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The mechanics of airway closure

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ABSTRACT

We describe how surface-tension-driven instabilities of the lung's liquid lining may lead to pulmonary airway closure via the formation of liquid bridges that occlude the airway lumen. Using simple theoretical models, we demonstrate that this process may occur via a purely fluid-mechanical "film collapse" or through a coupled, fluid-elastic "compliant collapse" mechanism. Both mechanisms can lead to airway closure in times comparable with the breathing cycle, suggesting that surface tension is the primary mechanical effect responsible for the closure observed in peripheral regions of the human lungs. We conclude by discussing the influence of additional effects not included in the simple models, such as gravity, the presence of pulmonary surfactant, respiratory flow and wall motion, the airways' geometry, and the mechanical structure of the airway walls.

1. Introduction

The pulmonary airways are lined with a thin liquid film extending from the trachea down to the alveoli. The film provides protection against infection and oxidation, and is believed to facilitate the transfer of gases between the pulmonary circulation and the inspired air at the level of the alveoli. The surface tension that acts at the film's air–liquid interface has a significant effect on the lung's mechanical behaviour and is responsible for 50–60% of the lung's elastic recoil. Pulmonary surfactant reduces the surface tension of the film and helps the fluid to spread over the airway surface. The liquid lining usually forms a thin, relatively uniform layer on the airway wall but it is possible for the airway to become blocked by the liquid, resulting in airway closure. It is the main aim of this paper to describe the various mechanisms involved in this process.

Throughout this paper we shall distinguish airway closure (which involves the formation of a liquid blockage) from the purely structural collapse of the airway walls in response to external or internal forces. The latter can occur, e.g. during expiratory flow limitation, discussed in the article by Bertram (2008), and tends to leave the airway lumen open and thus available for respiration. We shall demonstrate, however, that the structural collapse of the airway wall can aid the formation of liquid blockages, and furthermore, that the formation of an occlusion can itself cause a structural collapse.

Experimental evidence that airway closure occurs in healthy human lungs was first described by Burger and Macklem (1968) whose elegant studies provided evidence of small-airway closure during expiration, when the lung's residual volume was approached. Animal studies of airway closure by Hughes et al. (1970) found histological evidence that during lung deflation, the site of airway closure was confined to the very small airways (≈0.4–0.6 mm in diameter).

In healthy lungs, airway closure occurs only in the small airways, towards the end of expiration when the airway diameters are smallest and, by virtue of mass conservation, the liquid film is at its thickest. The liquid blockages normally rupture during the early stages of inspiration. The development of more permanent occlusions or the occurrence of airway closure in the larger airways is either a consequence of certain pathological conditions (e.g. an increase in the volume of fluid in pulmonary oedema, or an increase in the surface tension in neonatal respiratory distress syndrome); or the result of deliberate medical interventions, such as the installation of a liquid plug in the larger airways during surfactant replacement therapy; see e.g. Espinosa and Kamm (1998) and the article by Grotberg et al. (2008). The tendency for airway closure to occur is also increased during sleep, general anaesthesia and in obesity (Appelberg et al., 2007; Rothen et al., 1998).

The principal mechanical effect responsible for airway closure is the surface tension acting at the interface between the liquid lining and the air in the lumen. Fig. 1 shows a sketch of the cross-section through an idealised, straight, circular airway of radius a, lined with a thin, static film of uniform thickness $h_0 \ll a$. The surface tension acting at the curved interface induces a jump in pressure across the

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interface, and the pressure in the fluid is given by the Young–Laplace equation

$$p_{\text{fluid}} = p_{\text{int}} - \sigma\kappa, \tag{1}$$

where p_{int} is the air pressure in the lumen, σ is the surface tension and κ is the mean curvature of the air–liquid interface. For the uniform, axisymmetric liquid film shown in Fig. 1 the mean curvature is constant and given by $\kappa = 1/(a - h_0)$, i.e. it is inversely related to the radius of the air–liquid interface.

Eq. (1) shows that spatial variations in the interfacial curvature generate pressure gradients in the fluid. Hence, if the uniform liquid lining is disturbed, the induced pressure gradients drive flows that will redistribute the fluid and this process may lead to airway closure via a mechanism that Kamm and Schroter (1989) termed "film collapse". We shall discuss this mechanism in Section 2.

Another mechanical property that contributes to airway closure is the elastic nature of the airway walls, which deform in response to the pressures exerted on them. Denoting the external (pleural) pressure acting on the airway by p_{ext}, the net (compressive) load experienced by the airway wall in Fig. 1 is

$$p_{\text{wall}} = p_{\text{ext}} - p_{\text{fluid}} = p_{\text{ext}} - p_{\text{int}} + \sigma\kappa. \tag{2}$$

This compressive load is resisted by the wall's internal stiffness (characterised here by its Young's modulus E and the wall thickness h_{w}) and by the structural support provided by the parenchymal tethering, represented here by distributed elastic springs of stiffness k.

Eq. (2) shows that the structural collapse of the airway wall may be caused by an increase in the pleural pressure, for example under conditions of pneumothorax and/or pleural effusion, and/or by a reduction in the internal pressure, e.g. during expiratory flow limitation. The last term in Eq. (2) indicates that it is also possible for an airway to collapse if the compressive load generated by the liquid lining becomes sufficiently large. Kamm and Schroter (1989) observed that the latter provides a mechanism for airway closure via a destabilising feedback between the fluid and solid mechanics: if the airway wall is compressed, the curvature of the air–liquid interface will increase, causing an increase in the compressive load on the wall (via the final term in Eq. (2)), which will further increase the compression. Kamm and Schroter (1989) referred to this process as "compliant collapse" and we shall discuss this mechanism in Section 3. The propensity of an airway to become occluded by this mechanism is largely determined by the ratio of the surface-tension-induced pressure jump over the air–liquid interface to the wall stiffness. Since the curvature of the air–liquid interface is greatest in the smallest airways, they are most likely to be susceptible to "compliant collapse". In emphysema, destruction of parenchymal tissue and reduced tethering decreases the airway stiffness and may allow the occurrence of such collapse in larger airways.

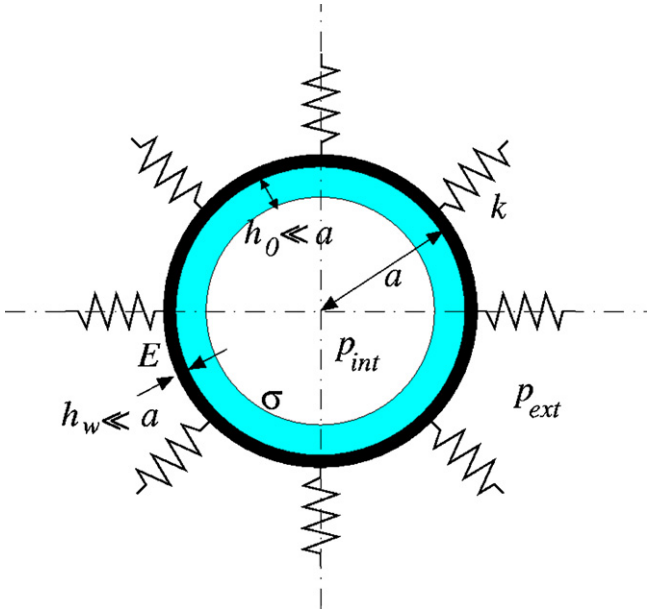

Fig. 1. A simple model of an elastic airway (radius a, wall thickness h_{w} and Young's modulus E), supported by external tethering (representing the parenchyma, and modelled as distributed springs with spring stiffness k), and lined with a thin liquid film of uniform thickness h_0. The surface tension at the air–liquid interface is σ and the airway is subjected to an external (pleural) pressure p_{ext}. The pressure in the lumen is p_{int}.

We note that the competition between surface tension and wall stiffness can also be cast in energetic terms. The equilibrium configurations of the liquid-lined airway are characterised by a minimum of the total energy, comprising the surface energy (given by the product of surface tension and the area of the air–liquid interface) and the strain energy (the elastic energy stored in the deformed airway walls). The compression of the airway wall reduces the former but increases the latter. The airway will therefore tend to collapse if the axisymmetric, axially uniform configuration sketched in Fig. 1 has a higher total energy than a corresponding collapsed/occluded configuration. In that case, the system will evolve towards a new equilibrium configuration of lower total energy, i.e. the collapsed state.

In this paper, we describe the details of both the "film collapse" and "compliant collapse" mechanisms and their interaction. We begin with the purely fluid-mechanical "film collapse", which tends to occur when the surface tension is much smaller than the wall stiffness, before turning our attention to the more complex fluid-elastic "compliant collapse", which occurs when the surface tension is relatively high. In both cases we include the minimum number of physical effects required to elucidate the mechanism. In particular, we neglect the effects of gravity, the presence of surfactant, the curvature of the airways and the presence of airway bifurcations. In addition, the models of the lining liquid and airway wall are kept deliberately simple. The influence of the neglected effects is discussed in Section 4, in which we also consider some remaining open questions.

2. "Film collapse": liquid plug formation in rigid axisymmetric vessels

In larger airways the surface tension is small, relative to the airway stiffness, hence the surface-tension-induced compression does not produce significant wall deformations and the airway wall is essentially rigid. The redistribution of the liquid from a thin lining film into an occluding liquid bridge can then occur via a classical fluid-mechanical instability, known as the Rayleigh–Plateau instability which is also responsible for the surface-tension-driven breakup of liquid jets into individual droplets (Plateau, 1873; Rayleigh, 1879)

To explain the origin of the instability, Fig. 2 illustrates how the fluid in a uniform liquid film that lines an axisymmetric airway responds to an axisymmetric perturbation of its thickness from the initial value h_0 to $h(z)$. The mean curvature, κ, of the axisymmetric air–liquid interface is given by the sum of its two principal curvatures, i.e. the curvatures along the length of the airway (the principal axial curvature) and in its cross-section (the principal circumferential curvature); for small-amplitude perturbations to the film thickness we have $\kappa \approx d^2h/dz^2 + 1/(a - h)$; see, e.g., Gauglitz and Radke (1988). The principal axial curvature, d^2h/dz^2, is negative where the film is thickest and positive were the film is thinnest. The principal circumferential curvature, $1/(a - h)$, is always posi-

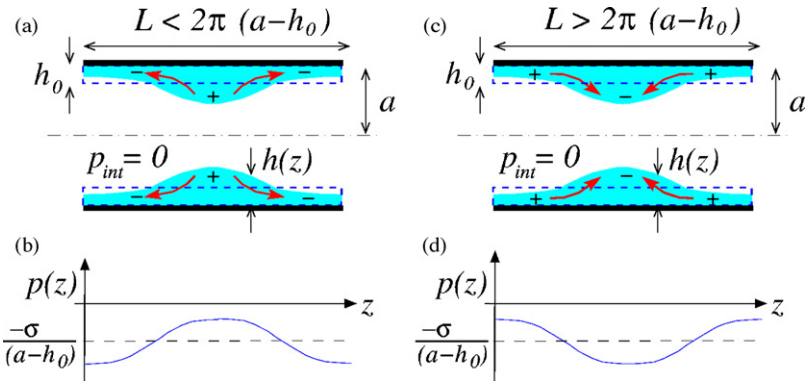

Fig. 2. Illustration of the axisymmetric Rayleigh–Plateau instability. Sinusoidal perturbations to an initially uniform film of thickness h_0 create pressure variations that drive flows within the fluid. (a) and (b) If the wavelength of the perturbation L, is less than the initial circumference of the air–liquid interface, the fluid will return to the axially uniform state. (c) and (d) Perturbations with a wavelength in excess of the initial circumference of the air–liquid interface will generate flows that cause the perturbation to grow in amplitude.

tive and greatest where the film is thickest. From Eq. (1) it follows that the axial curvature generates a pressure distribution that attempts to return the fluid in the liquid lining to an axially uniform state, with a high pressure in the thick lobes and low pressure in the depleted regions. Conversely, the circumferential curvature is destabilising in the sense that it tends to drive yet more fluid into the regions where the film thickness is already elevated. The relative importance of these two competing effects depends on the axial wavelength, L, of the perturbation. For short-wavelength perturbations the (stabilising) variations in the axial curvature dominate, and as a result the fluid pressure increases in the regions where the film is thickest, generating flows that return the fluid to its axially uniform state, as shown in Fig. 2(a). Conversely, if the axial wavelength of the perturbation is sufficiently large, the destabilising effect of the circumferential curvature dominates, leading to a reduction in the fluid pressure in the thickest regions, driving more fluid into these regions, and enhancing the non-uniformity of the film further. This scenario is illustrated in Fig. 2(c).

A formal linear stability analysis (e.g. Goren, 1962) shows that the liquid lining is unstable to sinusoidal perturbations, along the length of the airway, whose wavelength L exceeds the circumference of the undeformed air–liquid interface so that $L > 2\pi(a - h_0)$. This threshold may also be derived from energetic considerations by determining the configurations that minimise the interfacial energy (or, equivalently, the area of the air–liquid interface), subject to the constraint that the volume of fluid contained in the liquid lining remains constant; see e.g. Everett and Haynes (1972). Within the energy-based framework, the competition between stabilising/destabilising axial/circumferential effects is related to the fact that undulations of the air–liquid interface along the length of the airway, tend to increase the interfacial area (as shown in the longitudinal sections sketched in Fig. 2), while the reduction in the interface radius in the thick-film regions tends to decrease it.

A similar argument may be employed to demonstrate that the uniform liquid film is stable to perturbations in the transverse plane (Hammond, 1983). This is illustrated in Fig. 3 which shows that the variations in the curvature of the air–liquid interface, induced by a perturbation to its shape, generate flows that return the interface to an axisymmetric configuration.

Once a suitable initial perturbation to the air–liquid interface has initiated the axisymmetric Rayleigh–Plateau instability, the fluid in the liquid lining continues to redistribute until the system reaches a new equilibrium configuration with lower interfacial energy. In this configuration the air–liquid interface must again be a surface of constant mean curvature—if it were not, the pressure gradients induced by non-uniformities in the curvature would continue to drive a flow. Fig. 4 shows the system's possible axisymmetric equilibrium configurations: a cylindrical air–liquid interface, bounding an axially uniform film (Fig. 4a); an unduloid-shaped interface, bounding an annular collar of fluid (Fig. 4b); and occluding liquid bridges (Fig. 4 c,d) in which the fluid is bounded by two spherical caps that meet the vessel walls at a certain contact angle, γ. In the lung the fluid in the liquid lining wets the airway walls, implying a zero contact angle.

The volume of fluid required to form the "minimal" liquid bridge shown in Fig. 4(c) is given by

$$V_{\min} = \frac{2\pi a^3}{3} \frac{2\sin^3\gamma + 3\cos^2\gamma - 2}{\cos^3\gamma}.$$

We note that this provides a lower bound on the volume of fluid required to form an occlusion in an axisymmetric airway because it is unlikely that a "minimal" liquid bridge (in which the opposing air–liquid interfaces just touch on the airway's centreline) can be formed via a continuous redistribution of the fluid initially contained in an axially uniform film. The actual minimal film thick-

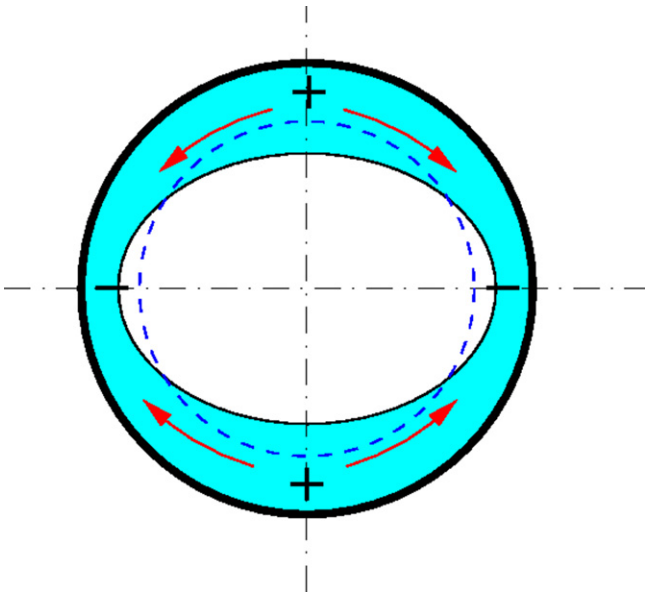

Fig. 3. Sketch illustrating the stability of the liquid lining with respect to non-axisymmetric perturbations. Non-axisymmetric perturbations to the film thickness generate surface-tension-induced circumferential pressure gradients that drive the fluid back towards the axisymmetric configuration.

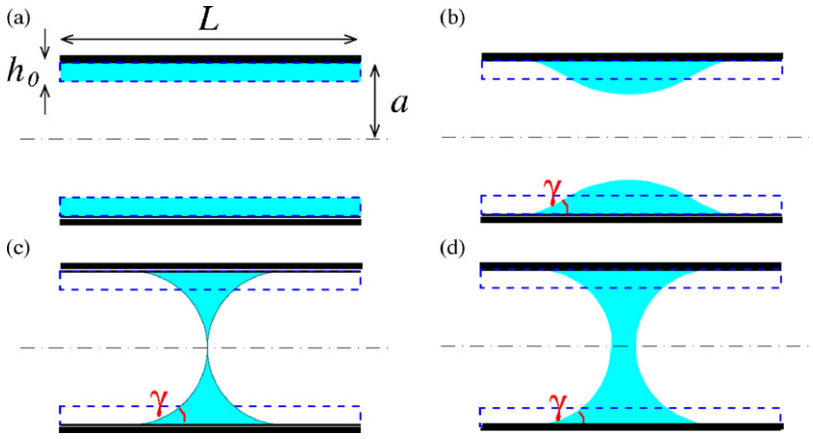

Fig. 4. Possible equilibrium configurations for the liquid lining in an axisymmetric airway: (a) a uniform liquid film; (b) an unduloid; (c) a minimal liquid bridge; (d) a finite-thickness liquid bridge. In all four cases, the air–liquid interface is a surface of constant mean curvature. In (b–d) γ is the contact angle between the air–liquid interface and the airway wall.

ness, $h_{\min}$, required for the formation of an occluding liquid bridge can only be determined by following the system's evolution after the onset of the initial instability to determine whether it evolves towards a non-occluding unduloid configuration (as in Fig. 4b) or towards a finite-thickness liquid bridge (as in Fig. 4d).

Numerical simulations (e.g. by Gauglitz and Radke, 1988; Johnson et al., 1991) and experiments (e.g. by Cassidy et al., 1999) indicate that a film thickness of at least 12% of the vessel's radius is required for an occluding liquid bridge to form.

The temporal development of the instability in an axisymmetric tube is shown in Fig. 5 for a case in which $h_0 < h_{\min}$ so that the system evolves towards a non-occluding unduloid. Fig. 5 presents axial sections through the liquid-lined airway at three different times. Also shown is the total pressure exerted along the length of the airway wall, comprising the constant external pressure, p_{ext}, and the surface-tension-induced pressure $\sigma\kappa$ exerted by the liquid film; the pressure in the lumen was set to zero, $p_{\text{int}} = 0$. (Note that the results in Fig. 5 were actually calculated with an elastic airway wall, but the wall deformation remains small because the wall is relatively stiff.)

Fig. 5(a) shows the early stages of the system's evolution during which the perturbation to the air–liquid interface, and hence its curvature, is approximately sinusoidal. During this stage the perturbation to the film thickness grows exponentially, so that $|h(z,t) - h_0| \sim \exp(\lambda t)$. The growth rate λ is given by

$$\lambda = \frac{\sigma}{3\mu}\left(\frac{h_0}{a}\right)^3 \frac{n^2}{a-h_0}\left(\frac{a^2}{(a-h_0)^2} - n^2\right), \tag{3}$$

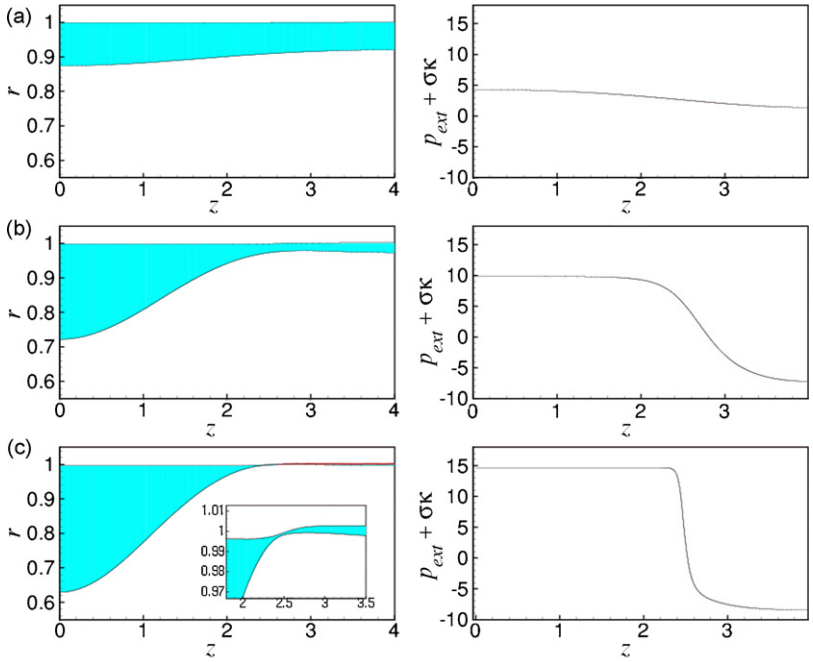

Fig. 5. Evolution of the axisymmetric fluid-elastic instability: The figures on the left show the evolution of (one half of) the growing axisymmetric lobe; the figures on the right show the total inward pressure (comprising the surface-tension-induced fluid pressure $\sigma\kappa$, and the external pressure, p_{ext}) acting on the airway wall. As the lobe grows, the fluid exerts a large compressive load on the wall. The inset in (c) shows details of the induced wall deformation and the thin "neck region" that bounds the main lobe. Modified from White and Heil (2005).

where $n = 2\pi a/L$ is the wavenumber of the axisymmetric perturbation; see e.g. White and Heil (2005). The above expression reflects the fact that the instability is driven by surface tension (the growth rate increases with σ) and resisted by viscous effects (the growth rate decreases with an increase in the fluid's viscosity, μ, and with a reduction in the film thickness, h_0).

As fluid is drawn into the growing lobe, the air–liquid interface approaches a shape of constant mean curvature and as a result the pressure in the lobe becomes approximately uniform; see Fig. 5(b). During the final stages of the fluid's redistribution, a thin "neck region", shown in the inset in Fig. 5(c), tends to develop at the end of the growing lobe. This region offers a large viscous resistance to the flows that continue to slowly drain fluid from the remaining thin-film region into the main lobe as it evolves towards the unduloid-shaped collar, its ultimate equilibrium configuration.

For films whose initial thickness exceeds $h_{\min}$, the initial stages of their evolution is similar to that shown in Fig. 5. However, once the minimum radius of the air–liquid interface is reduced below a certain threshold, the evolution accelerates dramatically as the interface contracts to form an occlusion.

The overall timescales required for an occlusion to form are very sensitive to the initial film thickness, h_0. However, the final stages of the "film collapse" proceed extremely rapidly, allowing the development of an occluding liquid bridge within a single breathing cycle; see e.g. Johnson et al. (1991).

3. "Compliant collapse": fluid-elastic instabilities

3.1. Axisymmetric wall deformations

The effect of wall elasticity on the dynamics of the Rayleigh–Plateau instability was first investigated by Halpern and Grotberg (1992, 1993). They showed that the reduction in fluid pressure in the region of the growing lobe, shown in the plots on the right of Fig. 5, can lead to a significant compression of the airway wall. The wall compression reduces the radius of the air–liquid interface even further and thus facilitates the formation of an occluding liquid bridge. The (relatively small) wall deformation induced by the fluid pressure can be seen in the inset in Fig. 5(c).

Halpern and Grotberg (1992, 1993) also considered cases in which the axisymmetric wall deformations are much larger than those shown in Fig. 5. However, such cases are unlikely to be observed in practice because compressed cylindrical tubes tend to buckle non-axisymmetrically when the compression exceeds a certain threshold; see e.g. Yamaki (1984). This buckling instability arises because the bending stiffness of thin-walled elastic tubes is much smaller than their extensional stiffness. Beyond a certain degree of compression it is more energetically favourable for the tube wall to buckle non-axisymmetrically than to undergo further axisymmetric deformations. Observations of occluded airways *ex vivo* show that the formation of occlusions does indeed tend to be accompanied by the non-axisymmetric collapse of the airway walls; see e.g. Hughes et al. (1970).

3.2. Non-axisymmetric wall deformations

If the wall deforms non-axisymmetrically, a wider class of equilibrium states are possible than for purely axisymmetric deformation. Hill et al. (1997) and Rosenzweig and Jensen (2001) computed the non-axisymmetric equilibrium shapes of axially uniform, liquid-lined tubes. Fig. 6 shows typical results from Rosenzweig and Jensen's (2001) study. The combination of the large pressure jump over the highly curved air–liquid interface and the external pressure causes the initially axisymmetric airway wall to buckle non-axisymmetrically. The fluid in the liquid lining redistributes into isolated pockets formed by the lobes. Compared to the axisymmetric configuration shown in Fig. 6(a), the buckled states have a much lower total energy because the non-axisymmetric collapse allows a significant reduction in the area of the air–liquid interface, while the bending-dominated wall deformation only requires relatively small strain energies.

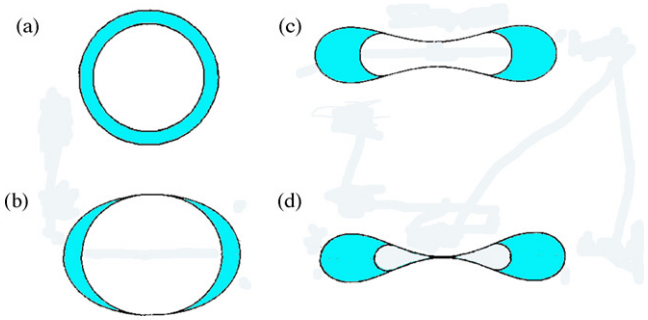

Fig. 6. Cross-sections through an axially uniform, collapsed airway loaded by the surface-tension-induced fluid pressure and the external pressure. After Rosenzweig and Jensen (2001).

In the case shown in Fig. 6(d), the non-axisymmetric collapse results in a massive reduction in the airway lumen although a small central air core remains open and thus available for respiration. For larger values of the surface tension and/or greater volumes of fluid in the liquid lining, the non-axisymmetric collapse can also lead to complete airway closure.

Axially non-uniform equilibrium configurations were calculated by Heil (1999a,b). Fig. 7 shows a sequence of static equilibrium configurations of an airway that is occluded by a liquid bridge and subjected to different values of the external (pleural) pressure, p_{ext}. The volume of fluid contained in the liquid bridge is just sufficient to form a minimal liquid bridge, such as the one shown in Fig. 4(c), when the airway is in its undeformed, axisymmetric state. As the airway collapses, the liquid bridge spreads out and subjects an increasing fraction of the airway's length to a compressive load.

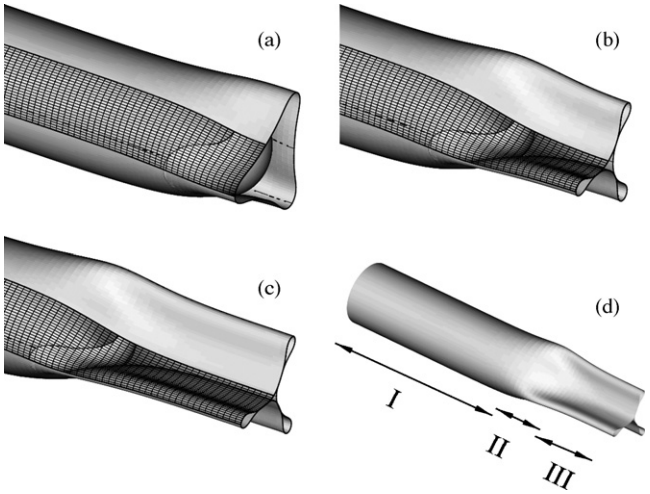

Fig. 7. (a–c) Sequence of static equilibrium shapes of a non-axisymmetrically buckling airway, occluded by a liquid bridge. The volume of fluid is sufficient to form an occluding liquid bridge in the axisymmetric airway. Only one half of the (symmetrically collapsed) airway and one of the two air–liquid interfaces are shown. Configurations (a) and (b) are statically unstable. The stable configuration shown in (c) (and again in (d)) has three distinct regions: (I) the undeformed airway; (II) a transition region which contains the air–liquid interface; (III) a liquid-filled, uniformly collapsed region in which large parts of the airway wall are in opposite wall contact. From Heil (1999b).

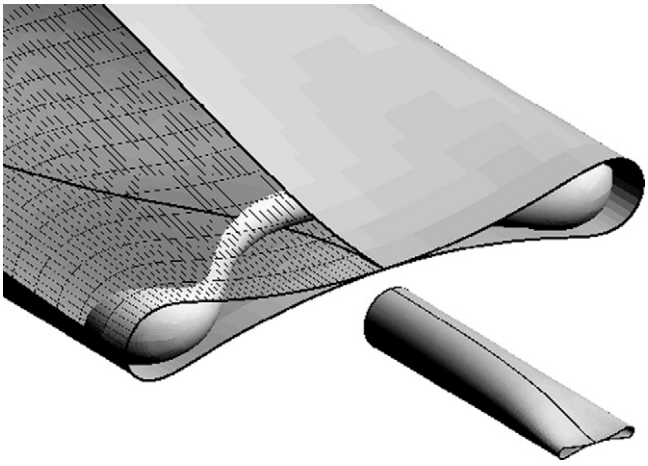

Fig. 8. A minimal liquid bridge occluding a non-axisymmetrically buckled airway. The liquid bridge contains only about a tenth of the volume of fluid required to occlude the airway in its axisymmetric state. Only one half of the (symmetrically collapsed) airway and one of the two air–liquid interfaces are shown. The small inset shows the overall shape of (one half of) the occluded airway. From Heil (1999a).

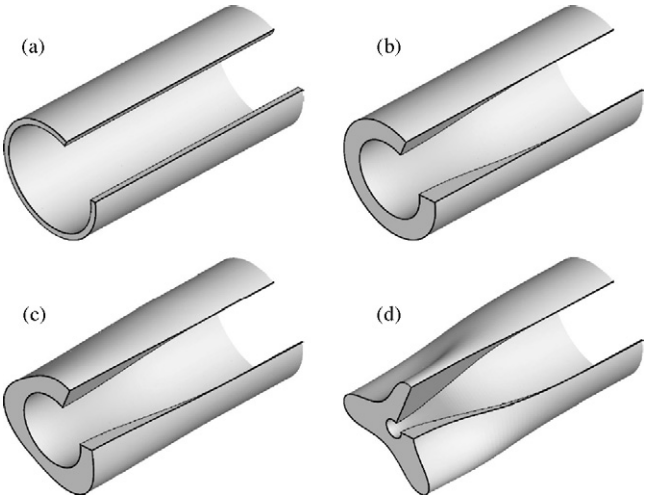

Fig. 9. Evolution of a non-axisymmetric fluid-elastic instability. (a) The initial, axisymmetric, axially uniform state; (b) the evolving axisymmetric Rayleigh–Plateau instability: fluid drains into the axisymmetric lobe and creates a strong compressive load on the airway wall; (c) the early stages of non-axisymmetric collapse: the airway wall is beginning to buckle; (d) late stages of non-axisymmetric collapse, just before the radius of the air–liquid interface is reduced to zero. Only one half of the (symmetrically collapsed) airway is shown and a sixth of the liquid-lined airway is cut away to show thickness of the liquid lining. From Hazel and Heil (2005).

Furthermore, the curvature of the air–liquid interface increases strongly with the degree of collapse, leading to a rapid increase in the compressive load on the wall. The combination of these two effects is strongly destabilising and the two intermediate configurations shown in Fig. 7(a) and (b) are, in fact, statically unstable. This indicates that if an elastic airway were occluded by an axisymmetric liquid bridge it would collapse further into a much more strongly deformed configuration, such as the one shown in Fig. 7(c) where the occurrence of opposite-wall-contact over a significant fraction of the occluded segment generates sufficiently strong elastic restoring forces to balance the large compressive load generated by the liquid bridge.

Heil (1999a) also demonstrated that non-axisymmetric airway collapse allows the formation of occluding liquid bridges with far less fluid than would be required to occlude an axisymmetric airway. Fig. 8 shows an example of a non-axisymmetric minimal liquid bridge formed with a volume of fluid that is about a tenth of $V_{\min}$. The airway is held in a strongly collapsed configuration by the pressure jump over the two highly curved air–liquid interfaces that bound the liquid bridge. The plot shows only one half of the symmetrically collapsed vessel and one of the two menisci. The minimum liquid bridge configuration is characterised by the two opposite air–liquid interfaces just touching in the symmetry plane. We note that the airway collapse is restricted to the immediate vicinity of the liquid bridge—away from the occlusion the airway rapidly reopens to its undeformed axisymmetric shape.

3.3. Dynamic non-axisymmetric collapse

As in the axisymmetric case, the mere *existence* of occluding liquid bridges that contain a relatively small volume of fluid does not imply that these can be realised via a continuous evolution from an initial state in which the axisymmetric airway is lined by a thin, uniform layer of fluid. In two-dimensional simulations, Heil and White (2002) demonstrated that the axially uniform collapsed states considered by Hill et al. (1997) and Rosenzweig and Jensen (2001) may be realised, provided that the initial compressive load exceeds the critical buckling pressure of a two-dimensional elastic ring.

In three-dimensional simulations, White and Heil (2005) and Hazel and Heil (2005) demonstrated that the occurrence of non-axisymmetric instabilities *during* the system's axisymmetric evolution towards a non-occluded equilibrium state may cause the formation of occluding liquid bridges from fluid volumes that are too small to form an axisymmetric liquid bridge. Moreover, the mechanism does not require the initial compressive load to exceed the buckling pressure of the tube. The process is illustrated in Fig. 9. Fig. 9(a) shows the axisymmetric airway, lined with a uniform liquid film which is unstable to the primary, axisymmetric Rayleigh–Plateau instability. Following the onset of this instability, fluid drains into an axisymmetric lobe, as shown in Fig. 9(b), causing an increase in interfacial curvature and a reduction of the fluid pressure, which increases the compressive load on the airway wall. When the compressive load exceeds a certain threshold, the airway begins to buckle non-axisymmetrically, as shown in Fig. 9(c). The resulting non-axisymmetric distortion of the air–liquid interface generates circumferential pressure gradients which set up draining flows. These act to return the air–liquid interface to an axisymmetric shape, and also oppose the wall's non-axisymmetric deformation (cf. Fig. 3). However, the total compressive load on the airway wall increases very rapidly as the radius of the air–liquid interface decreases, causing the non-axisymmetric collapse to accelerate dramatically towards a complete occlusion; see Fig. 9(d).

In both the two- and three-dimensional simulations, it was established that the timescales required for the non-axisymmetric collapse to occur are comparable to the duration of the breathing cycle, as is the case for axisymmetric collapse.

4. Discussion

The studies reviewed above demonstrate that surface-tension-driven instabilities of the airway's liquid lining can lead to airway closure via the formation of occluding liquid bridges. The instabilities are driven by the tendency of the fluid in the liquid lining to redistribute such that the area of the air–liquid interface (or, equivalently, its surface energy) is minimised. Wall elasticity facilitates airway closure through the "compliant collapse" mechanism and in the smaller airways, where the pressure jump over the

highly curved air–liquid interface can become comparable to the wall stiffness, non-axisymmetric airway collapse allows the formation of occluding liquid bridges with relatively small volumes of fluid. Moreover, the studies established that increasing the surface tension, decreasing the wall stiffness, and/or increasing the initial film thickness caused a more rapid development of the instability.

The studies described deliberately employed rather idealised models of the pulmonary airways and their liquid lining in order to focus on what we believe to be the most important mechanisms involved in the airway closure process. The inclusion of additional physical effects and/or the use of more realistic models for the fluid or solid mechanics, are likely to affect the precise details of the system's evolution but will not alter the fundamental instability mechanisms. We now briefly discuss how the airway closure process is affected by various mechanisms that we have ignored thus far.

4.1. Wall mechanics

The precise details of the wall mechanics appear to be irrelevant for most aspects of the "compliant collapse". For instance, both Halpern and Grotberg (1992) and White (2003) axisymmetric studies yield qualitatively similar results even though rather different wall models were employed. One feature of the instability that can be strongly affected by the specific wall model is the azimuthal wavenumber of the pattern that develops once the airway has buckled non-axisymmetrically. The three-dimensional models used by White and Heil (2005) and Hazel and Heil (2005) did not include any representation of the parenchymal tethering and assumed the airway wall to be a thin-walled shell structure of uniform thickness. The prediction of a three-lobed collapse pattern, therefore, only applies to airways with weak external support and relatively thin walls. Observations of occluded airways tend to show collapse with much larger azimuthal wavenumbers, consistent with theoretical investigations of the effects of external tethering (Wang et al., 1983) and the complex multi-layer structure of an actual airway wall (Wiggs et al., 1997). In addition, the buckled configurations of actual airways are not perfectly symmetric—a consequence of inevitable spatial non-uniformities in the parenchyma and the airway wall which may be exacerbated by diseases such as emphysema and asthma.

4.2. Gravity

If gravity acts in a direction transverse to the airway's centreline, fluid drains towards the "bottom" of the airway and the film thins (or even ruptures) at the "top", resulting in a strongly non-uniform distribution of fluid around the airway circumference. The surface tension forces that drive the formation of an occluding liquid bridge must therefore compete with the gravitational forces that drive the fluid towards the "bottom" of the airway. Estimates of the Bond number (a measure of the relative importance of gravitational and surface-tension forces) by Kamm and Schroter (1989) suggest that gravity has only a minor effect on the liquid film dynamics in the small airways and Dutrieue et al. (2005) found that airway closure in healthy subjects (where airway closure only occurs in these airways) is not affected by microgravity conditions, justifying the neglect of gravity in the studies presented here. In contrast, Duclaux et al. (2006) found that at sufficiently large values of the Bond number the Rayleigh–Plateau instability can be suppressed in rigid tubes, which suggests that in the larger airways transverse gravity may suppress airway closure by the "film collapse" mechanism.

4.3. Airway bifurcations

In vivo, the pulmonary airways are slightly curved and the distance between successive bifurcations is only a few tube diameters. Although short, such tube lengths are sufficient for the initial Rayleigh–Plateau instability to develop. Furthermore, Figs. 7–9 show that airway closure tends to be a strongly localised phenomenon. The presence of bifurcations at the end of the airway segments, which was not taken into account in any of the studies reviewed here, is therefore unlikely to have a strong effect on the airway closure process.

4.4. Centreline curvature

Jensen (1997) studied the effect of slight airway curvature on the distribution of fluid in the liquid lining but he only considered cases in which the volume of fluid was too small for occluding liquid bridges to form. The airway's centreline curvature was shown to cause the fluid to redistribute along the circumference to form a thicker layer on the "outside" wall (i.e. away from the centre of centreline curvature), resulting in a distribution of fluid similar to that achieved by transverse gravity. By analogy, therefore, it is possible that the Rayleigh–Plateau instability may be suppressed in small curved airways, but we are not aware of any studies that assess how the airway's centreline curvature affects the initial stages of the airway closure process; its later stages are unlikely to be affected by slight variations in the airway's initial shape as by then the process is driven by the rapid increase in the curvature of the air–liquid interface which is located at a significant distance from the airway walls.

4.5. The composition of the liquid lining

The studies reviewed here treated the liquid lining as a thin layer of homogeneous, Newtonian fluid. The exact composition and distribution of the liquid lining is still a matter of some debate (Dorrington and Young, 2001). It is generally accepted that the lining consists of an aqueous phase of relatively low viscosity immediately adjacent to the airway wall and a surfactant layer at the air–liquid interface (Geiser and Bastian, 2003). In the conducting airways, an upper mucus layer is present, but does not normally extend to the small airways in healthy lungs (Williams et al., 2006). Moreover, the active transport of fluid by beating cilia in the conducting airways, discussed in the article by Blake et al. (2008) in this special issue, leads to a totally different fluid-mechanical behaviour in these regions.

The aqueous layer is continuous in the central airways and the combined height of the layer and the underlying non-uniform topography, caused by variations in thickness of the epithelial cells, is approximately constant (Geiser and Bastian, 2003). *In vitro* experiments indicate that the epithelial cells can absorb and secrete liquid in order to control the thickness of the layer (Boucher, 2003). This active control of the layer thickness presumably explains why airways do not exhibit the "dry regions" predicted by theoretical models of the system's equilibrium configurations (e.g. Fig. 4), except in diseases such as cystic fibrosis where airway fluid regulation is defective (Boucher, 2007). The effect of such active control during airway collapse does not appear to have been investigated theoretically. A particularly interesting set of questions concerns the relative timescales of the control mechanism and collapse process. Can the control mechanism act over sufficiently fast timescales to suppress airway closure?

4.6. Surfactant

Airway closure is driven by surface tension and so the presence of surfactant has a strong effect on the dynamics of the process. An increase in surfactant concentration primarily leads to a net reduction in surface tension which increases the timescale for the development of the initial Rayleigh–Plateau instability (cf. Eq. (3)), and reduces the surface-tension-induced compression of the airway wall (cf. Eq. (2)), thus reducing the airway's propensity to collapse. Additionally, surfactant is advected by the fluid flow, leading to a higher surfactant concentration and, therefore, a lower surface tension in the regions where the film thickness increases. This reduces the growth rate of the Rayleigh–Plateau instability yet further but cannot suppress it altogether (Campana et al., 2004; Campana and Saita, 2006; Cassidy et al., 1999; Halpern and Grotberg, 1993; Otis et al., 1993).

4.7. Respiratory flow and wall motion

Estimates of the timescales required for the formation of occluding liquid bridges by the mechanisms discussed above indicate that the process is sufficiently rapid to be largely unaffected by the respiratory motion of the airway walls; see also Otis et al. (1993). However, a recent study by Halpern and Grotberg (2003) shows that, at least in certain parameter regimes, the periodic shear stresses generated by the respiratory flows may interact with the Rayleigh–Plateau instability and stabilise the air–liquid interface.

5. Summary

We have described the mechanics of airway closure—the formation of occluding liquid bridges via surface-tension-driven instabilities of the lung's liquid lining. Airway closure may occur as a consequence of a purely fluid-mechanical "film collapse", see Section 2, or alternatively a coupled fluid-elastic "compliant collapse", see Section 3. Although in principle these mechanisms operate throughout the lung, they are most likely to occur in the small airways where the curvature of the air–liquid interface (and hence the surface-tension-induced pressure change between the air in the lumen and the liquid lining the walls) is highest. Theoretical models predict that both mechanisms can lead to airway closure in times comparable with the breathing cycle, suggesting that surface tension is indeed the primary mechanical effect responsible for the observed closure in peripheral regions of the human lungs.

References

Appelberg, J., Pavlenko, T., Bergman, H., Rothen, H.U., Hedenstierna, G., 2007. Lung aeration during sleep. Chest 131, 122–129.

Bertram, C.D., 2008. Oscillating flow in collapsed tubes. Respiratory Physiology & Neurobiology 163, 256–265.

Blake, J.R., Smith, D.J., Gaffney, E., 2008. Modelling muco-ciliary transport. Respiratory Physiology & Neurobiology 163, 178–188.

Boucher, R.C., 2003. Regulation of airway surface liquid volume by human airway epithelia. Pflügers Archiv. European Journal of Physiology 445, 495–498.

Boucher, R.C., 2007. Cystic Fibrosis: A disease of vulnerability to airway surface dehydration. Trends in Molecular Medicine 13, 231–240.

Burger, E.J., Macklem, P., 1968. Airway closure: Demonstration by breathing 100% O_2 at low lung volumes and by N_2 washout. Journal of Applied Physiology 25, 139–148.

Campana, D.M., Di Paolo, J., Saita, F.A., 2004. A 2-D model of Rayleigh instability in capillary tubes—Surfactant effects. International Journal of Multiphase Flow 30, 431–454.

Campana, D.M., Saita, F.A., 2006. Numerical analysis of the Rayleigh instability in capillary tubes: The influence of surfactant solubility. Physics of Fluids 18, 022104.

Cassidy, K.J., Halpern, D., Ressler, B.G., Grotberg, J.B., 1999. Surfactant effects in model airway closure experiments. Journal of Applied Physiology 87, 415–427.

Dorrington, K.L., Young, J.D., 2001. Editorial III: Development of the concept of a liquid pulmonary alveolar lining layer. British Journal of Anaesthesia 85, 614–617.

Duclaux, V., Clanet, C., Quéré, D., 2006. The effects of gravity on the capillary instability in tubes. Journal of Fluid Mechanics 556, 217–226.

Dutrieue, B., Verbanck, S., Darquenne, C., Prisk, G.K., 2005. Airway closure in microgravity. Respiratory Physiology & Neurobiology 148, 97–111.

Espinosa, F.F., Kamm, R.D., 1998. Meniscus formation during tracheal instillation of surfactant. Journal of Applied Physiology 85, 266–272.

Everett, D.H., Haynes, J.M., 1972. Model studies of capillary condensation. I. Cylindrical pore model with zero contact angle. Journal of Colloid and Interface Science 28, 125–137.

Gauglitz, G.A., Radke, C.J., 1988. An extended evolution equation for liquid film breakup in cylindrical capillaries. Chemical Engineering Science 43, 1457–1465.

Geiser, M., Bastian, S., 2003. Surface-lining layer of airways in cystic fibrosis mice. American Journal of Physiology: Lung Cellular and Molecular Physiology 285, L1277–L1285.

Goren, S.L., 1962. The instability of an annular thread of fluid. Journal of Fluid Mechanics 12, 309–319.

Grotberg, J.B., Fujioka, H., Halpern, D., 2008. Liquid and surfactant delivery into pulmonary airways. Respiratory Physiology & Neurobiology.

Halpern, D., Grotberg, J.B., 1992. Fluid-elastic instabilities of liquid-lined flexible tubes. Journal of Fluid Mechanics 244, 615–632.

Halpern, D., Grotberg, J.B., 1993. Surfactant effects on fluid-elastic instabilities of liquid-lined flexible tubes: A model of airway closure. ASME Journal of Biomechanical Engineering 115, 271–277.

Halpern, D., Grotberg, J.B., 2003. Nonlinear saturation of the Rayleigh instability in a liquid-lined tube due to oscillatory flow. Journal of Fluid Mechanics 492, 251–270.

Hammond, P.S., 1983. Non-linear adjustment of a thin annular film of viscous fluid surrounding a thread of another within a circular cylindrical pipe. Journal of Fluid Mechanics 137, 363–384.

Hazel, A.L., Heil, M., 2005. Surface-tension-induced buckling of liquid-lined elastic tubes—a model for pulmonary airway closure. Proceedings of the Royal Society 461, 1847–1868.

Heil, M., 1999a. Minimal liquid bridges in non-axisymmetrically buckled elastic tubes. Journal of Fluid Mechanics 380, 309–337.

Heil, M., 1999b. Airway closure: liquid bridges in strongly buckled elastic tubes. ASME Journal of Biomechanical Engineering 121, 487–493.

Heil, M., White, J.P., 2002. Airway closure: Surface-tension-driven non-axisymmetric instabilities of liquid-lined elastic rings. Journal of Fluid Mechanics 462, 79–109.

Hill, M.J., Wilson, T.A., Lambert, R.K., 1997. Effect of surface tension and intraluminal fluid on mechanics of small airways. Journal of Applied Physiology 82, 233–239.

Hughes, J.M.B., Rosenzweig, D.Y., Kivitz, P.B., 1970. Site of airway closure in excised dog lungs: Histologic demonstration. Journal of Applied Physiology 29, 340–344.

Jensen, O.E., 1997. The thin liquid lining of a weakly curved cylindrical tube. Journal of Fluid Mechanics 331, 373–403.

Johnson, M., Kamm, R.D., Ho, L.W., Shapiro, A., Pedley, T.J., 1991. The non-linear growth of surface-tension-driven instabilities of a thin annular film. Journal of Fluid Mechanics 233, 141–156.

Kamm, R.D., Schroter, R.C., 1989. Is airway closure caused by a liquid film instability? Respiration Physiology 75, 141–156.

Otis, D.R., Johnson, M., Pedley, T.J., Kamm, R.D., 1993. Role of pulmonary surfactant in airway closure: a computational study. Journal of Applied Physiology 75, 1323–1333.

Plateau, J., 1873. Statique expérimentale et théorique des liquides soumis aux seules forces moéculaires. Volume Tome Second Paris: Gauthier–Villars.

Rayleigh, L., 1879. On the capillary phenomena of jets. Proceedings of the Royal Society of London 29, 71–97.

Rosenzweig, J., Jensen, O.E., 2001. Capillary-elastic instabilities of liquid-lined airways. ASME Journal of Biomechanical Engineering 124, 650–655.

Rothen, H.U., Sporre, B., Engberg, G., Wegenius, G., Hedenstierna, G., 1998. Airway closure, atelectasis and gas exchange during general anaesthesia. British Journal of Anaesthesia 81, 681–686.

Wang, C.Y., Watson, L.T., Kamat, M.P., 1983. Buckling, postbuckling and the flow through a tethered elastic cylinder under external pressure. ASME Journal of Applied Mechanics 50, 13–18.

White, J.P., 2003. Airway closure: Surface-tension-driven non-axisymmetric instabilities of liquid-lined elastic tubes. PhD thesis. University of Manchester.

White, J.P., Heil, M., 2005. Three-dimensional instabilities of liquid-lined elastic tubes—A lubrication theory model. Physics of Fluids 17, 031506.

Wiggs, B.R., Hrousis, C.A., Drazen, J.M., Kamm, R.D., 1997. On the mechanism of mucosal folding in normal and asthmatic airways. Journal of Applied Physiology 83, 1814–1821.

Williams, O.W., Sharafkhaneh, A., Kim, V., Dickey, B.F., Evans, C.M., 2006. Airway mucus: From production to secretion. American Journal of Respiratory Cell and Molecular Biology 34, 527–536.

Yamaki, N., 1984. Elastic stability of circular cylindrical shells. North-Holland, Amsterdam.