Development of the Respiratory PhysioPD™ Platform, a QSP Model to Investigate Biological Mechanisms Underlying Bronchoconstriction

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Introduction

- Bronchoconstriction can be a significant component of airway diseases and a safety concern as an adverse drug reaction for patients with respiratory diseases
- A quantitative mechanistic model of the biology, extent, and duration of bronchoconstriction could help identify risks prospectively and guide rational drug development

Objectives

- To investigate the following questions:
  - *What mechanisms give rise to bronchoconstriction following methacholine (MCh) challenge?*
  - *Can differences in inflammation and airway diameter explain the difference between healthy and asthmatic responses to MCh challenge response?*

Methods

Rosa PhysioPD™ Research Platforms can be used to elucidate connections between mechanisms and outcomes.

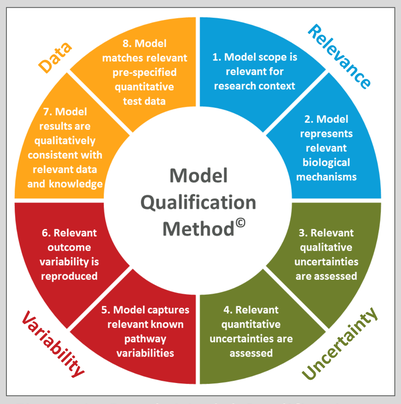

Figure 1. Rosa's Model Qualification Method[1] (MQM) was used to develop and qualify the Platform.

- Research mechanisms of bronchoconstriction and differences between healthy and asthmatic subjects
- Develop a Quantitative Systems Pharmacology (QSP) model (the Respiratory PhysioPD Platform) that represents biology and pharmacologic drug interactions
- Use model to investigate questions of interest

Literature Review: Reflex Arc

Bronchoconstriction involves an autonomic reflex arc at the neuromuscular junction (NMJ).

Figure 2 illustrates the response to MCh challenge[2,3]:

1. MCh or acetylcholine (ACh) binds to muscarinic receptors (M2, M3) on airway smooth muscle (ASM)
2. This activates mechanoreceptors of afferent neurons
3. Afferent sensory neurons conduct the impulse to the CNS, where signals are integrated, filtered, and relayed to efferent motor neurons
4. Signal to efferent neuron activation results in endogenous ACh release into the synaptic cleft
5. ACh binding to M2 receptors on the efferent neuron results in down-regulation of ACh release

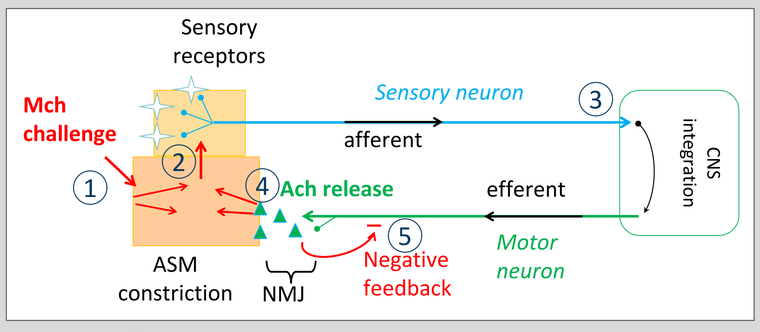

Figure 2. Reflex arc transmission in bronchoconstriction.

Literature Review: Inflammation

- Literature suggests that the degree of inflammation is correlated with clinical asthma severity[4]
- inflammation affects the reflex arc by inducing[5,6]:
  - Exaggerated bronchoconstriction response to initial stimulus
  - Heightened excitability of afferent and efferent neurons
  - Decreased ability to terminate the response due to impaired signal relay filters and M2 receptor function

Results: Mechanisms

The Respiratory PhysioPD Platform was constructed to include the key mechanisms of bronchoconstriction.

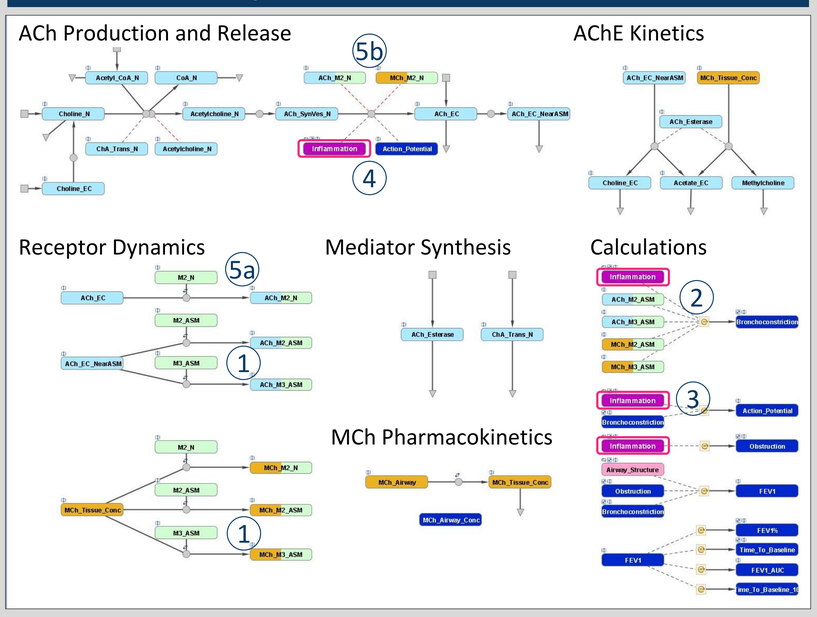

Figure 3. The Respiratory PhysioPD Platform represents a neuromuscular junction in the lung. It includes the mechanisms of bronchoconstriction (numbered 1 – 5, as in Figure 2. Inflammation effects are highlighted in pink.

- Model includes the reflex arc mechanisms (as in Figure 2) and the identified inflammation effects (Figure 3)
- Mechanisms of ACh production and clearance, such as acetylcholine esterase (AChE) dynamics, are also included
- To facilitate comparison to clinical data the forced expiratory volume in one second (FEV1) measurement is computed based on the following assumptions:
  - Bronchoconstriction and obstruction (e.g., mucus) reduce airway radius and increase resistance
  - FEV1 is inversely correlated to resistance

$$Airway\ Resistance \propto \frac{1}{r^4}$$

- In the absence of inflammation, the model simulations represent a healthy subject

1. Inflammation affects FEV1 max drop and recovery.

- The model captures the magnitude and dynamics of FEV1 response to MCh challenge in a healthy subject
- To assess the effect of inflammation on FEV1, the level of inflammation was progressively increased (Figure 4)
- FEV1 drop and recovery time increased, and AUC decreased with increasing inflammation
- At highest inflammation level, FEV1 does not recover – in the clinic, such a patient would need rescue medication

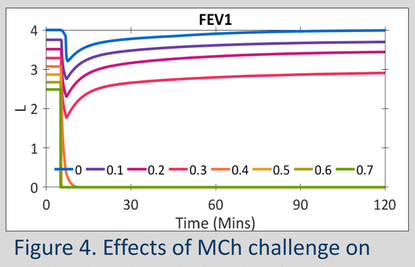

Figure 4. Effects of MCh challenge on FEV1 in healthy VP (top line) and under increasing levels of inflammation.

2. Endogenous ACh, not MCh, is the primary ligand engaging muscarinic receptors during MCh challenge.

- MCh PK was modeled building on prior work and data[7]
- MCh is cleared well before FEV1 returns to baseline

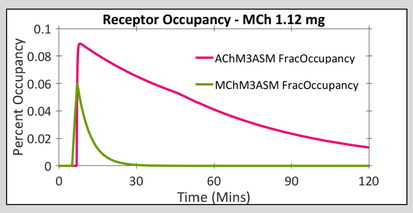

Figure 5. M3 muscarinic receptor occupancy by ACh (pink) and MCh (green) in a healthy VP in response to MCh challenge.

- Simulations suggest endogenous ACh is the ligand binding ASM muscarinic receptors to sustain response (Fig. 5)
- This effect is even greater in asthmatic patients, in whom less MCh triggers more bronchoconstriction (not shown)

Results: Asthmatic Virtual Patients

3. Variability in inflammation and airway obstruction results in variability in FEV1 response.

- Asthmatic VPs were developed by varying two parameters known to differ across clinical subjects:
  - The level of inflammation
  - Airway obstruction/remodeling
- VP responses were compared to clinical data from a pilot study in mild asthmatic patients (data on file)
  - Four MCh challenges, PD20 incremental in first two, cumulative in last two visits

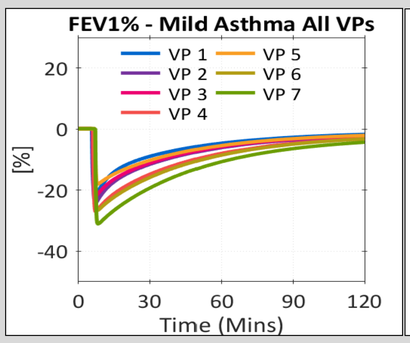

Figure 6. VP responses to MCh challenge with individual PD20 doses.

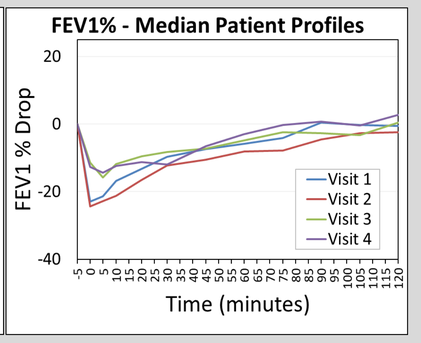

Figure 7. Median patient FEV1 profile from BI's clinical study.

- The VPs' FEV1 time profiles are different from each other (Figure 6) and qualitatively similar to real patient profiles (Fig. 7)
- VP cohort had similar median PD20, FEV1, and recovery time as the clinical cohort (Table 1)

VP	PD20 [mg]	FEV1 % Pred.	Time to Recovery [min]
1	0.49	89	74
2	0.3	78	65
3	0.2	93	62
4	0.15	78	80
5	0.1	86	59
6	0.075	97	83
7	0.06	79	103
VP Median	0.15	86	74
BI Trial Median	0.14	86	66

Table 1. VPs vs BI study median values.

Conclusions

- Analysis and simulation of bronchoconstriction mechanisms using the mechanistic model suggest that:
  - Endogenous ACh is the ligand that sustains prolonged bronchoconstriction in response to MCh challenge
  - Inflammation leads to neuronal hyperreactivity and attenuation of the negative feedback loop to shut down endogenous ACh release
  - Inflammation and airway obstruction can explain differences between healthy and asthmatic FEV1 responses to MCh challenge
- The model enables quantitative evaluation of therapies that interact with pulmonary muscarinic biology

References

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