Clustered ventilation defects and bilinear respiratory reactance in asthma

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HIGHLIGHTS

- Clustered ventilation defects are a hallmark of asthma observed in imaging studies.
- We present a new model of clustered ventilation defect formation in the lung.
- Noise-driven defect formation in asymmetric trees yields a combination of structural and dynamic defect formation.
- The reactance versus flow curve is bilinear, but the breakpoint is not coincident with the clustering bifurcation.

ARTICLE INFO

ABSTRACT

Imaging studies of asthmatics typically reveal clustered ventilation patterns, rather than homogeneous ventilation; furthermore, the variation of these clusters suggests that the causes are at least partially dynamic, rather than structural. Theoretical studies have indicated dynamic mechanisms by which homogeneous ventilation solutions lose stability and clustered solutions emerge. At the same time, it has been demonstrated experimentally that respiratory reactance characteristically has a bilinear relationship with lung volume, and that changes to this relationship are indicative of various aspects of disease progression and control. Moreover, the transition point in the bilinear reactance relationship is thought to relate to reopening/recruitment of airway units, and thus may be connected to the bifurcation via which clustered ventilation solutions emerge. In order to investigate this possibility we develop a new model, including both airway–airway coupling and airway–parenchymal coupling, which exhibits both clustered ventilation defects and also a bilinear reactance relationship. Studying this model reveals that (1) the reactance breakpoint is not coincident with the bifurcation; (2) numerous changes to underlying behaviour can alter the reactance breakpoint in ways which mimic the experimental data; and (3) the location of ventilation defects can be a combination of both structural and dynamic factors.

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1. Introduction

Clustered ventilation defects are a hallmark of asthma, wherein reversible airway narrowing occurs in a spatially organised way such that both hypo- and hyper-ventilated regions emerge (e.g. Tzeng et al., 2009; Layachi et al., 2013; Simon et al., 2012). Because these regions can vary from event to event, the causes are thought to be at least partially dynamic (Venegas et al., 2005; Leary et al., 2014), as opposed to structural, and understanding how and why they occur may shed light on the basic pathophysiology of asthma, which is not well understood.

Several theoretical models have been developed which address the formation of clustered ventilation defects (VDefs). Best known is the computational work of Venegas, Winkler and colleagues,

based on Anafi and Wilson (2001) and extended to a symmetric airway tree, beginning with Venegas et al. (2005) and used in numerous subsequent studies (e.g. Winkler and Venegas, 2007; Golnabi et al., 2014; Wongviriyawong et al., 2010; Winkler et al., 2015; Leary et al., 2014). The model of Donovan and Kritter (2015) employs similar ideas, but is constructed in such a way as to allow some degree of analytic understanding of how and why clustered VDefs occur (for example, analytic eigenvalues and eigenvectors allow understanding of the unstable modes of the system). However Donovan and Kritter (2015) made a significant assumption in neglecting the role of the conducting airway tree (airway–airway coupling), instead of relying on interactions among physically adjacent respiratory bronchioles and their dependent tissue (airway–parenchymal coupling) to drive clustered VDef formation. This approach has two key drawbacks: (1) the neglected role of the conducting airway tree is unclear and (2) without the upstream

airways, it is difficult or impossible to incorporate models of measured lung function.

Here we are driven to investigate the experimental results of Kelly et al. (2012, 2013), which demonstrate the utility of measuring respiratory reactance as a function of lung volume. These authors show that this relationship is reliably bilinear, and that the handful of parameters associated with that bilinear form are useful markers of lung function, asthma severity and asthma control. Furthermore, they postulate that the "breakpoint" in their bilinear form is related to reopening/recruitment of airway units. Such a transition, then, might be related to the bifurcation which occurs between homogeneous and clustered ventilation in the models of Donovan and Kritter (2015) and Venegas et al. (2005). The hypothesis is made more plausible by other evidence of the relationship between ventilation heterogeneity and impedance, e.g. Kaczka et al. (2009, 2011) and Lutchen et al. (2001). Thus, one interesting question is if the breakpoint and bifurcation are coincident.

In order to answer this question, we first construct a new model, based on Donovan and Kritter (2015), but now incorporating airway–airway coupling via flow through the conducting airway tree. This is necessary, in the first instance, because existing reactance (impedance) models require the behaviour of the conducting tree, but it also has the significant advantage that we are able to assess other theoretical implications of the previously neglected components.

This paper is then structured as follows. First, we augment the model of Donovan and Kritter (2015) to incorporate a conducting airway tree (with arbitrary geometry); this is not conceptually difficult, but leads to challenges associated with the resulting system of differential-algebraic equations (DAEs). Rather than attempting to solve the DAEs directly, we instead present a procedure which allows elimination of the algebraic constraints in any tree, resulting in a system of ordinary differential equations only. This eases both computational and theoretical issues considerably.

Using this newly developed model, then, we are able to show: (1) the bifurcation between homogeneous and clustered ventilation seen in Donovan and Kritter (2015) persists with the inclusion of airway–airway coupling via flow through the conducting airways; (2) the characteristic bilinear reactance relationship also that occurs in this model, but (3) the breakpoint and bifurcation that are *not* coincident. Instead the reactance breakpoint appears to reflect a transition driven by the highly nonlinear relationship between radius and impedance (and, because of the dependence between flow and radius, between flow and impedance). We also examine the locations and persistence of the locations of ventilation defects; that is, the extent to which they are dynamic as opposed to structural.

We further consider the ways in which the bilinear reactance parameters can be altered by the underlying system, suggesting ways in which asthmatic pathophysiology may differ from non-asthmatics; however, there are many potential combinations which lead to the same sort of changes in that relationship, and hence the inversion from observed data to underlying behaviour is not unique.

2. Model

Here we develop a new model based on Donovan and Kritter (2015) (which considers only the respiratory bronchioles), but now with the inclusion of an arbitrary conducting tree. Many of the underlying ideas are shared with Venegas and Winkler et al. (Venegas et al., 2005; Winkler and Venegas, 2007; Golnabi et al., 2014; Wongviriyawong et al., 2010; Winkler et al., 2015), and there are structural similarities with Stewart and Jensen (2015).
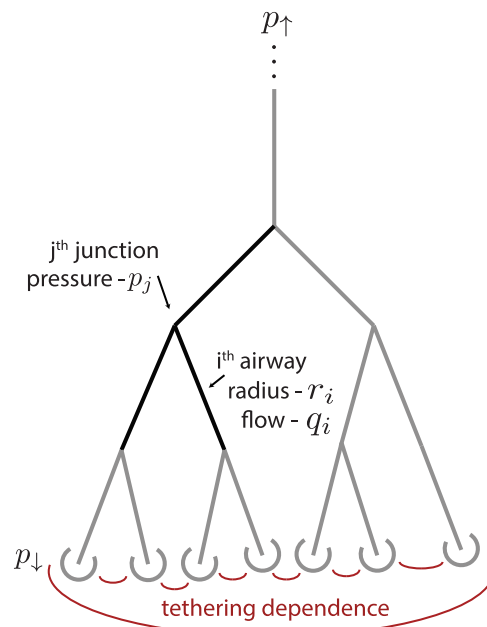

Fig. 1. Schematic illustration of model geometry and symbols. Two types of coupling are considered: airway–airway coupling via flow through the conducting airways (black and grey), and coupling via parenchymal interdependence (red). (For interpretation of the references to colour in this figure caption, the reader is referred to the web version of this paper.)

The setup is simple: we have airway luminal radius (r_i) and flow (q_i) in each airway, and pressure p_j at each junction[1]; these can be arranged in an arbitrary branching tree with $i = 1 \ldots N$ airways and $j = 1 \ldots M$ junctions. We denote the boundary pressures at the "top" of the tree $p_\uparrow$ (e.g. at the trachea in a full tree), and driving pressure $p_\downarrow$ and the "bottom" of the respiratory bronchioles. The arrangement is illustrated schematically in Fig. 1.

The evolution of these radii, pressures and flows is then given by: (1) the airway dynamics (including narrowing driven by ASM); (2) conservation of flow at the junctions; and (3) flow equations along each airway. That is, for each airway we have dynamics given by

$$\dot{r}_i = \rho\big(\phi(r_i; \mathbf{r}, \mathbf{p}, \mathbf{q}) - r_i\big) \tag{1}$$

based on Donovan and Kritter (2015) where ϕ is based on quasi-static experimental measurements and the construction gives first-order kinetics about those equilibria with timescale ρ. (Full details of ϕ are presented in Section 2.2, but for now are neglected for clarity.)

At each junction, we have conservation of flow

$$q_m = q_{d_1} + q_{d_2} \tag{2}$$

where the notation here indicates the mother and two daughter branches at each junction. We will later re-write this in terms of connectivity matrices.

Then in each airway, we assume Poiseuille flow

$$\Delta p_i = \alpha_i r_i^{-4} q_i \tag{3}$$

where Δp_i is the pressure difference from top to bottom of the ith airway (again, later in terms of connectivity matrices) and for compactness of notation we have combined the parameters associated with the flow into a single constant α_i for each airway.[2]

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[1] Here we neglect the pressure loss factor of Lambert et al. (1982).

[2] We present the model development in dimensional terms; units are parameter values are given in Appendix A.