Kinetics of respiratory system elastance after airway challenge in dogs

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Lauzon, Anne-Marie, and Jason H. T. Bates. Kinetics of respiratory system elastance after airway challenge in dogs. J Appl Physiol 89: 2023–2029, 2000.—We compared the time courses of lung mechanical changes with intravenous (iv) injection vs. aerosol administration of histamine, methacholine, and ACh in dogs. We interpret these results in terms of a spring-and-dashpot model of airway smooth muscle receiving activation via a tissue compartment when agonist is delivered by the iv route and through an additional airway wall compartment when it is delivered by the aerosol route. The model accurately accounts for the principal features of the respiratory system elastance response curves. It also accounts for the differences between iv and aerosol responses, supporting the notion that agonist delivered by aerosol has to traverse a longer pathway to the airway smooth muscle than does agonist delivered iv. The time constants representing diffusive exchange of agonist between compartments were not significantly different for the three agonists, suggesting that the three agonists shared a common principal means of clearance, which was presumably blood flow.

histamine; methacholine; acetylcholine; pulmonary blood flow; bronchial blood flow; pharmacokinetics

PRESUMABLY THE MOST RAPID and homogeneous way to deliver a bronchial agonist to the lungs is via a bolus injection into the circulation. The agonist is transported to the lungs through the pulmonary and bronchial circulations and diffuses across the endothelium and extracellular space to reach the airway smooth muscle. It is then cleared by the pulmonary and bronchial blood supplies and also possibly as a result of in situ degradation (8, 9, 21, 22). The dynamics of this process can be observed in the time course of pulmonary mechanics after agonist injection, which exhibits the relatively rapid rise and slower fall characteristic of pharmacokinetic systems (1, 11, 12).

However, bronchial agonists are usually applied to the lungs through the airways as an aerosol (e.g., Refs. 3, 8, 9), because this mimics the mode of delivery of many noxious environmental agents. Aerosol delivery is also less invasive than circulatory administration and thus results in less systemic exposure to the agonist. It seems natural to assume that the delivery of aerosolized agonist to the airway smooth muscle would be slower than by injection because of the time required for the aerosol to pervade the airways and alveoli and to diffuse across the epithelial barrier. Similarly, one might expect the recovery from aerosol to be slower than from intravenous (iv) injection, and indeed this has been observed for histamine (H) in dogs (9).

We hypothesized that a relatively delayed response to aerosol compared with iv delivery should reflect the dynamics of transit of agonist across the airway wall, which is presumably important in determining the efficacy of inhaled medications. Our goal in this study was, therefore, to develop a pharmacokinetic model to account for the kinetics of bronchoconstriction when agonists are administered either iv or by aerosol, with a view to assessing the time constant of airway wall transit. We based our model on measurements of the acute responses in canine lung elastance to both iv and aerosol administrations of H, methacholine (MCh), and ACh.

METHODS

Experimental. We performed experiments on five mongrel dogs weighing 16–27 kg. The dogs were deeply anesthetized with an iv bolus of pentobarbital sodium (28–43 mg/kg). A rigid cannula (20 mm ID) was inserted into the trachea. Mechanical ventilation was supplied by a volume ventilator (model 618, Harvard Apparatus, South Natick, MA) by using a tidal volume of 15 ml/kg at a frequency of 20 breaths/min. Tracheal pressure (Ptr) was measured via a side tap between the piston and the tracheal cannula with a piezoresistive pressure transducer (Fujikura FPM-02PG, Servoflo, Lexington, MA). Flow at the trachea (V) was measured with a heated Fleisch no. 2 pneumotachograph connected to a piezoresistive differential pressure transducer (MicroSwitch 163PC01D36, Honeywell, Scarborough, Ontario). The measured signals (V, Ptr) were low-pass filtered at 20 Hz with six-pole Bessel filters and then sampled at 100 Hz with a 12-bit analog-to-digital converter (model DT2801-A, Data Translation, Marlborough, MA). Acquisition of data was performed by using the ANADAT/LABDAT software package (RHT-InfoDat, Montreal, Quebec).

The dogs were mechanically ventilated at zero positive end-expiratory pressure throughout the entire experiment.
which consisted of a series of repeated runs each lasting 1 h. Each run began at time \( t = 0 \) with the iv injection of 130 mg pentobarbital sodium to maintain anesthesia and 2 mg pancuronium bromide for paralysis. At \( t = 5 \) min, an iv injection of 2 mg/kg indomethacin was given (except for the first run, which had 5 mg/kg) to reduce tachyphylaxis to repeated applications of bronchial agonist (19). At \( t = 10 \) min, three sighs to total lung capacity were given by briefly inflating the lungs to 3 kPa and then allowing complete expiration. At \( t = 15 \) min, continuous acquisition of \( \text{Ptr} \) and \( \dot{V} \) data was started, and 2 min later a bronchial agonist was given either by iv injection or by aerosol. Finally, at \( t > 45 \) min, data acquisition was stopped. The next run was begun at \( t = 60 \) min. Three pairs of such runs were performed in total. The first of each pair involved iv injection of an agonist, whereas the second involved aerosolization of the same agonist. The three agonists, H, MCh, and ACh, were used in random order. The iv doses were 1 mg H and 0.25 mg for both MCh and ACh. The aerosols were generated by an ultrasonic nebulizer ( DeVilbiss 90B), which delivers particles with a mass median diameter of 0.5–10.0 \( \mu \)m (85% are 4.5–6.0 \( \mu \)m) from solutions of 50 mg/ml of H and 12.5 mg/ml of both MCh and ACh. Each aerosol was delivered continuously through a side port in the inspiratory line of the mechanical ventilator until the peak in \( \text{Ptr} \) had reached \( \sim 75\% \) of the peak value observed during the previous run with the injected agonist. This took typically \( \sim 1 \) min. We found that the final \( \sim 25\% \) of the response was manifest after cessation of aerosol; therefore, the final degree of bronchoconstriction produced by the aerosol matched that produced by iv injection.

Data analysis. The equation

\[
\text{Ptr}(t) = \text{Ers} \dot{V}(t) + \text{Rrs} \dot{V}(t) + P_0
\]

(1)

where \( \text{Ers} \) is respiratory system elastance, \( \text{Rrs} \) is respiratory system resistance, and \( \dot{V} \) is volume, was fit to the data collected during each 30-min measurement period by recursive least squares with a memory time constant of 1 s (10). This gave 30-min signals for \( \text{Ers} \) and \( \text{Rrs} \). \( P_0 \) is the static elastic recoil pressure at that value of \( \dot{V} \) arbitrarily defined to be zero and thus conveniently serves to absorb any errors in the baseline values of \( \text{Ptr} \), \( \dot{V} \), and \( V \). We used \( \text{Ers} \) as our measure of bronchial response because it had a better signal-to-noise ratio than \( \text{Rrs} \) and most likely reflects the same phenomena.

The \( \text{Ers} \) signals obtained in the present study were smoothed using a running mean with a 4-s window and then decimated to 1 Hz. The mean baseline value of \( \text{Ers} \) (i.e., that value just before onset of bronchoconstriction) from all dogs for all experimental runs was 2.30 ± 0.29 (SD) kPa/l. The SD of baseline \( \text{Ers} \) in any one dog was 6%. The \( \text{Ers} \) signals obtained with both injection and aerosol did not return to baseline at 30 min after agonist application but instead plateaued at a level typically about one-third of the peak level above baseline. This residual degree of bronchoconstriction was only reversed when the three total lung capacity sighs were given before the next run.

The \( \text{Ers} \) signals obtained with iv injection of agonist were true impulse response functions in the sense that an iv bolus represents an impulsive input compared with the time scale of the response in mechanics. The \( \text{Ers} \) signals obtained after aerosol, however, could not be considered impulse responses in the same way, because the aerosol was given over a period of \( \sim 1 \) min. Therefore, to make the two sets of signals comparable, we convolved the iv \( \text{Ers} \) signals with a unity area box function to simulate the effect of administering the agonist uniformly over 1 min rather than as a sharp bolus. Solid areas refer to the \( \text{Ers} \) signals obtained during iv injection, we mean the signals obtained by convolving the original signals with the 1-min box function. Figure 1 shows the \( \text{Ers} \) signals obtained up to 10 min from all dogs (mean ± SD) after both iv injection convolved with the box function (shaded areas) and aerosol (solid areas) for all three agonists investigated. The baseline values have been set to zero, and the peak values in each case have been normalized to unity to allow shape comparison.

Model development. We first consider the responses to injection (shaded areas in Fig. 1). For all agonists, there is an initial, brief period during which \( \text{Ers} \) remains at baseline, which we presume reflects the circulatory transit time re
required for agonist to reach the lungs from the injection site. This is followed by a rapid increase in Ers to a fairly sharply defined peak. The duration of this rising portion is in the order of 1 min, which is the width of the box function we used to convert the response from that of a bolus injection to one representing an infusion over 1 min. Indeed, before convolution, the 20−80% rise times of the iv injection Ers signals were an average of 11 s. This suggests that, once agonist was delivered to the muscle, its response was fully manifest in much <1 min, similar to the rate of contraction of single airways seen in rat lung explants (23). Thus most of the rise time of the convolved Ers was accounted for by the spreading effect of the convolution and thus presumably represents physical delivery of agonist to the airway smooth muscle. By the same token, we presume that physical delivery of agonist to the epithelium was the principle rate-limiting step in the onset of response to aerosol. Our model of Ers dynamics must, therefore, embody the notion that the magnitude of the response is proportional to the local accumulation of agonist at the level of the airway smooth muscle.

We now consider how to link a change in smooth muscle activation to a change in what we actually measured, namely Ers. The relationship between these two quantities is certain to be quite nonlinear. However, the actual changes in Ers that we achieved in our experiments were relatively small, as a fraction of baseline Ers; therefore, we will assume that the change in Ers is proportional to the force generated by the airway smooth muscle. For the same reason, we will also assume that the airway smooth muscle shortens by an amount proportional to the increase in muscle force. This is readily modeled by placing a spring (elastic constant E) in parallel with a force generator (Fig. 2A), where the active force F(t) produced by the generator is proportional to the local accumulation of agonist, whereas the length of the spring can be taken to represent the degree of airway narrowing in some fashion. However, a spring on its own will return to its original unstressed length when the active muscle force is over. Experimentally, Ers did not return to baseline but instead plateaued at a somewhat elevated level (Fig. 1), similar to observations that have been made in previous studies (1, 5). Ers only returned to baseline after we briefly inflated the lungs to 30 cmH₂O. To account for this effect empirically in our model, a dashpot (resistance R) is included in series with the spring (Fig. 2A). Now when the muscle shortens, the dashpot moves at a rate proportional to the active force so that the length of the total spring-dashpot assembly (the analog of muscle length) is reduced. Subsequent relaxation of the spring returns the assembly to a shorter length than that which it had initially.

This construct can now be incorporated into the model of the kinetics of bronchial agonist and its distribution for iv administration shown in Fig. 2B. When agonist is administered iv, it reaches the lungs via the pulmonary vasculature from which it enters a tissue compartment (representing endothelium, connective tissue, interstitial fluid, etc.). Its concentration within this compartment is s(t). The tissue compartment then exchanges agonist diffusively with an airway smooth muscle compartment, which represents the immediate vicinity of the smooth muscle. The agonist concentration a(t) within the airway smooth muscle compartment is what determines F(t) (Fig. 2A). To have a mechanism for eliminating agonist and permitting recovery from bronchoconstriction, the airway smooth muscle compartment also has a clearance pathway with a time constant c (Fig. 2A).

We used this model to mimic our 600-s iv data (Fig. 1) by having an agonist concentration profile i(t) in the pulmonary vasculature (Fig. 2A) begin at zero for 5 s (representing a transit delay for the injected agonist to reach the lungs), then rise immediately to a constant value for 60 s (representing the 1-min infusion), and then finally fall to zero again for the remaining 520 s. The distance d between the two horizontal
bars in Fig. 2A was taken as our surrogate of smooth muscle length, with $E$ being taken as inversely proportional to $d$. The smooth muscle time constant $\tau$ ($= R/E$) was given a fixed value, as it represents a physical property of the smooth muscle and the lungs and, therefore, should presumably not vary with different agonists. We found by trial and error that a value for $\tau$ of 600 s gave good results. The remaining model parameters $k$ and $c$ were then adjusted to produce the best fit between the measured iv Ers curves for H, MCh, and ACh and the simulated curves. The equations of the model and their numerical solution are detailed in the APPENDIX.

The aerosol Ers curves (Fig. 1) are smoother and shifted to the right compared with the iv curves. This suggests that agonist must traverse an additional compartment when administered as an aerosol. This also seems reasonable on anatomic grounds, as an aerosol must first accumulate on, and then penetrate, the mucous and epithelial layer lining the airway before reaching the interstitium and finally the airway smooth muscle. We, therefore, postulate the existence of an airway wall compartment that receives an input of agonist $i(t)$ from the airway lumen that follows the same time profile as the iv input from the vasculature. The agonist concentration in the airway wall compartment is $w(t)$. The airway wall compartment then diffusively exchanges agonist with the tissue compartment with a time constant $m$ (Fig. 2C). The resulting changes in Ers were simulated in the same way as for the iv administration using the previously determined values of $k$ and $c$, except this time the airway wall compartment was included and the value of $m$ was adjusted to produce the best fit between measured and modeled curves.

RESULTS

Figure 3 shows the mean normalized iv data from all animals together with the fits obtained with the model in Fig. 2B. The means and SDs of the best-fit model parameters ($\tau$, $c$, and $k$) obtained from individual animals are given in Table 1. Figure 3 also shows the mean normalized aerosol Ers curves together with the best-fit model curves. Table 1 also lists the means and SDs of the best-fit values of $m$ obtained from individual animals.

Although the mean value of $m$ for MCh seems higher than for the other agonists (Table 1), there were no significant differences in any model parameter among agonists ($P < 0.05$, paired t-test).

DISCUSSION

The temporal responses to various agonists given both iv and by aerosol have been reported by others (3, 8, 9). However, our study is the first, to our knowledge, to compare the iv and aerosol responses to H, MCh, and ACh by using the same methodology and to try and interpret these responses in terms of a pharmokinetetic-type model. Figure 3 shows that our model accounts for the essential features of the Ers time course for both iv and aerosol administration, including the rapid rise, the transient peak, and the slower recovery. Furthermore, the transformation from the iv to the aerosol response is accurately accounted for (Fig. 3) in terms of a single airway wall compartment (Fig. 2C).

The Rrs signals we obtained in our dogs tended to be rather noisy, often exhibiting spurious oscillations of comparable magnitude to the changes induced by the agonists. We presume this reflected a poor signal-to-noise ratio resulting from the rather small bronchoconstrictive responses that we elicited. In contrast, the Ers signals were considerably smoother, probably reflecting the fact that the majority of the mechanical impedance of the lungs during normal ventilation is elastic rather than resistive. This means that Ers is more precisely determined by the data than is Rrs. We, therefore, used Ers as our measurements of bronchoconstrictive response, rather than the more usual Rrs. It has been shown previously on numerous occasions (e.g., Refs. 1, 2, 6, 14) that bronchoconstriction invari-
ably causes corresponding changes in both Rrs and Ers. Indeed, as far as one could tell from visual inspection of the data from the present study, the Rrs and Ers signals were very similar apart from their different levels of noise, suggesting that they both contained the same information about the dynamics of bronchoconstriction. Our laboratory has previously found this to be the case in dogs receiving much larger doses of bronchial agonist (Fig. 1 of Ref. 12). The reasons why this is so may relate to the fact that the airways and parenchyma are intimately juxtaposed so that a constricting airway will induce stresses in the adjoining parenchyma, thereby making it stiffer. Also, experimental evidence points to bronchoconstriction being an inherently inhomogeneous event (1, 13, 15), which seems reasonable given that airways differ in their mechanical properties, amounts of smooth muscle, and access to the vasculature. Consequently, bronchoconstriction produces regional time constant differences that get worse as the overall level of constriction increases and that produce increases in dynamic lung elastance (1, 14). We thus conclude that either Rrs or Ers can be used as an index of bronchial response to an agonist. Our measurements of Ers also included the elastance of the chest wall. However, we do not believe that significant changes in chest wall mechanics should occur with bronchoconstriction, compared with the changes taking place in the lung; therefore, we took changes in Ers to indicate changes in lung elastance.

Figure 1 suggests that the recovery from ACh was slightly more rapid than from the other two agonists. This is what we would expect given the more rapid enzymatic degradation of ACh (20). Similar observations were obtained by Kelly et al. (9) for iv administration of the three agonists, although, again, their time constants were somewhat different from ours, perhaps because of differences in experimental methods and dose of agonists. There are plenty of reasons for suspecting that the clearance rates should be different for all three agonists, as the enzymes responsible for local degradation of H and MCh and ACh are different (9). Cartier et al. (3) found that recovery from aerosolized MCh was much slower than that from aerosolized H in humans, although this contrasts with the iv results of Kelly et al. (9), perhaps because of species and methodological differences. It has also been shown that pulmonary blood flow influences recovery from H but not MCh and ACh (9), whereas bronchial blood flow affects recovery from H (8) and MCh (21). Despite this, however, there were no significant differences in the values of c for any of the agonists (Table 1). This may have been due to the large variability in the values of the model parameters among animals. Such variability could have obscured any differences among parameters because of differences in clearance mechanisms. Even so, the essential similarities of the values of c lead us to conclude that a common predominant mechanism was responsible for the clearance of all agonists in our experiments, and the obvious candidate is blood flow.

Our data clearly show (Fig. 1) that recovery is slower for aerosol delivery than for iv. Kelly et al. (9) made similar observations for H in dogs and concluded that this was due to a greater volume of distribution for the aerosol than for the injected agonist. Our model incorporates a specific mechanism whereby this greater distribution volume is achieved, namely the presence of an additional compartment representing the airway wall and any other structures that a drug must traverse when delivered by aerosol as opposed to iv (Fig. 2C). Such an additional compartment seems reasonable on anatomic grounds, as an aerosol must first accumulate on, and then penetrate, the mucous and epithelial layer lining the airway before reaching the interstitium and finally the airway smooth muscle. The effect of this compartment is both to delay the peak in the response and to slow its subsequent decay (Fig. 3).

The parameter m represents diffusive exchange of agonist across the airway wall compartment and has a value in the order of 1 min, albeit with large interanimal variation (Table 1). This quantity presumably has significance for the efficacy of drug delivery by aerosol and would be expected to change with alterations in the thickness of the airway wall and associated components. For example, damage to the epithelium by cationic proteins (4) might be expected to decrease m.

Our model is extremely simplistic. For example, the spring-and-dashpot muscle representation in Fig. 2A neglects many details that have been shown to pertain to real airway smooth muscle, such as plasticity to length changes (7). However, for our present purposes, we merely require a construct that behaves empirically like the contractile machinery activated during our experiments. A key feature of our data is that Ers recovered to an elevated level (Fig. 1) that was only returned to baseline with a deep lung inflation. This phenomenon may be due to some regions of the distal lung becoming closed off during bronchoconstriction and only being reopened with a large inflation. Such closure was postulated to account for some of the observations in our previous study of the acute time course of bronchoconstriction to H in the dog (1). Also, the recent computer modeling studies of Lutchen et al. (13) support the notion that bronchoconstriction is attended by diffuse closure of lung units.
A key assumption we made in developing the aerosol model is that the delivery of agonist from the tissue compartment to the airway smooth muscle compartment is the same for both aerosol (Fig. 2B) and iv (Fig. 2C) administration. This is almost certainly not precisely the case in practice. Studies in rats, for example, have shown different patterns of constriction in the lung and different signatures of change in mechanical impedance with the two modes of administration (15, 16, 18). However, we have no idea how to incorporate such mode-dependent effects into our model or even whether they are important compared with the processes for which we have accounted. We, therefore, assume that they are not important and offer as support for this notion the fact that the model curves fit the mean data well (Fig. 3) and seem to be able to account for the differences between iv and aerosol dynamics with only a single addition parameter ($m$).

Interestingly, our study shows that the bronchoconstrictive response to a short application of bronchial agonist is transient, regardless of whether the application is by injection or by aerosol. Thus even though there is a period of a few minutes around the peak aerosol responses in Fig. 1 when Er is not changing very rapidly (particularly for H and MCh), the responses all begin to decay immediately after peaking, without there being any clear plateaus at the peak. Cartier et al. (3) measured the response to aerosolized H and MCh in humans and reported response plateaus of ~17 and 75 min, respectively, before recovery. These recovery times are very much greater than ours, and we are not sure how to account for differences of this magnitude, especially as our recovery times are similar to those of other investigators (9). A possible explanation is that Cartier et al. (3) defined the plateau arbitrarily as being the time during which their response was within 20% of the maximum; thus the response was actually recovering slowly during the designated plateau phase. Also, they measured their responses in terms of lung conductance, which is the inverse of resistance and, consequently, appears to change less terms of lung conductance, which is the inverse of resistance, than the value of the model parameters chosen to achieve a best fit between the simulated and measured Ers curves.

APPENDIX

The equation describing the rate of change of agonist in the tissue compartment in the iv model (Fig. 2B) is

$$V_s \frac{dx(t)}{dt} = q(t) + \alpha [a(t) - s(t)]$$  \hspace{1cm} (2)

where $V_s$ is the volume of the tissue compartment, $t$ is time, $q(t)$ is the flow of agonist into the tissue compartment from the pulmonary vasculature, and $\alpha$ is a rate constant for exchange between the tissue and airway smooth muscle compartments. The $a(t)$ and $s(t)$ quantities are shown in Fig. 2B. Rearranging Eq. 2 gives

$$\frac{ds(t)}{dt} = q(t) \frac{1}{V_s} + \frac{\alpha}{V_s} [a(t) - s(t)]$$

$$= i(t) + \frac{1}{k} [a(t) - s(t)]$$

where $i(t)$ and $k$ are shown in Fig. 2B. Similarly, for the airway smooth muscle compartment (Fig. 2C), one obtains

$$\frac{da(t)}{dt} = \frac{1}{c} [s(t) - a(t)] - \frac{1}{c} a(t)$$

where $c$ is a model parameter. The $a(t)$ was taken as proportional to active force $F(t)$ in the smooth muscle model (Fig. 2A), which obeyed the equations

$$F(t) = E x(t)$$

and

$$E x(t) = R \left[ \frac{dd(t)}{dt} - \frac{dx(t)}{dx} \right]$$

where $x(t)$ is the extension of the spring, and the remaining quantities are shown in Fig. 2A. Equations 3–6 were integrated at 100 Hz by using first-order Euler integration, with $i(t)$ as described in the text and with the values of the model parameters chosen to achieve a best fit between the simulated and measured Ers curves.
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