

The route of antigen delivery determines the airway and lung tissue mechanical responses in allergic rats

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Summary

Background Previous results have shown tissue constriction in allergic animals following inhalation of an antigen. Further studies have demonstrated a differing response pattern in airway and parenchymal mechanics following inhaled (i.h.) or intravenous (i.v.) delivery of methacholine (MCh).

Objective The purpose of this study was to compare the acute allergic response in airway and parenchymal mechanics following i.h. and i.v. antigen challenge.

Methods Brown Norway rats were sensitized to ovalbumin (OVA). Rats were anaesthetized, paralysed, and thoracotomized, and lung input impedance (ZL) between 0.5 and 21 Hz was measured using small-amplitude pseudo-random oscillations at control, after saline, and for up to 1 h after either i.h. ($n = 7$) or i.v. ($n = 5$) administration of OVA. ZL was evaluated in terms of airway resistance (Raw) and inertance (Iaw), and a constant phase tissue parenchymal damping (G) and elastance (H).

Results Following i.h. OVA challenge elevations were found in Raw [192 ± 32 (SE) %], G ($223 \pm 21\%$), and H ($141 \pm 5\%$). Raw showed higher elevation after i.v. challenge ($418 \pm 57\%$), whereas the elevation in G ($278 \pm 30\%$) and H ($130 \pm 4\%$) was approximately equal to those seen following inhalation of an antigen.

Conclusions Delivery (i.v.) of an antigen produces a significantly higher response in airway resistance, whereas inhaled antigen results in a mixed airway and parenchymal response.

Keywords: airway mechanics, pulmonary mechanics, forced oscillations, acute allergic response

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Introduction

In recent years, it was shown that altered viscoelastic properties of the parenchyma contribute significantly to the observed constriction following the administration of bronchoactive agents [1–13]. These studies mostly examined the differences in airway and parenchymal responses following exogenous bronchoactive agents, such as methacholine (MCh) or histamine [1,2,5,6,12,13]. Furthermore, the results of recent studies comparing airway and parenchymal responses following intravenous (i.v.) or inhaled (i.h.) administration of MCh suggest a more pronounced parenchymal contribution to the overall mechanical

response of the lung when the agent is aerosolized [5,7,12]. The lung response to an inhaled antigen in allergic animal models is also well documented, with findings that the airways and lung tissues both contribute to the overall acute allergic respiratory response [8–10].

Most of these studies, however, utilized alveolar capsules to partition the airway and parenchymal responses [1,2,5,7–10]. Nevertheless, because of the limited number of capsules, under-sampling of the highly inhomogeneous local alveolar pressure regions may bias the separation of the airway and parenchymal properties [14]. Recently, Hantos and co-workers developed an alternative method to separate airway and parenchymal mechanics by modelling low-frequency pulmonary impedance spectra (ZL). Since ZL reflects the mechanical properties averaged for the whole

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lung, this approach offers a more representative picture about the overall mechanical status of the airways and the parenchyma under both control [3,11,12,15–17] and constricted conditions [3,11,12,15]. Nevertheless, this technique has been only used to study the lung response to exogenous constrictive agents. The role of the airway and parenchymal constriction in the acute allergic response following antigen challenge has not been systematically explored.

Therefore, we questioned whether the route of the delivery of the antigen influences the airway and tissue contributions to the overall the lung response, as is the case with MCh [5,7,12]. Furthermore, we investigated whether previous results showing tissue constriction in allergic animals following inhalation of an antigen was a result of artifactual (i.e. capsule related) or real changes occurring in the airways and the parenchyma. To investigate these questions, we induced constriction with i.v. or i.h. administration of ovalbumin (OVA) in OVA-sensitized Brown Norway (BN) rats and partitioned the response into airway and parenchymal components by modelling the low frequency ZL spectra.

Materials and methods

Animals and sensitization

Adult BN rats of both sexes (130–250 g) were studied. Animals were actively sensitized with an intraperitoneal (ip) injection of 0.5 mL of a sterile suspension of 0.1 mg OVA and 50 ng of ricin in saline. Animals were housed in a 'clean' animal house and were studied 9–14 days after sensitization, which is the peak of the immunoglobulin E (IgE) response in this strain [18].

OVA-specific IgE titres were estimated by ELISA according to the method of van Halteren *et al* [19]. In summary, microtitre plates (Falcon flexible assay plate 3912, Becton Dickinson, CA, USA) were coated overnight at 4 °C with mouse anti-rat IgE in PBS (1 µg/mL). Doubling dilutions of standards and samples were added and incubated for 3 h. Digoxigenin conjugated OVA was added (1:4000) and incubated for 1 h, followed by sheep anti-digoxigenin conjugate (1:1000) for 1 h. The peroxidase substrate tetramethylbenzidine was used for colour development and the reaction was stopped by 1 M H₂SO₄. The plates were read spectrophotometrically at 450 nm with an enzyme-linked immunosorbent assay (ELISA) plate reader (Automated Microplate Reader EL311, BIO-TEK Instruments Inc., VT, USA). Titres were expressed as reciprocal log₂ titre. Only those animals with a titre > 1:640 were included in the experiments.

Physiological preparation

Animals were anaesthetized with a mixture of hydrochloride (90 mg/kg) and xylazine (5 mg/kg) 1 mL/kg ip and

maintained with 0.1 mL i.v. hourly. The tail vein was cannulated for the purposes of drug delivery. Tracheostomy was performed, and a metal cannula (length = 12 mm inner diameter = 2 mm) was inserted into the distal trachea. Mechanical ventilation (Model 683: Harvard Apparatus, South Natick, MA, USA) was maintained at a frequency of 90 breaths/min, a tidal volume of 9 mL/kg and a positive end expiratory pressure of 2 cmH₂O. Paralysis was achieved using pancuronium bromide (2 mg/mL; 1 mg/kg initial dose, supplemented every 30 min by 0.05 mL iv). The thorax was opened with midline sternotomy, and the ribs were widely retracted.

Impedance measurements

ZL was measured using the wave-tube technique [12,20,21]. At end expiration the ventilatory circuit was switched from the ventilator to the loudspeaker-in-box system. The loudspeaker-in-box system was connected to the animal via a 114 cm length of polyethylene tubing (2 mm inner diameter). Solid state pressure transducers (ICS model 33NA002D) were placed at each end of the wave-tube (P1, loudspeaker end; P2, cannula end). The loudspeaker was driven using a computer-generated small-amplitude pseudo-random signal containing 15 non-integer-multiple components between 0.5 and 21 Hz. The signals from P1 and P2 were low-pass filtered at 25 Hz, and digitalized at a sampling rate of 128 Hz. The pressure transfer functions P1/P2 were computed by fast Fourier transformation from the 6-s long recordings, using a 4-s time window and 98% overlap. By using the transmission line theory, ZL can be calculated from the P1/P2 spectra, as the load impedance of the wave-tube [12,20,21]:

$$ZL = Z0 \sinh(\gamma L) / [(P1/P2) - \cosh(\gamma L)]$$

where L is the length of the wave-tube, Z0 and γ are the characteristic impedance and the complex propagation wave number, respectively, both determined by the geometrical data and the material constants of the tube and the air.

Parameter estimation

A model containing airway and tissue compartments was fitted to ZL. The airway compartment contained a frequency-independent airway resistance (Raw) and an inertance (Iaw), while the tissue compartment was characterized by constant phase parameters representing tissue damping (G) and elastance (H) [16]:

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

where *j* is the imaginary unit, ω is the angular frequency, and the exponent α is expressed as $\alpha = 2/\pi \arctan(H/G)$. Lung tissue hysteresivity (η) [22] was calculated as G/H. The ZL

data at frequencies coinciding with the heart rate and its harmonics were excluded from the model fitting. The model parameters were obtained by using a relative fitting criteria, i.e. by minimizing the following objective function:

$$F = [(1/m) \sum_{i=1}^m [|ZL(\omega_i) - ZL'(\omega_i)|^2 / |ZL(\omega_i)|^2]]^{1/2}$$

where F is a measure of the 'goodness-of-fit' of the model.

Challenge protocol

Animals were challenged with saline or OVA either via i.h. or i.v. In the i.h. challenge, 5 mL of saline or OVA (5% OVA: wt/v in saline) was nebulized with a jet nebulizer (LC PLUS, Pari-Werk, GmbH, Germany) driven by 5 L/min air, attached to the inspiratory port of the respirator for 5 min. In the i.v. challenge, 0.1 mL of saline or OVA (1% OVA: wt/Vol. in saline) was followed by a 0.15 mL saline flush.

Study protocol

Rats were divided into two groups: (1) aerosol antigen group ($n = 7$) and (2) intravenous antigen group ($n = 5$). Before each experimental protocol started, the volume history was standardized with a sigh produced by two successive inspiratory phases delivering a tidal volume double normal. Control measurements were then made until four successive measurements showed a stable lung preparation. All animals were then challenged with saline either via i.h. or i.v. Following saline challenge measurements were taken every 1 min for 10 min representing the baseline for each animal. The animals were then challenged with OVA by either i.h. or i.v., and ZL data were collected every minute for up to 1 h.

In each group the control and the baseline ZL spectra were ensemble averaged. Following antigen challenge the peak response in Raw data were used for analysis. The allergic responses to antigen challenge are expressed as the percentage from baseline.

Statistical analysis

Variances in parameters were expressed as standard errors. Paired t -test was used to compare the baseline parameters to those obtained after i.v. or i.h. OVA challenges. Because of the difference in weights between the two groups, the mechanical parameters obtained at the baseline, peak response and the maximal increases from baseline following antigen challenges were normalized for weight. Two-sample t -tests with equal variances were subsequently used on the maximal increase from baseline-weight normalized

data to compare the effects of i.h. and i.v. OVA on the model parameters. Significance was accepted with $P < 0.05$.

Results

Control measurements in each animal were made prior to saline challenge. Because of the differences in animal size between groups, baseline lung parameters were normalized for weight. Parameter values for the weight normalized data at baseline, peak response following antigen challenge and the maximal increase from baseline (peak-baseline) for both antigen delivery methods are shown in Table 1. Peak responses occurred within 10 min of challenge in all rats independent of antigen delivery method. Following weight normalization, no significant differences were seen between any of the baseline parameters in either treatment group.

Intravenous antigen challenge

Representative ZL data obtained in baseline condition and following i.v. antigen challenge are demonstrated on Fig. 1. Administration of the antigen (i.v.) resulted in an increase in the real part of ZL (RL) at all frequencies. The parallel shift seen at the higher frequencies represents an increase in Raw, while the increase in the slope of the low frequency section of RL indicates an increase in G. The imaginary part of ZL (pulmonary reactance, XL) showed decreases across all frequencies with the change being more obvious in the lower frequencies indicating an increase in H. Antigen infusion induced a significant increase in all respiratory parameters. A substantial elevation in Raw ($418 \pm 57\%$ of baseline, $P < 0.005$) was noted. A moderate increase in G and η ($278 \pm 30\%$, $P < 0.02$ and $212 \pm 20\%$, $P < 0.001$, respectively) was observed, while H showed a slight increase ($130 \pm 4\%$, $P < 0.05$). Iaw decreased following challenge ($54 \pm 13\%$, $P < 0.05$).

Aerosol antigen challenge

Figure 2 demonstrates the ZL curves for a representative rat received aerosolized antigen. Inhaled antigen challenge produced similar change in ZL to that seen with i.v. delivery; however, the parallel shift at high frequencies of RL was less marked indicating a proportionally smaller increase in Raw. Antigen challenge (i.h.) generated non-significant changes in airway parameters, with an increase in Raw ($192 \pm 32\%$ of baseline, $P = 0.07$) while Iaw decreased ($80 \pm 14\%$). Significant increases were seen in all tissue parameters with a moderate increase in G ($223 \pm 21\%$, $P < 0.001$), while H and η increased to a lesser extent ($141 \pm 5\%$, $P < 0.0001$ and $158 \pm 14\%$, $P < 0.005$, respectively).

Table 1. Weight normalized baseline, peak and maximal increase above baseline following antigen challenge

	Inhaled			Intravenous		
	Baseline	Peak	Increase	Baseline	Peak	Increase
Raw (cmH ₂ O/s/kg/L)	11.3 ± 2.1	24.1 ± 7.9	12.9 ± 5.9	13.9 ± 3.1	55.2 ± 8.9	41.2 ± 6.7*
Iaw (cmH ₂ O/s ² /kg/L)	0.06 ± 0.01	0.04 ± 0.01	−0.01 ± 0.01	0.09 ± 0.02	0.05 ± 0.02	−0.04 ± 0.01
G (cmH ₂ O/kg/L)	147.3 ± 17.3	313.1 ± 24.1	165.8 ± 21.2	116.9 ± 31.6	298.2 ± 67.7	181.3 ± 45.2
H (cmH ₂ O/kg/L)	608.8 ± 33.7	855.1 ± 46.2	246.3 ± 24.4**	471.7 ± 103.9	614.0 ± 141.1	142.3 ± 39.0
η	0.24 ± 0.03	0.37 ± 0.03	0.13 ± 0.03	0.25 ± 0.06	0.49 ± 0.05	0.24 ± 0.01*
Fitting error (%)	3.82 ± 0.32	4.13 ± 0.64		4.43 ± 0.22	3.96 ± 0.22	

* $P < 0.02$; ** $P < 0.04$; G, parenchymal damping; H, elastance; η, lung tissue hysteresivity.

The model fitted equally well during control and constricted conditions independent of the antigen delivery method ($F < 5\%$). The acute allergic respiratory response was influenced by the method of antigen delivery. The increase in Raw, and in η following i.v. delivery was significantly greater than the increase in these variables following inhaled antigen ($P < 0.02$, respectively). In contrast inhaled antigen delivery caused a significantly greater increase in H ($P < 0.04$).

Discussion

The results of the present study demonstrate that both the airway and pulmonary parenchyma contribute to the early phase allergic pulmonary response following antigen challenge in sensitised BN rats, whether delivered by either i.h. or i.v. routes. While the parenchymal responses were approximately equal in the two groups of rats, the magnitude of the maximal increase from baseline in Raw was about threefold greater when the antigen was delivered intravenously.

The model used in the present study to partition ZL into airway and parenchymal components has been used in a number of previous studies to measure lung mechanics under both control [3,11,12,14–17] and constricted [3,11,12,15] states in various species. Several studies have shown that under baseline conditions, the lungs behave in a homogenous fashion and that estimates of airway and parenchymal mechanics are accurate [11,12,14]. Inhomogeneous constriction of peripheral airways can result in an artifactual increase in G, but H is a reliable indicator of a real tissue change [11,12,15,23]. Although constrictor agents have been shown to increase η (i.e. the increase in G always exceeds that in H) [1–3,5,7,11,12], a change in G that is not accompanied by a qualitatively similar change in H might indicate an artifactual change in G as a result of inhomogeneous peripheral airway constriction. By using a

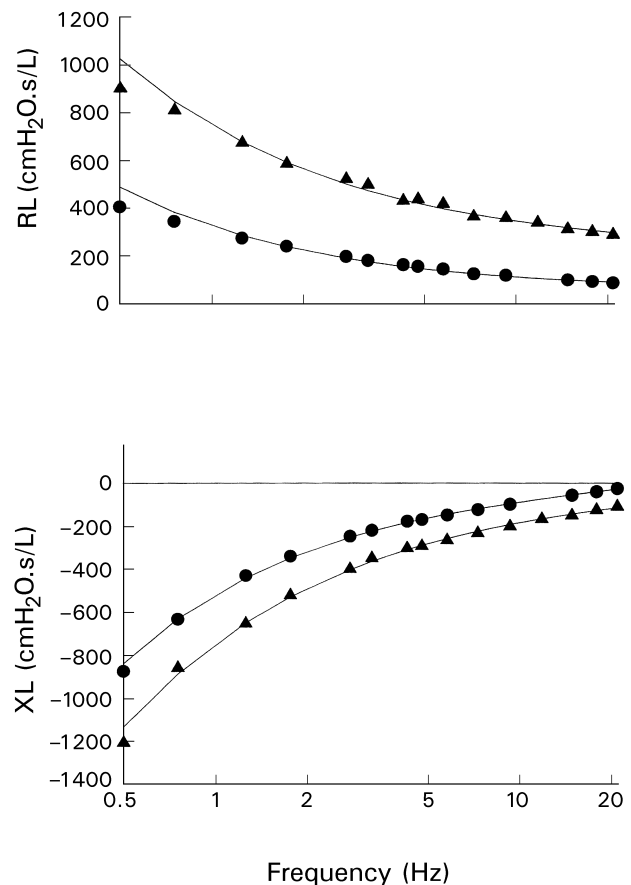


Fig. 1. Real (RL) and imaginary (XL) parts of the pulmonary impedance in a representative rat following saline (●) and i.v. antigen (▲) challenges. Mean ± SD values following saline challenge were obtained by averaging 4–6 successive measurements. Lines denote the corresponding model fits.

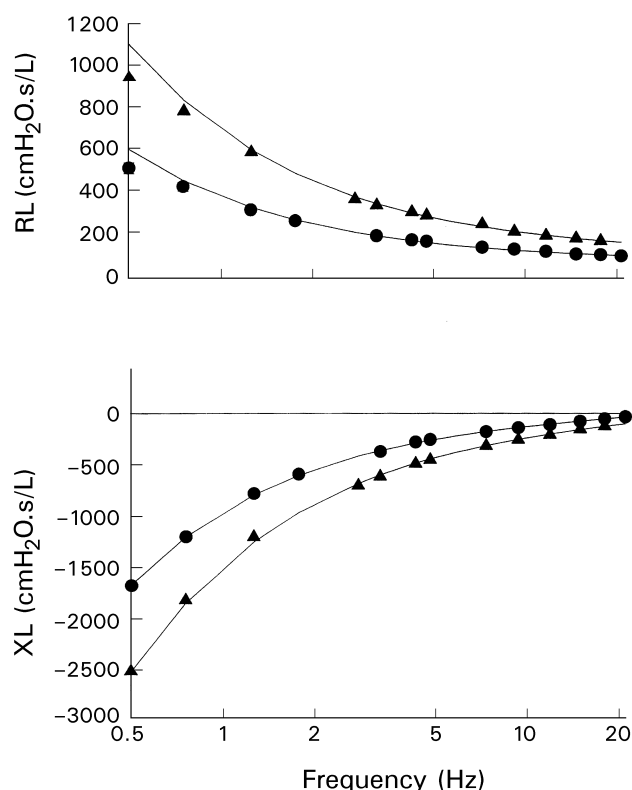


Fig. 2. Real (RL) and imaginary (XL) parts of the ZL in a representative rat from saline (●) and i.v. antigen (▲) challenges. Mean $\pm$ SD values following saline challenge were obtained by averaging 4–6 successive measurements. Lines denote the corresponding model fits.

distributed periphery lung model to simulate ZL data in control and constricted conditions, Hantos *et al.* demonstrated that inhomogeneous peripheral constriction not only causes an artifactual increase in G, but under these circumstances the model systematically underestimates the real law. Therefore we suggest that the significant decreases in law reflect the same phenomenon: inhomogeneous peripheral airway constriction [15].

Antigen challenge (iv versus ih)

Following i.v. antigen challenge significant increases from baseline were seen in all lung parameters. In particular a fourfold increase from baseline was seen in Raw while only moderate changes in tissue parameters were noted. This was in direct contrast to the pattern following i.h. antigen challenge, where statistically significant changes were noted only in the tissue parameters. Previous studies have found a significant increase in both Rti and Raw following aerosol antigen challenge [8–10]. This is similar to the results from our study, although the increase in Raw

($192 \pm 32\%$ of baseline) just failed to reach statistical significance ($P=0.07$). Three animals within the i.h. group had a acute allergic response of less than 150% of baseline. This coupled with small group numbers may explain this failure to reach statistical significance.

Several groups have investigated the delivery-dependant response in rats associated with a MCh challenge [5,7,12] with conflicting results. Salerno *et al.* [12] reported an almost pure tissue response following aerosol MCh. The increase in Rti in this study was attributed to an increase in EL rather than η . In contrast a mixed airway/tissue response was seen with the increase in Rti being significantly influenced by η but not EL following i.v. challenge [7]. Using similar concentrations of MCh Petak *et al.* [12] reported a significant delivery dependant response in Raw and law following an i.v. challenge. Elevations in G and H were shown to be significantly associated with aerosol delivery of MCh [12]. In contrast Nagase *et al.* [5] found a mixed airway/tissue response following both i.v. and i.h. delivery of high concentration MCh. I.v. MCh was found to cause a significantly higher airway response than aerosol MCh. The reverse was found in the tissues, with aerosol delivery causing a significantly greater response in the tissues. The responses in the peripheral airways following aerosol MCh were found to be highly heterogenous and associated with significant lung tissue distortion. The authors concluded that the changes in Rti following aerosol delivery were due to heterogenous parenchymal tissue distortion rather than actual contraction of the peripheral contractile elements [5]. These differences in the pattern of response with mode of stimulus appear to relate to the amount of constrictor delivered to the lung, with higher concentrations of MCh being associated with marked peripheral tissue distortion.

We have reported changes in Raw and η that were significantly greater after i.v. than following i.h. antigen challenge, while i.h. antigen challenge resulted in a significantly greater increase in H. law tended to decrease to a greater degree following i.v. delivery of antigen, this however, did not reach statistical significance ($P<0.07$). The responses in G were independent of antigen delivery route. However, the secondary artifactual increases in G resulting from increased peripheral inhomogeneities in the airways following i.v. antigen challenge may be a contributing factor to our results [3,6,11,12,15,23]. Indeed, the delivery dependant changes in η may be an indication of this phenomenon. Our results are similar to those of other investigators using low concentrations of MCh via i.v. and aerosol routes of delivery [7,12].

Nagase *et al.* have illustrated that following both inhaled antigen and constrictor challenges that morphological changes in airway and tissue structure were well correlated with increases in both Raw and Rti, respectively [5,10].

Salerno *et al.* [24] demonstrated that in parenchymal strips located subpleurally there was no relationship between amount of bronchial wall contained in the parenchymal strip and its contractile response. The authors concluded that smooth muscle within the alveolar duct or the parenchyma itself contributed to the contractile response of the parenchymal strip. In another study, Nagase *et al.* [25] characterized the acute allergic response in bronchial rings and parenchymal strips. They found the allergic response in the airway was completely ablated by serotonin receptor blockers, in particular a 5-HT₂ receptor blocker. In contrast, the contractile response of the parenchyma was abolished only by the combination of serotonin and leukotiene antagonists, demonstrating that (a) mediators other than serotonin were involved and (b) the parenchymal response is not secondary to an airway response [25]. These studies provide evidence that the variations seen in the model used in this study are a reflection of structural changes occurring in both the airways and the parenchymal tissue following antigen delivery.

The acute phase allergic response to an allergen is a function of the effector cell density and location. Mast cells have been shown to be integrally involved in the generation of the acute inflammatory response to administered antigen in sensitised animals [26]. Mast cells participate in the inflammatory reaction by release of both preformed and *de novo* synthesized inflammatory mediators following cross linking of surface bound IgE by specific allergen [26]. In the rat, two major types of mast cells have been identified; connective tissue mast cells (CTMC) and mucosal mast cells (MMC) [27–29]. The location and density of these cells differs throughout the respiratory tract [30]. MMC predominate in the epithelium and lamina propria of the airways whereas CTMC predominate in the submucosa of the airways and the parenchyma of the lung [30]. The mediators released by the MMC and CTMC are different both in type and quantity, e.g. MMC contain a lower concentration of serotonin than CTMC and do not contain leukotriene C₄ (LTC₄) or prostaglandin D₂ (PGD₂) [31]. The data reported by Nagase *et al.* would suggest that CTMC may be involved in the parenchymal response while MMC facilitate the airway response to allergen challenge. There are a number of possibilities which might explain the different patterns of response following aerosol (predominantly parenchymal) and i.v. (predominantly airway) delivery. Different accessibility of the two mast cells might account for this difference, i.e. CTMC may be more readily reached by the aerosol, whereas MMC may be more readily reached by i.v. delivery. Alternatively, the difference between i.h. and i.v. might be a reflection of different doses of allergen presented to mast cells (relatively more delivered i.v.). The results of the present study do not give any direct information regarding these possible actions.

However, the fact that the same pattern of response has been reported by us and others for MCh suggest that different concentration delivered by the two routes may be the most likely explanation [5,7,12].

In summary, the present study has shown that both the airways and the pulmonary parenchyma contribute to the acute allergic response in sensitised BN rats. This response was found to independent of delivery method in Iaw, and G. Raw and η showed a delivery-dependent response, increasing to a significantly higher level following i.v. antigen challenge, while H responded more significantly to inhaled antigen. Differences in the relative distribution of antigen or in the absolute dose of antigen delivered by each route may explain this phenomenon.

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