Journal of Theoretical Biology 333 (2013) 102–108

Contents lists available at SciVerse ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Modelling airway smooth muscle passive length adaptation via thick filament length distributions

Graham M. Donovan*

Department of Mathematics, University of Auckland, New Zealand

HIGHLIGHTS

- Airway smooth muscle (ASM) is implicated in asthma and airway constriction.
- Relationship between exerted force and ASM length is critical for airway behaviour.
- Long-term changes in force–length relationship are governed by length adaptation.
- New model of ASM with length adaption, based on Huxley's sliding filament theory.
- Critical role for the distribution of filament lengths, based on recent data.

ARTICLE INFO

Article history:
Received 11 December 2012
Received in revised form
28 February 2013
Accepted 18 May 2013
Available online 28 May 2013

Keywords:
Crossbridge model
Myosin filament length distribution
Airway constriction
Asthma

ABSTRACT

We present a new model of airway smooth muscle (ASM), which surrounds and constricts every airway in the lung and thus plays a central role in the airway constriction associated with asthma. This new model of ASM is based on an extension of sliding filament/crossbridge theory, which explicitly incorporates the length distribution of thick sliding filaments to account for a phenomenon known as dynamic passive length adaptation; the model exhibits good agreement with experimental data for ASM force–length behaviour across multiple scales. Principally these are (nonlinear) force–length loops at short timescales (seconds), parabolic force–length curves at medium timescales (minutes) and length adaptation at longer timescales. This represents a significant improvement on the widely-used cross-bridge models which work so well in or near the isometric regime, and may have significant implications for studies which rely on crossbridge or other dynamic airway smooth muscle models, and thus both airway and lung dynamics.

1. Introduction

Understanding the behaviour of airway smooth muscle (ASM) is crucial to understanding the reversible airway obstruction central to asthma. A layer of ASM surrounds each airway in the lung, and ASM activation thus leads to airway narrowing (and, potentially, closure). Similarly the relaxation of ASM may reverse airway narrowing or closure; mechanisms which limit the ability of ASM to exert force are especially important.

The relationship between airway calibre and force is thus central to understanding the dynamic processes associated with asthma, and ASM exhibits a rich series of behaviours in this regard. These are often termed *force–length* relationships, where of course the length of the ASM wrapped around the airway is connected with airway calibre.

There are three characteristic behaviours widely seen in active ASM, each occurring at a different scale. It is important to note that in what follows we consider only the active component of ASM, with the passive component excluded.

- *Force–length loops*: At the shortest timescale, with length oscillations measured in seconds, ASM exhibits a characteristic, nonlinear, hysteretic force–length 'loop' where the degree of hysteresis and nonlinearity are dependent on the amplitude and frequency of the length oscillations (Mijailovich et al., 2000; Bates et al., 2009). These are sometimes referred to as 'banana-shaped' and a typical example is reproduced in the left panel of Fig. 1.
- *Force–length curves*: At an intermediate timescale, measured in minutes, changes in the length of ASM affect a change in the ability of the muscle to exert force. Typically the peak of this force–length curve, where maximal force is exerted, is at what is called the *adapted length*. Increases or decreases away from this adapted length result in reductions in exerted force, and

* Tel.: +64 9 923 8780.
E-mail address: g.donovan@auckland.ac.nz

0022-5193/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jtbi.2013.05.013

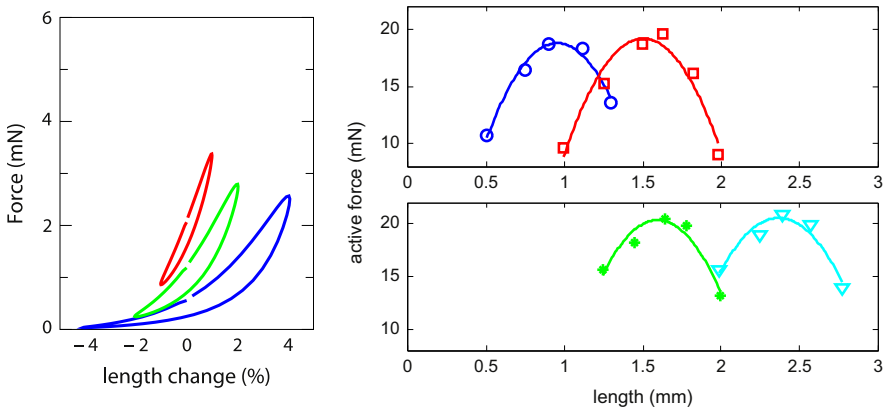

Fig. 1. Characteristic ASM behaviours. Left panel: Force–length loops, data from Bates et al. (2009). These force measurements are taken with length oscillations imposed with amplitude 1, 2 and 4% of reference length and frequency 2 Hz. Right panels: Force–length curves and adaptation, data from Wang et al. (2001) with best-fit quadratics. Here in the top (bottom) panels the muscle is passively shortened (lengthened) to a new adapted length and allowed to re-equilibrate over 24 h. At each adapted reference length, the characteristic ($1-L^2$) shape is observed, with adaptation simply shifting this shape left and right along the length axis. Peak force for each adapted length is roughly constant.

the typical shape might be roughly characterised by an inverted quadratic (Wang et al., 2001; Gunst and Stropp, 1988). Typical data are reproduced in the right panels of Fig. 1, where one should consider for now only a single curve. The peak of any single curve is the adapted length; if the muscle is shortened or lengthened away from this value the exerted force will be decreased as shown after 5 min.

- *Length adaptation*: If left at a new length for a sufficiently long time, ASM will adapt to its new length, now exerting peak force at this new length (Wang et al., 2001; Bossé et al., 2008)—thus ASM can exert maximal force at any length. Moreover, if the force–length curve protocol is repeated at this new adapted length, the same characteristic shape is observed, which can be seen in the experimental data reproduced in the right panels of Fig. 1, where the two panels illustrate passive shortening and lengthening, from top to bottom.

Because of the importance of ASM force–length dynamics to understanding airway and asthma dynamics, it is thus important to understand the origins of each of these representative behaviours. In this manuscript a new mathematical model of ASM is presented which accounts for all three via the explicit inclusion of thick filament length distributions. While existing models may account for one or more, none reproduce all; this is discussed in more detail below.

A number of models of ASM exist in the literature, and these can primarily be classified into two groups: viscoelastic models, and crossbridge models. The former category describes the muscle behaviour empirically using mechanical analogues (i.e. springs and dashpots) and is able, depending on the construction, to reproduce at least some of the characteristic force–length behaviours (i.e. Bates et al., 2009). The latter group is based on the sliding-filament model of Huxley (1957), which has been extended by several groups to incorporate important phenomena specific to smooth muscle (i.e. Hai and Murphy, 1988; Mijailovich et al., 2000; Wang et al., 2008). Later models of this type are capable of predicting reasonable force–length loops on the shortest timescale, but the combination of force–length curves and length adaptation remains unexplained with this family of models. In general, for existing crossbridge models the force–length curve is a length-independent constant rather than the desired parabolic shape, and thus the concept of adaptation is moot as the muscle already exerts equal force at all lengths.[1] It is possible to impose, empirically, a force–length relationship which approximates the experimental data merely by a multiplicative scaling factor (i.e. Politi et al., 2010); however this approach has neither a biophysical basis, nor does it allow for adaptation.

Recently, the hypothesis that the force exerted by ASM is controlled by the ASM length-dependent overlap between adjacent thin filaments has gained traction (Seow, 2005; Ali et al., 2007; Seow and Fredberg, 2011; Syyong et al., 2011; Brook and Jensen, in press), and thus that changes in muscle length lead to changes in filament overlap and thus altered ASM force. Combined with the quantitative measurement of the distribution of thick filament lengths found in ASM, this allows the construction of a crossbridge-type model in which crossbridge binding sites are preferentially available within and near the thin filament overlap region, and dependent on the thick filament length distribution. The distribution of thick filament lengths provides a stochastic component, which determines the availability of binding sites. Away from the filament overlap region, then, binding sites are increasingly unavailable and thus exerted muscle force is reduced. This is the central hypothesis on which this model is based, and it provides a simple and elegant explanation for the characteristic force–length behaviours at all three scales. This has potentially important implications for understanding airway and asthma dynamics, and for other models which depend upon crossbridge or ASM dynamics as one of their constituent parts (i.e. Anafi and Wilson, 2001; Venegas et al., 2005; Politi et al., 2010; Amin et al., 2010).

There are other models in the literature which address length adaptation, including the empirical and viscoelastic type approaches of Ijpma et al. (2011) and Lambert et al. (2004), as well as the 2D cytoskeletal network model of Silveira et al. (2005). Here instead this phenomenon is incorporated into the well-known framework of the crossbridge model, obtaining appropriate force–length behaviours across the three scales discussed above.

2. Model

2.1. The crossbridge model

In order to understand the theoretical framework of the model presented in this manuscript, it is useful to outline briefly

[1] This is true for the model of Wang et al. (2008) and a 5 min re-equilibration period: by the measurement time the muscle has already re-equilibrated. Strictly (*footnote continued*) speaking the result depends upon the model recovery timescale and the recovery time allowed by the protocol, but no such combination exists which simultaneously yields appropriate force–length curves and adaptation in a traditional crossbridge model.