Constant Phase Model's Sensitivity to Increasing Doses of Methacholine

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Abstract

The Constant Phase Model is an important approach for assessment of respiratory mechanics as its parameters have important physiological interpretations. As it is used extensively for fitting impedance data for mice and other small animals, particularly under effect of bronchoconstricting drugs, it becomes relevant to analyze how impedance magnitude respond to this stimulation accordingly to the model's parameters. This study intends to evaluate the different behaviors under increasing methacholine (MCh) doses through a sensitivity analysis to measure the model's responsiveness. Also, there is an evaluation of how the sensitivity coefficients change relatively to each MCh dose, in observation of a relation between the doses and the evolution of the impedance's absolute value and the parameters. Results suggests that increasing MCh doses accentuate the dissipative effects, which means that the contribution of conservative parameters to impedance's magnitude is reduced while the dissipative parameters relevance are increased. In addition to it, in observation of the strictly growing behavior of the sensitivity coefficients' deviation from Phosphate Buffered Saline (PBS) coefficients, one can notice how this pattern evolves as the MCh doses changes.

Keywords

Sensitivity • Constant phase model • Methacholine doses

1 Introduction

In assessment of respiratory mechanics, the input impedance measure, defined as the ratio in frequency domain of the tracheal pressure and the airflow in the airways, is a powerful tool to analyze how the respiratory system behaves. Its interpretation becomes valuable to analyze the respiratory system state when there is a link to the system physiology, which is obtained through fitting specific mathematical models to such data. A model largely employed to such purpose is the Constant Phase Model (CPM), whose parameters are airway resistance (R), airway inertance (I), tissue elastance (H), related to energy stored in the tissue and the tissue viscance (G), related to tissue dissipation of energy [1]:

$$Z(\omega) = R + j\omega I + \frac{G - jH}{\omega^{\alpha}} \tag{1}$$

where, $\alpha = (2/\pi) \cdot \text{atan}(H/G)$ and $\omega = 2\pi f$.

This model has been used to fit impedance data in mice, rats and dogs [2]. Often this data is obtained through multiple measures of tracheal pressure under increasing bronchoconstrictor drug doses, i.e. methacholine (MCh). Such a procedure can vary the values obtained, depending on how the drug is applied. The most used approach is the bolus technique, which is a unique drug application that has a maximum response near the moment in which the application is made, but also a responsiveness that decay through time. In contrast, there is the continued infusion technique, used by Thamrin et al. [3], in order to evaluate the CPM's sensitivity coefficients and uncertainty of its parameters.

Considering the relevance of the MCh to the impedance measure, it becomes natural questioning how higher doses of this bronchoconstrictor drug can influence impedance response in contrast to the low doses. However, it is important to emphasize that the difference between the two application methods, as previously discussed, is very relevant to respiratory system response. For the sake of

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R. Costa-Felix et al. (eds.), *XXVI Brazilian Congress on Biomedical Engineering*, IFMBE Proceedings 70/1, https://doi.org/10.1007/978-981-13-2119-1_3

comparison, in this study, we will consider the impedance measure under increasing MCh doses using bolus technique in comparison to the results obtained by Thamrin et al. [3].

2 Methods

2.1 Measurement and CPM Parameter Estimation

All experiments involving laboratory animals were evaluated and approved by the 'Ethics Committee for Animal Use' (N° 15 on pgs. 16 of Book 3, 03/27 2014) from the Institute of Biomedical Sciences—University of São Paulo. The procedures are according to the Brazilian National Law number 11794 from 10/08/2008, which regulates all research activities involving animal use in the country.

The experiment was performed in 9-week female Balb/c mice (n = 5) (23.11 ± 1.27 g). The animals were sedated with an intraperitoneal (i.p.) injection of Ketamine (120 mg/kg) and Xylazine (12 mg/kg). The tracheostomy and cannulation were performed with a metal cannula 18G (BD Company, Brazil).

Then, the animal was connected to a small animal ventilator (flexiVent version 5.2, SCIREQ, Canada) and ventilated in quasi-sinusoidal wave form with a tidal volume of 10 mL/kg, PEEP of 3 cmH_2O and respiratory frequency of 150 breaths per minute. The right jugular vein was dissected by inserting a needle attached to a flexible PVC tube (Critchley Electrical Products PTY, Australia).

The respiratory muscles were blocked with pancuronium bromide (1 mg/kg i.p.) and two alveolar recruitment maneuvers were performed (up to the value of 30 cmH_2O).

After the recruitments, PBS (Phosphate Buffered Saline) was injected through the right jugular vein and 15 perturbations of 3 s each were performed. The perturbations were composed of a sum of 13 sinusoids (Hz): 1, 1.5, 2.5, 3.5, 5.5, 6.5, 8.5, 9.5, 11.5, 14.5, 15.5, 18.5 and 20.5. There was a 2 min interval between the PBS and each new dose.

The same perturbations were performed for all doses of Methacholine (MCh): 30, 100, 300, 1000 µg/kg and the MCh also was injected through the right jugular vein in bolus. Automation routines of the ventilator control program were used to perform the perturbations.

Thus, we took the average between all PBS measurements in order to fit CPM to one average impedance. As we are using bolus technique for applying MCh, we took the average between the second impedance measurement of each animal, which was the highest MCh response among all measurements.

The CPM parameters (R, I, G and H) estimation for the average impedances were made by the minimization of an error function, whose entries are grouped by the vector $\theta = (R, I, G, H)$ [3, 4]:

$$\phi(\theta) = \left[\frac{1}{p}\sum_{i=1}^{p} |Z_d(f_i) - Z_m(f_i)|^2\right]^{1/2} \quad (2)$$

where p is the quantity of frequencies considered in the study, $Z_d(f_i)$ is the measured impedance and $Z_m(f_i)$ is the model prediction for the impedance, both calculated at frequency f_i.

2.2 Sensitivity Coefficient

As defined by Beck and Arnold [5], it is possible to consider a sensitivity coefficient to evaluate how fast the model changes as the constants (R, I, G and H) change. It also provides important physiological information about the contribution of airways and tissue to the impedance. Here, we considered the pondered partial derivative of $|Z|$ with respect to the parameter θ calculated at the frequency f_i [3]:

$$X_\theta(f_i) = \frac{|\theta|}{|Z|}\frac{\partial |Z|}{\partial \theta}(f_i) \quad (3)$$

As we calculated an analytic expression of the partial derivative for each θ, we were able to calculate the numerical value of this expression for each frequency f_i.

2.3 Model for Sensitivity Coefficients

Considering the Eq. (3), one can get analytic expressions for each one of the sensitivity coefficients. Although, the expressions would get over complicated to compute the distance between the functions. For simplifying, we consider a model containing exponential functions:

$$X_\theta(f) = \beta_1 e^{\beta_2 f} + \beta_3 e^{\beta_4 f} + \beta_5 \quad (4)$$

The function $X_\theta(f)$ is defined for each sensitivity coefficient in terms of the frequency, then the domain of the functions is the closed interval $[1\,\text{Hz}, 20.5\,\text{Hz}]$.

2.4 Parameter Estimation for Sensitivity Model

The sensitivity coefficients are fitted to the model exposed by Eq. (4) through the minimization of the error function,

whose entries are determined by the vector $\beta = (\beta_1, \beta_2, \beta_3, \beta_4, \beta_5)$, which are the model constants:

$$\phi(\beta) = \left[\frac{1}{n-1}\sum_{i=1}^{n}\left(\frac{X_\theta(f_i) - X_\theta^*(f_i)}{X_\theta(f_i)}\right)^2\right]^{1/2} \quad (5)$$

where $X_\theta(f_i)$ is the sensitivity coefficient magnitude taken by expression (3) and $X_\theta^*(f_i)$ is the prediction of the model, both calculated at frequency f_i, and n is the quantity of frequencies considered in the study. Through the process of the minimization of $\phi(\beta)$, it's possible to determine the constants of the model for each sensitivity coefficient.

2.5 Distance Function Evaluation

As a way to show, numerically, how sensitivity coefficients change as the methacholine infusion rate changes, we will take calculations of the distance between the functions fitted to each sensitivity coefficients using Eq. (4). The distance is a parameter to define how different two functions are, as it can be zero if both functions are the same.

Considering two continuous functions $f(x)$ and $g(x)$, whose domain is the closed interval $[a, b]$, the distance between those two functions is defined as [6]:

$$\|f - g\| = \sqrt{<f - g, f - g>} \quad (6)$$

where the operation $<.,.>$ is defined by:

$$<f, g> = \int_a^b f(x)g(x)dx \quad (7)$$

As we have considered functions for the sensitivity coefficients in the domain of frequency [1 Hz, 20.5 Hz], we get to:

$$\|p(f) - q(f)\| = \left[\int_1^{20.5}(p(f) - q(f))^2 df\right]^{1/2} \quad (8)$$

This number, that consists of a measure of distance between the functions, allows us to evaluate how much of difference exists between them, as if this number approaches zero, the function $p(f)$ approaches $q(f)$. Considering this approach, for the sake of comparison, we will take the distance of each coefficient (relative to 30 μg kg^{-1}, 100 μg kg^{-1}, 300 μg kg^{-1} and 1000 μg kg^{-1} MCh dose, respectively) in relation to the PBS coefficients, which is precisely the deviation from PBS.

3 Results

3.1 Impedance Fit

We took the average between the impedance's measurements of each animal and then obtained an average impedance for each MCh dose. The CPM was then fitted to these values as a way to describe the respiratory system's average parameters for each case. Observing Fig. 1, one can note how MCh contributes for rising Re(Z) and Im(Z), which also contributes to impedance's absolute value (|Z|) gain. It can be interpreted as the bronchoconstriction effect turning the breathing into a more effortful task.

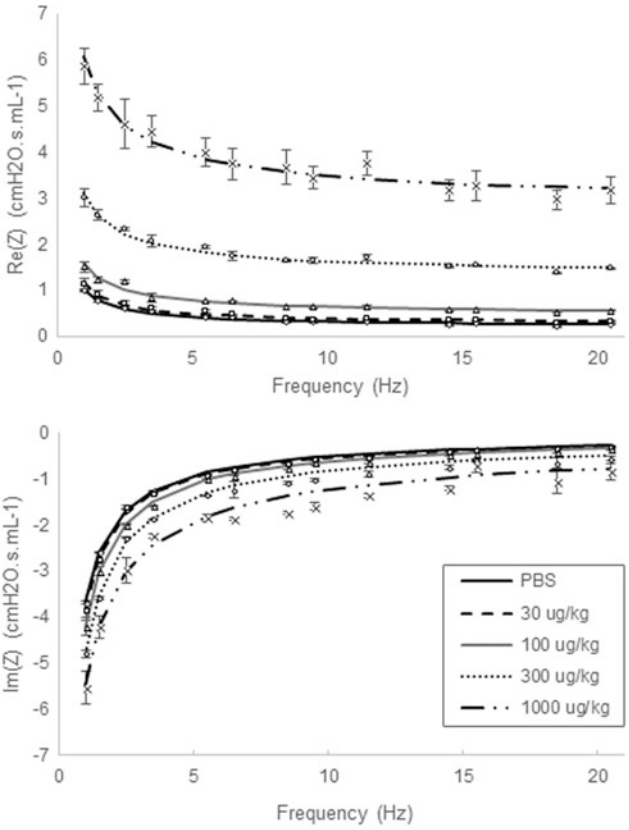

Fig. 1 Typical CPM fit for each MCh dose using the average taken by impedance data versus frequency. The notation Re(Z) and Im(Z) indicates, respectively, the real part and imaginary part of Z. The continuous line indicates the model fit and the open symbols are located specifically at the average of measurements of all mice for the respective frequency at each MCh dose. The bars describe the standard deviation for each point

3.2 Methacholine Pattern

We took calculations for the sensitivity coefficients of the average impedance values. After taking the calculations for the coefficients in the known frequencies, we calculated the constants $\beta = (\beta_1, \beta_2, \beta_3, \beta_4, \beta_5)$ that best suited those points using the minimization of the error defined by Eq. (5). This process allows to evaluate de behavior of the sensitivity coefficients analytically. The graphic results for the model fit are shown in Fig. 2. The fitting error, in all cases, was less than 5%.

Distinguished patterns can be observed at each case, but the overall behavior is that the sensitivity coefficients related to the R parameter increases with frequency while the I coefficients remains essentially the same. The G coefficient tends to increase slowly with frequency at small MCh doses

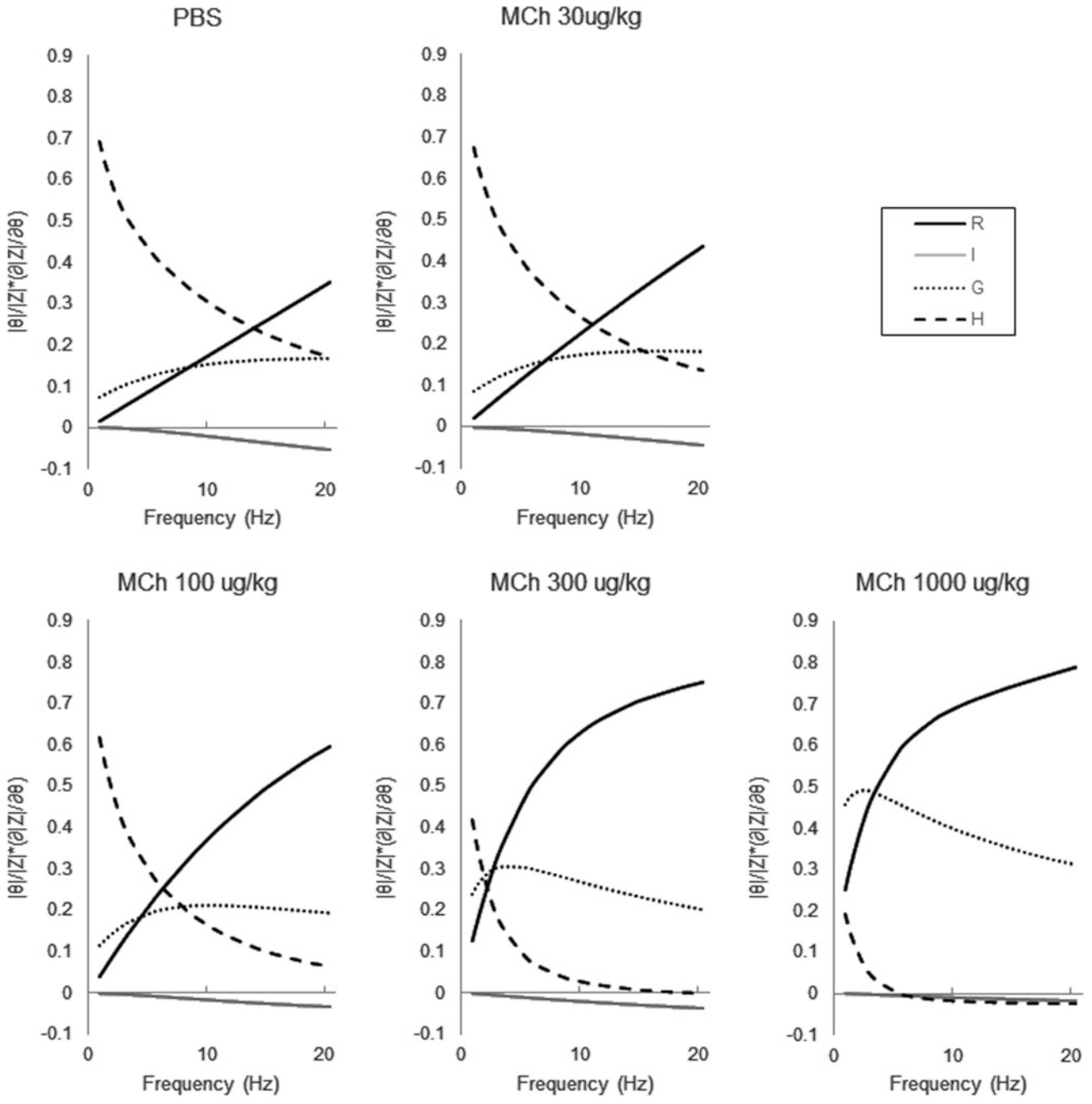

Fig. 2 Plots of sensitivity coefficients with respect to each parameter considering each one of the methacholine doses and the PBS conditions, calculated using the average impedance data, versus frequency

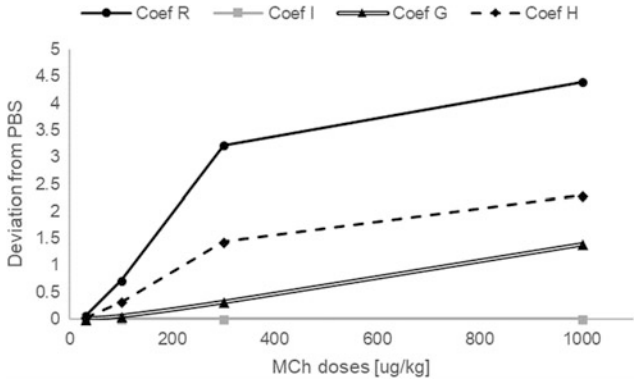

Fig. 3 Evolution of deviation between the sensitivity coefficients for higher MCh doses and the PBS sensitivity coefficients, which are those taken with no MCh influence. On the horizontal axis we dispose MCh doses in μg/kg

and decay slightly at higher frequencies in higher MCh doses while H coefficient decay fast with frequency in all cases.

3.3 Changing Evaluation of the Coefficients

The result of how deviation between the MCh doses' sensitivity coefficients and PBS coefficients evolves according to methacholine's doses is shown by Fig. 3. It is possible to notice that, for all sensitivity coefficients, there is an increasing behavior in the distance. It shows that, as the MCh doses increase, the sensitivity pattern becomes more different than the initial one (PBS). The major gain occurs between the initial doses (100 and 300 μg/kg) and after it the growing rate becomes lower, but still considerable.

4 Discussion

As shown by Fig. 2, the sensitivity coefficients with respect to R and G become more significant as the methacholine dose rises. It shows a correlation between the degree of bronchoconstriction and the susceptibility of the lungs to these parameters, which are both of dissipative nature.

In the specific case of the coefficient R, as MCh dose increases, the rising slope becomes higher at lower frequencies and the magnitude becomes more representative. Considering the coefficient G, in all cases we get a rise until around 4 Hz and then it starts to decline. However, at higher MCh doses, the magnitude becomes more relevant.

Both, R (airway resistance) and G (tissue viscance), are descriptive parameters of the model for dissipative aspects in the lung [1, 2, 7]. The parameter R is proportional the dissipated energy in the airways and G is a constant that is related to the loss of energy through the tissue [1]. This appointment is relevant to see that as the bronchoconstriction rises, the dissipative aspect of the respiratory system starts to prevail, then there is more resistance to the breathing activity, as expected. Then, a bigger energetic effort in the breathing activity, dedicated to conduct the air thorough the airways and to inflate the lungs' tissue, is made.

Analyzing the coefficient H, as the MCh dose increases it becomes less significant in magnitude [3]. In particular, we can highlight the contribution to the sensitivity at lower frequencies [3]. Considering the fact that parameter H (tissue elastance) has a conservative nature and is associated with the energy stored in form of potential elastic energy in the tissue [1], the behavior of this parameter shows that, at a bigger bronchoconstriction degree, the impedance's absolute value becomes less susceptible to elastance at higher frequencies, then it is possible to conclude that the impedance rely less on the conservative aspect of the lungs' tissue at this state.

Through the perspective of Fig. 3, the deviation from PBS grows constantly with the MCh dose, which shows that model's sensitivity pattern varies accordingly to bronchoconstriction degree. In other words, increasing doses of MCh will contribute for the model's sensitivity patterns to be invariably different from patterns of previous doses. These arguments work for sensitivity coefficients related to R, G and H. However, the deviation related to the parameter I keeps constant for all doses. It is due to the fact that the magnitude of I itself is very low while the uncertainty associated is very high [8]. In fact, the sensitivity related to I is small and negligible, as the magnitude of the parameter has influence over it.

In summary, the deviation analysis aspects and the behaviors exposed by Fig. 2, when analyzed together, indicate the accentuation of impedance's sensitivity pattern for each parameter, which means, in general terms, that the impedance value becomes more susceptible to R and G and less sensitive to H as the bronchoconstriction increases at higher frequencies.

Considering that if the sensitivity related to some parameter is low, a higher distortion on this parameter will affect less the impedance. It indicates that in this situation that physiological aspect is less relevant when compared to others. This conclusion, when followed by parameters' error analysis, as proposed by Thamrin et al. [3] and Lutchen [4], allows a deep understanding of how impedance magnitude varies in terms of physiological parameters.

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