Holzman, 1994; Nunn, 1990). Involvement of the cholinergic pathway by direct stimulation of the muscarinic receptors is frequent in the perioperative period, particularly during tracheal intubation (Gal, 1980) or mechanical stimulation of the airways, i.e. bronchoscopy or bronchial suction. The muscarinic receptors can also be activated following acetylcholine liberation via vagal stimulation, such as manipulation of the upper airways. Another mechanism responsible for the respiratory complications is triggered by the histaminergic pathway. Most of the anesthetic drugs, such as thiopentone, morphine and neuromuscular blocking agents are known to induce histamine release into the circulation (Doenicke et al., 1995; Hirshman et al., 1985; North et al., 1987). Furthermore, lung function deteriorations observed after allergic reactions or cardiopulmonary bypass are also mediated primarily by endogenous histamine release.

Dopamine is frequently used as an inotropic drug to elevate cardiac output. In addition to the beneficial cardiac effect of this drug, the few previous studies addressing its ability to alter the airway tone reported controversial results (Babik et al., 2003; Cabezas et al., 1999; Chen and Shue, 1992; Michoud et al., 1984). Some papers reported a bronchoconstrictive effect of dopamine (Chen and Shue, 1992), whereas others demonstrated neutral airway effects (Thomson and Patel, 1978) or relaxation of an elevated bronchial smooth muscle tone (Cabezas et al., 2003). Dopamine was effective in reversing cholinergic bronchoconstriction, whereas it enhanced the histamine-induced bronchoconstriction (Chen and Shue, 1992). Therefore, the differences in the activated pathway to preconstrict the airways may have importance.

Therefore, we aimed at clarifying the effects of dopamine on the respiratory system by comparing its potential to alter the airway tone via two major pathways (i.e. cholinergic and histaminergic) involved in the perioperative adverse respiratory events.

2. Materials and methods

2.1. Ethics approval

This study was approved by the Experimental Ethics Committee of the University of Szeged Szeged, Hungary, on the 7th of December 2012 (no. I-74-50/2012), and authorized by the National Food Chain Safety

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and Animal Health Directorate of Csongrád County, Hungary (no. XIV/ 152/ 2013, Chairperson Cs. Farle) on the 9th January 2013. The procedures were performed according to the guidelines of the Scientific Committee of Animal Experimentation of the Hungarian Academy of Sciences (updated Law and Regulations on Animal Protection: 40/2013. (II. 14.) Government of Hungary), following the EU Directive 2010/63/ EU on the protection of animals used for scientific purposes, and reported in compliance with the ARRIVE guidelines.

2.2. Animal preparations

Experiments were performed in two groups of New Zealand White rabbits (2.0–2.68 kg), with 9 rabbits in the dopamine-treated group and 7 rabbits in the control group.

Anesthesia was induced by an intramuscular injection of xylazine (5 mg/kg, CP-Xylazin 2%, Produlab Pharma, Raamsdonksveer, The Netherlands) followed by an intravenous dose of sodium pentobarbital (30 mg/kg) through a cannula placed in the marginal ear vein which was used for anesthesia throughout the whole protocol by regular IV injections (5 mg/kg every 30 min). A polyethylene cannula was inserted in the trachea through a tracheostomy following the subcutaneous administration of local anaesthetics (lidocaine, 2-4 mg/kg). The rabbits were placed on a heating pad and the tracheal cannula was connected to a small animal ventilator (Model 683, Harvard Apparatus, South Natick, MA, USA), and mechanically ventilated with room air (3035 breaths/min, tidal volume 7 ml/kg). The femoral vein was catheterized with a 3lumen catheter for drug delivery, a femoral artery was catheterized (PV2013L07, Pulsion Medical Systems, Munich, Germany) and attached to a pressure transducer (PV8115, Pulsion Medical Systems, Munich, Germany) for measurement of systemic blood pressure and thermodilution measurements. A jugular vein was also catheterized and used for transpulmonary thermodilution measurements. Neuromuscular blockade was achieved by repeated IV administration of pipecuronium (0.1 mg/kg, every 30 min, Arduan, Richter-Gedeon, Budapest, Hungary). Expired carbon-dioxide (CO_2) traces were monitored by using a mainstream capnograph (Novametrix, Capnogard®, Andover, MA, USA) connected between the tracheal cannula and the Ypiece of the ventilator circuit. Body temperature was kept in the 39 ± 0.5 °C range by using the heating pad.

2.3. Measurement of respiratory mechanics

The measurements of the input impedance spectra of the respiratory system (Zrs) were carried out by forced oscillations (Babik et al., 2017; Fodor et al., 2014). Mechanical ventilation was ceased at end-expiration for an 8-s long period and the tracheal cannula was connected to a loudspeaker-in-box system to deliver the forced oscillatory signal. The loudspeaker delivered a computer-generated small-amplitude (< ± 1 cmH_2O) pseudo-random signal in the interval 0.5–21 Hz through a screen pneumotachograph (11 mm ID), which was used to measure the gas flow (V') with a differential pressure transducer (model 33NA002D; ICSensors, Milpitas, CA, USA). An identical pressure transducer was used to measure the pressure at the airway opening with reference to the atmosphere (P_{ao}).

The P_{ao} and V' signals were low-pass filtered at 25 Hz and sampled with an analogue–digital board of a microcomputer at a rate of 256 Hz. Fast Fourier transformation with 4-s time windows and 95% overlapping was used to calculate the Zrs spectra (Zrs = P_{ao}/V'). Three to four Zrs spectra were recorded at each experimental step which were ensemble-averaged for further analysis.

2.4. Estimation of airway and parenchymal parameters

The airway and parenchymal mechanical properties of the respiratory system were separated by fitting a model to the averaged Zrs spectra by minimizing the differences between the measured and modelled impedance values. The model consisted of an airway compartment containing airway resistance (Raw) and airway inertance (Iaw), and a constant-phase tissue unit (Hantos et al., 1992) characterized by tissue damping (G) and elastance (H):

$$Zrs = Raw + j\omega Iaw + (G - jH)/\omega^{\alpha}$$

where j is the imaginary unit, ω is the angular frequency (2πf), and α is (2/π) arctan (H/G).

2.5. Hemodynamic monitoring

Systemic hemodynamic parameters including the systolic (Psys) and diastolic (Pdias) arterial blood pressure and mean arterial pressure (MAP) were monitored by a transpulmonary arterial thermodilution system (PiCCO; Pulsion Medical System, Munich, Germany). The apparatus consists of a 4 F arterial catheter inserted into the femoral artery and a central venous catheter placed in a jugular vein. The thermal indicator bolus (3 ml of < 8 °C saline) was injected into the right atrium via the central venous line and the monitor determined the cardiac output (CO) from the thermodilution curve.

2.6. Experimental protocol

The timeline of the experimental protocol is illustrated in Fig. 1. After the animals reached a steady-state condition 510 min following completion of surgical preparation, lung volume history was standardized by two moderate hyperinflations (double tidal volume) by occluding the expiratory port of the ventilator. Baseline respiratory mechanical parameters were assessed by measuring a data set of 34 reproducible Zrs recordings along with CO measurement. Following the establishment of the baseline values, the animals were randomly given either methacholine (MCh, 5 μg/kg/min) or histamine (Hist, 10 μg/kg/ min) as a constrictor agonist by a continuous IV infusion. After establishing a stable level of bronchoconstriction determined by a steady-state increase of Raw (within 5%, approximately 15 min after its onset), another Zrs data set was recorded with 1-min interval between the individual measurements and CO was also registered. Dopamine was then administered to the animals of the dopamine group (Group DA) by means of a continuous IV infusion (5 μg/kg/min), while the administration of constrictor agonist was sustained. After 5 min, a next set of Zrs spectra were recorded along with CO data. Both infusions were then ceased, and following a 30-min recovery period, a second baseline was established in a similar fashion. Rabbits were then administered the other constrictor agonist by a continuous IV infusion and measurements were carried out after stabilization of the bronchoconstriction. Dopamine was administered again at 5 μg/kg/min and Zrs and CO measurements were carried out after 5 min. The dose of dopamine was finally elevated to 15 μg/kg/min, followed by recording Zrs and CO data after 5 min. Systemic hemodynamic parameters were registered at each

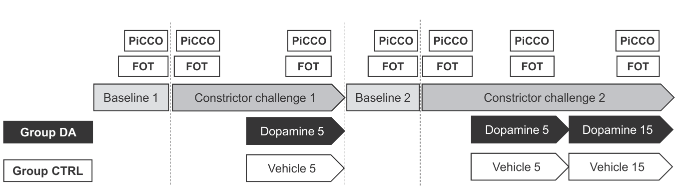

Fig. 1. Scheme of the experimental protocol. DA: dopamine, CTRL: control, PiCCO: cardiac output measurements, FOT: respiratory mechanical measurements. Constrictor challenge: continuous infusion of either methacholine or histamine.

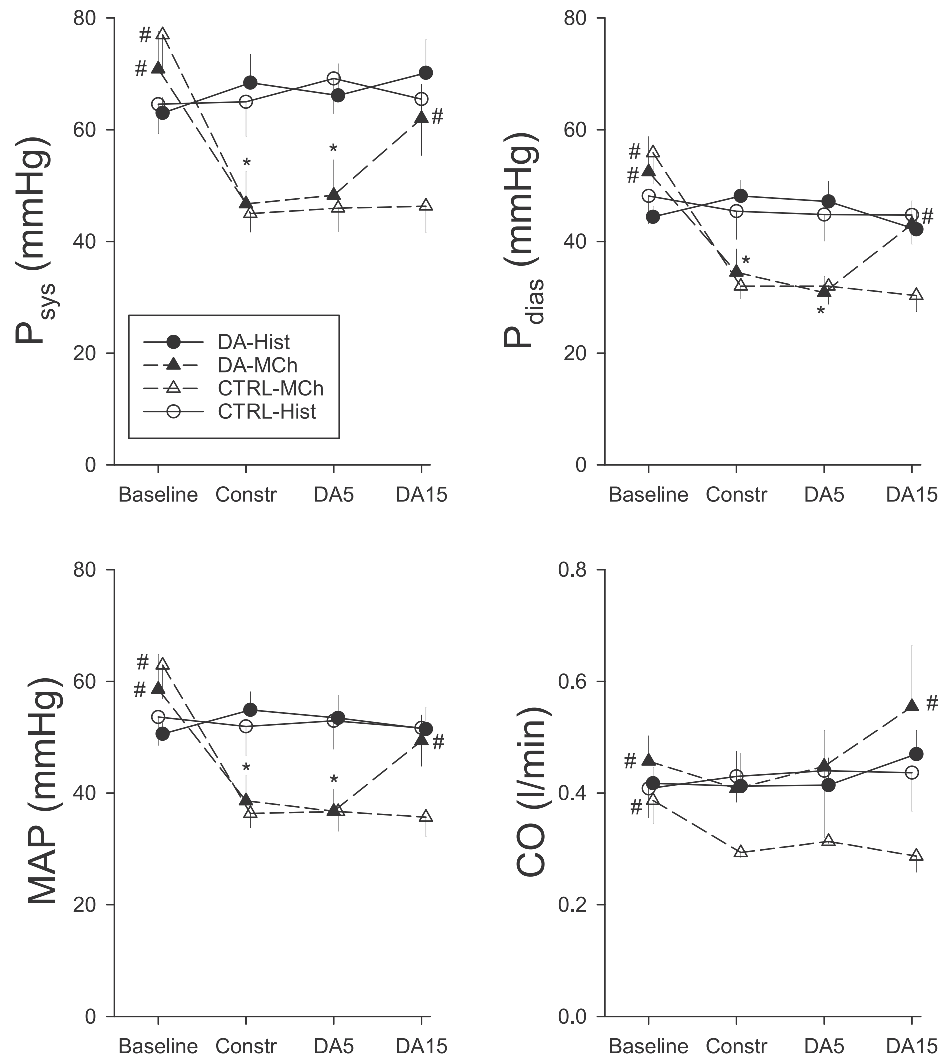

Fig. 2. Hemodynamic changes to methacholine, histamine and dopamine infusions. Psys: systolic blood pressure, Pdias: diastolic blood pressure, MAP: mean arterial pressure, CO: cardiac output, DA: dopamine, Hist: histamine, MCh: methacholine, CTRL: control, Constr: MCh or Hist infusion alone. *: $p < 0.05$ Hist vs MCh within a condition, #: $p < 0.05$ vs. Constr within a group.

step. The same experimental protocol was carried out in the rabbits included in the control group (Group CTRL), however instead of the inotrope, only saline was administered.

2.7. Statistical analysis

The scatters in the parameters were expressed as SE values. The Shapiro-Wilk test was used to test data for normality. Three-way repeated measures of analysis of variances (ANOVA) with the factors experimental group (Group DA or Group CTRL), experimental step (baseline, constrictor, constrictor and dopamine) and constrictor agonist (Hist or MCh) was used to assess the effects dopamine on the respiratory mechanical and hemodynamic parameters. The Holm-Sidak multiple comparison procedure was applied to compare the different conditions (for repeated measures) or agonist types (for independent groups). Correlation analyses between the variables were performed by using Spearman correlation tests. Sample size was estimated based on the Raw values as the primary outcome variable with an expected 25% difference in the lung responsiveness, a power of 0.8 and two-sided alpha error of 0.05. The estimation resulted in a required sample size of 5 for each group, based on the MCh-induced changes in Raw in our earlier study (Porra et al., 2016). The statistical tests were performed within the *R* environment with the *lme4* (Bates et al., 2015) and *lsmeans* (Lenth, 2016) packages and SigmaPlot 13 (Version 13, Systat Software, Inc. Chicago, IL, USA), with a significance level of $p < 0.05$.

3. Results

Hemodynamic effects of the constrictor challenges and the concomitant dopamine administrations are demonstrated in Fig. 2. There was no evidence for a change in any circulatory parameters to Hist, while MCh infusion significantly decreased all blood pressure variables ($p < 0.001$). During MCh infusion, the higher dose of dopamine infusion elevated all blood pressure parameters ($p < 0.05$) and CO significantly ($p = 0.039$) demonstrating its positive inotropic activity.

Respiratory mechanical responses to the constrictor agonists and to the simultaneous infusions of dopamine are depicted in Fig. 3. MCh and Hist both deteriorated the mechanical properties of the respiratory system with significant elevations in Raw ($p < 0.001$) and G ($p < 0.02$) and significant decreases in Iaw ($p < 0.04$). There was no further change in any of the respiratory mechanical parameters in the CTRL group, proving the stability of both constrictor-induced deteriorations. Conversely, dopamine decreased Raw in the presence of both MCh ($p < 0.03$) and Hist ($p < 0.05$).

To further clarify the effects of dopamine on the respiratory mechanics in the presence of MCh or Hist induced constriction, respiratory

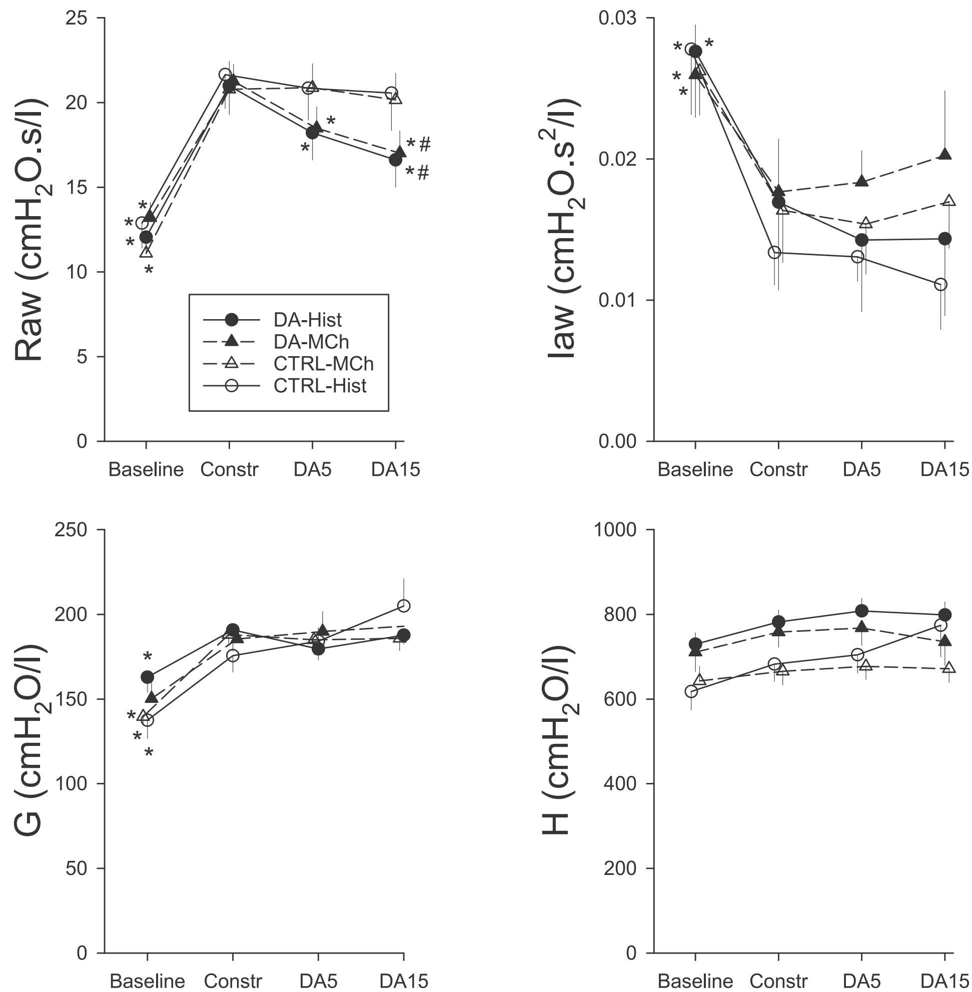

Fig. 3. Respiratory mechanical responses to methacholine, histamine and dopamine infusions. Raw: airway resistance, Iaw: airway inertance, G: respiratory tissue damping, H: respiratory tissue elastance. DA: dopamine, Hist: histamine, MCh: methacholine, CTRL: control, Constr: MCh or Hist infusion alone. *: $p < 0.05$ vs. Constr within a group, #: $p < 0.05$ vs. Group CTRL with the same constrictor agonist.

mechanical changes were also expressed relative to the values obtained when the constrictor agonist was applied alone (Fig. 4). In the CTRL group, no respiratory mechanical responses were observed. However, dopamine induced significant decreases in Raw ($p < 0.03$) in the presence of both bronchoconstrictor agonists with no significant difference between Hist and MCh. There was no evidence for a statistically significant effect of dopamine on the respiratory tissues.

4. Discussion

Respiratory mechanical changes to dopamine were assessed in the present study in an in vivo animal model mimicking clinical scenarios encountered in anesthesia and intensive care management, where the bronchial tone may be elevated by histaminergic and cholinergic pathways. Besides the well-established beneficial cardiovascular effects of dopamine, our findings demonstrate the ability of dopamine to alleviate bronchoconstriction mediated by both cholinergic and histaminergic pathways. Conversely, dopamine had no effect on the respiratory tissue mechanics.

The current forced oscillatory airway and respiratory tissue parameters agree well with those obtained earlier in similar sized rabbits (Babik et al., 2017; Bayat et al., 2009). They also show good qualitative concordance with previous data if the differences in methodology (i.e. open vs closed chest) or body weight are taken into account (Doras et al., 2015; Habre et al., 2002). Furthermore, the pattern and magnitude of the responses in the respiratory mechanical parameters to Hist and MCh are also in accordance with previous results obtained under similar experimental conditions (Habre et al., 2002, 2006; Hantos et al., 1995).

An important feature of our experimental protocol is the existence of a steady-state bronchoconstriction induced by Hist and MCh. In agreement with previous results (Habre et al., 2001), stability of bronchospasm in response to MCh can be achieved by sustained infusions. While in case of Hist, a gradually decreasing response can be anticipated due to tachyphylaxis, this phenomenon is more prominent in the beginning of the challenge (Lutchen et al., 1994). Indeed, the 15-min stabilization period was sufficient to obtain steady-state bronchoconstriction as proved by the lack of changes in Group CTRL (Fig. 3).

Regarding the cardiovascular responses of dopamine, it reversed fully detrimental cardiovascular changes when the constrictor agonist induced significant losses of blood pressure and cardiac output (e.g. MCh). This effect is in accordance with the positive inotropic properties of dopamine. In case of Hist, the doses required to induce similar bronchial responses to MCh did not compromise the cardiovascular system. Thus, in the presence of a normal cardiac function, dopamine did not cause further improvements in agreement with previous data obtained in rabbits at identical doses (Gosliga and Barter, 2015).

No differences were detected in the pattern and magnitude of the respiratory mechanical effects of MCh and Hist: both agents induced constriction of the central conducting airways indicated by the elevations in Raw. In the single-compartment model Iaw is known to reflect the mass of the gas in the airways and G reflects lung tissue damping.

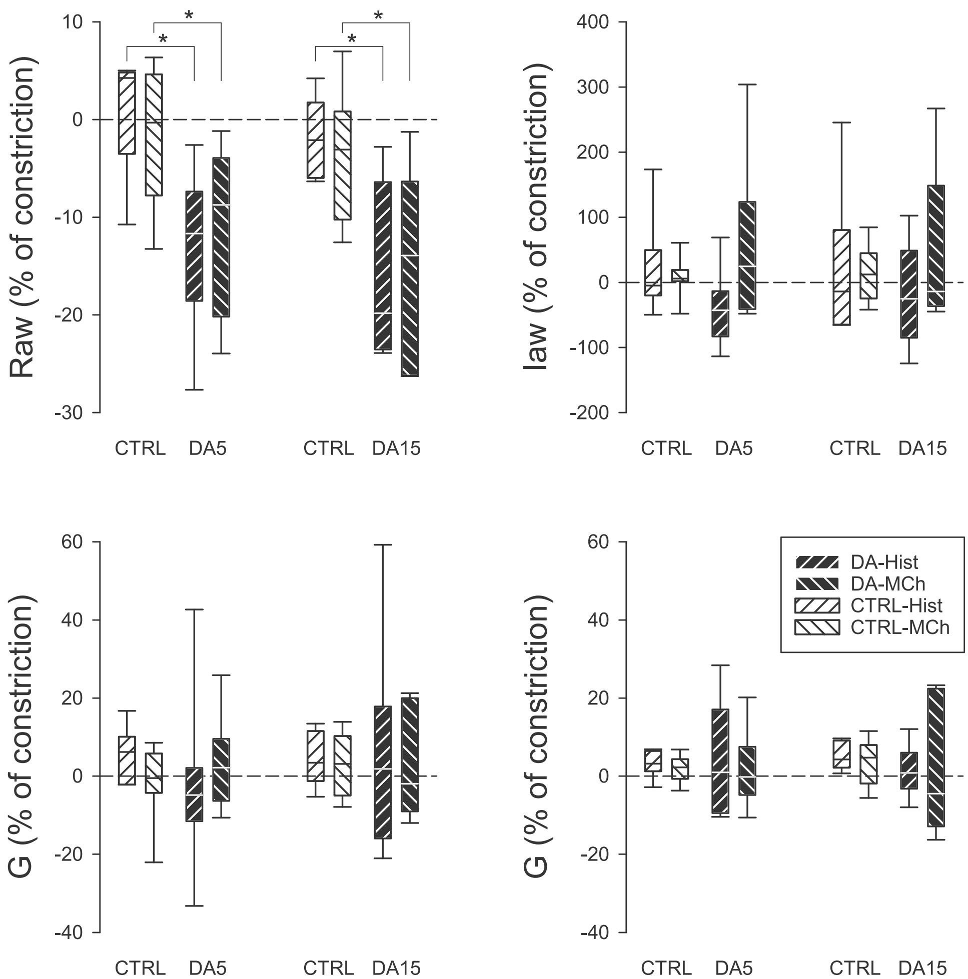

Fig. 4. Respiratory mechanical responses to dopamine infusions relative to those obtained with methacholine or histamine infusions alone. Raw: airway resistance, Iaw: airway inertance, G: respiratory tissue damping, H: respiratory tissue elastance. DA: dopamine, Hist: histamine, MCh: methacholine, CTRL: control, Constr: MCh or Hist. *: $p < 0.05$ Hist vs MCh within a condition.

However, in case of development of peripheral ventilation heterogeneities, decreases in Iaw associated with elevations in G occur (Doras et al., 2018; Lutchen et al., 1996; Petak et al., 1997). Under these circumstances dopamine infusions lowered airway resistance, indicating the potential of this inotrope to relax central airway smooth muscle. The lack of dopamine-induced changes in G and Iaw suggest that the peripheral heterogeneities caused by MCh or Hist were not alleviated.

The most remarkable finding of the present study is the lack of differences between the pattern and the magnitude of the bronchodilator effects of dopamine in the presence of MCh or Hist. In accordance with this finding, there was a statistically significant correlation between relative magnitude of the bronchodilator responses to dopamine in the presence of MCh and Hist ($r = 0.64$, $p = 0.038$, data not shown). The existence of this relationship indicates that greater improvements to dopamine in the presence of one agonist are also associated with proportionally greater changes to the same dose of dopamine in the presence of the other. These results demonstrate that the beneficial bronchial effect of dopamine is mediated by means of pathways other than direct histaminergic or cholinergic antagonism. Considering previous data, the bronchodilation effects of dopamine may be mediated by stimulation of bronchial β_2 adrenergic receptors (Cortijo et al., 1984) or dopamine receptors subtypes D1 or D2 (Cabezas and Velasco, 2010; Mizuta et al., 2012, 2013). Since bronchi have no sympathetic innervation (van der Velden and Hulsmann, 1999), the involvement of a neurally-mediated action of DA is unlikely, direct stimulation of dopamine and/or adrenergic receptors is more probable. However, the exact identification of the individual roles of these mechanisms may be subject of further studies.

A limitation of the present study might be related to the route of application of dopamine. While we applied dopamine intravenously, previous studies evidenced bronchodilation in asthmatic patients undergoing acute asthma attack when inhaled dopamine was applied (Cabezas et al., 2003). Previous studies also described a different pattern of the effect of MCh depending on the administration route (Petak et al., 1997; Strengell et al., 2013). While the pattern of bronchoconstriction was more homogeneous in case of the intravenous route as evidenced by high resolution imaging, the summarized changes were comparable between intravenous and inhalation route with no significant differences in total respiratory resistance and elastance (Strengell et al., 2013). The same principle may be applied to dopamine, i.e. the two routes likely exerting comparable respiratory effects with some differences in the heterogeneity and systemic haemodynamics.

In summary, airway and respiratory tissue mechanical changes were characterized following administrations of dopamine at 2 different doses against two constrictor stimuli. Our findings revealed that in addition to the well-established beneficial cardiovascular effects of dopamine, this inotrope ameliorates both cholinergic and histaminergic bronchoconstriction in a similar degree. Measurement of airway and respiratory tissue mechanics in an in vivo model revealed that the reversal of bronchoconstriction by dopamine is dominant in the central conducting airways, while the responses in the peripheral airway and tissue compartments were less apparent. The concomitant presence of the already established beneficial cardiovascular effects of dopamine and its dose- and stimulus-independent bronchodilator activity may have importance when the circulatory and respiratory systems are both impaired, such as in patients with heart failure associated with bronchial hyperreactivity or in those with an elevated bronchial tone subsequent to impaired circulatory function. Under these circumstances both the improved cardiovascular and respiratory functions to dopamine may be particularly beneficial.

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