

Why are infants prone to wheeze?

Physiological aspects of wheezing disorders in infants

Urs Frey

Summary

Wheezing in infants is common and increasing in prevalence. Infants are particularly prone to wheezing due to developmental differences in airway mechanics compared to adults. These effects are enhanced in the presence of airway inflammation. Wheezing in infants is related to flow limitation which is a function of airway calibre and airway wall compliance. This review discusses the factors contributing to flow limitation and hence, wheezing. It tries to make the link between risk factors influencing airway structure, and thus function, with particular emphasis on the special phys-

iological peculiarities of infants and lung growth. While in adults inflammation and remodelling alone may explain structural and functional changes in wheezing disorders, this review proposes a model emphasising that in infants inflammation, remodelling and airway development have to be considered as a continuously interacting system.

Key words: infants; lung function; wheezing disorders; flow limitation; airway wall mechanics; airway inflammation; remodelling

Wheezing disorders in infants

Childhood respiratory disease remains an important cause of mortality and morbidity, accounting for up to one-third of general practitioner consultations. There is a growing body of evidence from epidemiological studies [1–3] confirming a link between childhood lower respiratory illness (LRI) and wheezing and the development of adult chronic respiratory disease [1, 4]. The nature of this link, the biological mechanisms which mediate it, and the genetic and environmental factors which influence its expression have been the focus of a considerable research effort in recent years.

Predictors of wheezing

One concept evoked to explain this association is that of “programming” – the permanent alteration of the structure and function of organs and tissues by factors operating during sensitive periods in fetal or early postnatal life [1]. Factors implicated in “programming” of the respiratory system include fetal nutrition [1, 5, 6], fetal exposure to maternal smoking during pregnancy [7, 8], and exposure to environmental allergens [9, 10] or viral respiratory infections [11–13] during infancy. The issue of a genetic predisposition to asthma or atopy is also pertinent [10, 12] and it is likely that, for childhood asthma at least, outcome is determined by a combination of familial and environmental

factors. Some of these factors are also potential “programmers” of the developing immune system. It has been suggested that exposure to viral infections in early infancy in those who are genetically susceptible to atopic disorders may favour dominance of TH-1 lymphocytes and reduce the expression of atopic disorders as mediated by competing TH-2 lymphocyte populations [12, 14]. From these experiences it becomes obvious that developmental aspects of the lung and particularly of the airways may play a crucial role in wheezing disorders in infants. Most striking are studies looking at the influence of antenatal smoking on airway function at birth and subsequent wheezing disorders. It has been suggested that infants of mothers who smoked during pregnancy achieve lower maximal flows through their airways than healthy infants and that this flow limitation is related to subsequent wheezing disorders in the first three years of life (e.g. [8, 15]). *Thus airway function seems to be an important “programmer” for wheezing disorders in infants.*

Airway development in early infancy

As with other body tissues and organs, fetal and early postnatal life is a period of rapid growth and development of the respiratory system [16]. Bronchial development and airway branching are mainly complete by the 16th week of gestation and,

thereafter, airways increase in size and complexity only [17]. True alveoli do not begin to develop until about 28 weeks gestation and increase rapidly in number, size and complexity during the first 3–4 years of life [17]. In a full term infant, lung volume doubles by 6 months and triples by 1 year. These different growth patterns of the airways and parenchyma (ie, disynaptic growth) during fetal and early life result in airways that are relatively large in relation to lung volume at birth, when airway conductance may be higher than at 2–3 months of age [16]. The extent to which gender differences in these growth patterns contribute to the increased incidence and severity of respiratory illnesses observed in boys is unclear. Although some remodelling of the lung may occur during the first year of life following prenatal and perinatal insults, there appears to be considerable tracking of respiratory function from the end of the first year of life to late childhood [16].

The somatic growth that occurs during the first year of life is accompanied by major developmental changes in respiratory physiology [16], including changes in the shape, compliance and deformability of the rib cage. The highly compliant chest wall of the newborn infant gradually stiffens during the first year of life. Infants also modulate expiratory flow in order to dynamically elevate functional residual capacity (FRC) above the level passively determined by the outward recoil of the chest wall and the inward recoil of the lung, an important strategy to establish and maintain an adequate lung volume in the presence of a highly compliant chest wall. This can be achieved by three mechanisms: the post-inspiratory muscle activity, laryngeal braking and the decrease of the expiratory time below the time constant of the respiratory system. Transition to a more relaxed pattern of expiratory flow occurs between 6–12 months of age. Another consequence of a highly compliant chest wall is an increased tendency of the peripheral airways to close during tidal breathing in early infancy, which results in impaired gas exchange in the dependent parts of the lung. This, together with the small absolute size of the airways, increases susceptibility to airway obstruction in the infant and young child [16].

While there is clear evidence that airway responsiveness is present from birth, the contribution of pre-existing alterations in airway geometry and lung mechanics or pathological changes such as airway oedema and mucus hypersecretion to wheezing and LRIs may be of importance. Smooth muscle tone is modulated by a balance between slowly adapting receptors, which normally evoke smooth muscle relaxation, and rapidly adapting receptors and pulmonary C fibres, which normally promote cough and broncho-constriction. In newborn infants, the coupling between smooth muscle and slowly adapting receptors is influenced by the mechanical properties of the cartilage of the large airways, elastic recoil of the lung-chest wall system, as well as the relatively reduced number of rapidly adapting receptors. Any given increase in airway resistance may reflect differing combinations of airway smooth muscle shortening and relative thickness of the airway wall. Thus, airway inflammation will increase and potentiate the effect of smooth muscle shortening on airway resistance, although the overall effect may vary with airway generation, being counteracted in the small airways by elastic lung recoil. Thus, in infants, the balance between central airway wall compliance, peripheral airway resistance and lung recoil may differ from that of older children and adults, resulting in different patterns of airflow limitation with age.

The importance of this balance between airway diameter and airway wall mechanics in wheezy infants has also been stressed by pharmacological studies. While broncho-dilators are capable of reversing broncho-constriction due to smooth muscle activation, they might have more complex or even deleterious effects in cases with developmental disturbances of airway mechanics. Pharmacological studies have shown that broncho-dilators may affect not only airway diameter in infants, but may even increase flow limitation by reducing airway smooth muscle tone and therefore increasing airway wall compliance [18]. Particularly in infants with severe disturbance of airway wall mechanics such as tracheomalacia, broncho-dilators can have adverse effects [19].

The physiology of wheezing

Flow limitation occurs in the airways when actual flow equals the maximal flow (V_{\max}) within the airway tree. At high lung volumes the flow limiting site in the human airways is typically in the second and third generation of branching. As lung volume decreases and airway calibre decreases, the flow-limiting site moves peripherally and V_{\max} decreases. Flow limitation in a compliant tube is accompanied by flutter of the walls at the site of flow limitation [20]. This occurs to balance the

energy of the system, as the driving pressure, in excess of that required to produce V_{\max} , is dissipated, hence causing the walls to “flutter”. In the presence of airway obstruction, this flutter may become large enough to generate sound, heard as wheezing. Thus expiratory wheezing is a sign of expiratory flow limitation [21]. Note that wheezing always implies flow limitation, but flow limitation can occur without audible wheeze. In children with mild asthma, wheeze may be heard during

forced expiration (including during a cough) but may be absent during tidal breathing. As the severity of the asthma increases and airway narrowing worsens, flow limitation may occur during tidal expiration and wheezing may be heard during tidal breathing. Interestingly, flow limitation can occur in healthy infants even in the absence of dyspnoea, the role of which is not yet clear.

Maximal expiratory flows, airway wall compliance and wheezing disorders

Maximum flows achieved during forced expiration are directly related to airway cross-sectional area (calibre) and inversely related to airway wall compliance [22] which itself is a function of the elastic recoil of the surrounding tissue. The classical concept of wheezing in infants is based on flow limitation due to airway narrowing. This airway narrowing is mainly induced by inflammatory processes causing mucosal swelling, folding and smooth muscle activation. The degree to which this airway narrowing occurs is a function of the smooth muscle contraction as well as the pre- and afterload of the surrounding tissue (coupling). However, there has been little emphasis on the mechanical characteristics of the airway wall itself.

Developmental differences in airway wall mechanics

As mentioned above, elastic recoil and airway stability are very different in infants due to developmental differences of lung physiology and the dynamic equilibrium of the end-expiratory level. The importance of airway wall compliance for flow limitation in infants has been emphasised in morphological studies showing that airway wall compliance in newborns is much higher than in adults leading to more flow limitation [23–29]. Animal work in lambs suggests that this is due to developmental differences in tracheal cartilage composition as well as differences in airway smooth muscle tone and longitudinal tension. It has also been suggested that therapeutic interventions in infants – eg, artificial ventilation in preterm infants – may alter the airway wall structure/function relationship [23].

Differences in airway wall mechanics due to inflammation and remodelling

While developmental differences may alter airway wall mechanics, airway inflammation can also have an effect on airway wall mechanics. In infant inflammatory airway disease, these physiological differences enhance the effect of the disease process in comparison to adults. Airway inflammation will increase and potentiate the effect of smooth muscle shortening on airway resistance, because the coupling between smooth muscle and slowly adapting receptors is influenced by the mechanical properties

of the large airways and the elastic recoil of the lung/chest wall system. Any given increase in airway resistance may reflect differing combinations of altered baseline airway wall compliance, airway smooth muscle shortening and relative thickness of the airway walls due to inflammation, resulting in different patterns of airflow limitation.

Since the *contractile state of airway smooth muscles* contributes dominantly to the wall mechanical properties, the effects of inflammation on baseline airway smooth muscle tone has to be considered. An important local mediator of neuro-muscular interaction is nitric oxide (NO). Recently, it has been emphasised that the baseline airway smooth muscle tone may be influenced by local concentrations of NO [30]. Baseline airway wall compliance will be determined by baseline airway smooth muscle tone, which in turn may be influenced by localised NO concentrations. NO is not only produced by the constitutive nitric oxide synthase (cNOS) but also by the inducible nitric oxide synthase (iNOS), which is present in epithelial cells as well as monocytes and macrophages, and which can be stimulated by pro-inflammatory cytokines. Thus potentially, during airway inflammation baseline smooth muscle tone may be altered. There is recent evidence that smooth muscle cells themselves change their mechanical properties, if they are exposed to asthma related pro-inflammatory cytokines and growth factors [31].

Post-inflammatory airway remodelling can alter airway wall structure. The airway wall of adult patients with asthma is usually characterised by an increased thickness involving an increase in muscle mass, thickening of the reticular basement membrane, structural changes of the extracellular matrix (collagen, elastin, fibronectin, laminin, glycosaminoglycans), an increase in mucous glands and in vessel area, all leading to reduced airway calibre (summarised in [32]). In infants, however, little is known of these structural mechanisms and particularly of their physiological effect in wheezing disorders and during airway growth. The correlation between adult respiratory disease and infants wheezing [10] emphasises the importance of this topic.

All this evidence suggests that it may not be sufficient to limit measurements to that of flow limitation of the airways, but that *more detailed information concerning the separate influences of airway wall mechanics and airway diameter* might be important in order to understand the pathophysiology of wheezing disorders in infants. Until now it has only been possible to measure flow limitation in infants using forced expiratory manoeuvres by the rapid chest compression technique. These techniques do not allow the contribution of airway diameter and airway wall mechanics to be assessed.

Measuring flow limitation in infants using the rapid thoracic compression technique

Forced expiration can be measured in infants using the rapid thoracic compression technique (RTC) [33]. The RTC technique produces forced expiratory flows by the sudden application of pressure to the thorax and abdomen at the end of tidal inspiration, using an inflatable thoraco-abdominal jacket connected to a positive pressure reservoir. Flow is measured at the mouth with an pneumotachograph attached to a mask sealed around the infant's nose and mouth and a flow-volume curve constructed. RTC, initiated at end-inspiration, then produces a expiratory flow volume curve, with exhalation continuing to a volume below the

previous FRC. RTC manoeuvres are performed with increasing jacket pressures until the pressure that produces the highest expiratory flows is determined. Use of the RTC has led to major advances in the understanding of the normal growth and development of the respiratory system and of respiratory diseases in infancy [8, 15, 34]. However, maximum flows achieved during forced expiration are directly related to airway cross-sectional area (calibre) and inversely related to airway wall compliance [22], so that the technique cannot determine the contribution of these two properties to overall airway function.

Measurements of airway wall compliance

There has been an increasing need for a technique that can measure airway wall mechanics independently of airway calibre. Several investigators have determined airway wall elasticity from excised airways at various stages of lung development [23-29] or used invasive approaches [35]. These in vitro techniques are an interesting approach for studying structure/function relationship of the airways during development, however may not fully reflect the in vivo situation where airway wall tension is markedly influenced by the elastic recoil of the surrounding tissue.

New concepts of measuring airway wall mechanics

Until recently it was not possible to non-invasively obtain a direct or indirect measure of airway wall mechanics in spontaneously breathing infants. One proposed method to non-invasively measure airway wall mechanics is based on respiratory input impedance measurements using forced oscillatory techniques [36]. These techniques expose the respiratory system to a sinusoidal pressure wave generated by a loudspeaker and the resulting oscillatory flow is measured. If the oscillatory pressure changes ($P(\omega)$) are sufficiently small, the respiratory system will behave in a linear fashion and the so-called respiratory impedance ($Z(\omega)$) can be calculated from the ratio of $P(\omega)$ and the corresponding oscillatory flow $V(\omega)$. $Z(\omega)$ is a complex variable and contains information of the resistive, elastic and inertive properties of the respiratory system. Dependent on the frequency (ω) of the applied pressure wave, $Z(\omega)$ will contain different mechanical information. The response to very slow pressure oscillations (<1 Hz) will contain information on lung tissue, and then with increasing frequency airway resistance will influence $Z(\omega)$. At very high frequencies (>100 Hz) $Z(\omega)$ will contain information on airway wall mechanics.

At high frequencies the applied pressure wave exhibits acoustic properties and anti-resonance phenomena occur in the airway [36], comparable to the sound generation in an organ pipe. In a single elastic tube, the frequency at which these anti-resonances occur depend on the length of the tube and its wall properties, as the wave propagation velocity in an elastic tube is different from free sound wave speed. These high frequency impedance techniques have recently been adapted for non-invasive use in infants, allowing the question of the interactions between airway wall mechanics and flow limitation and thus wheezing disorders in infants to be answered. The high frequency forced oscillation technique for use in infants [37, 38] and newly introduced high speed interrupter technique [39, 40] are both capable of measuring high frequency respiratory input impedance. These techniques have shown, that in analogy to measurements in adults, the anti-resonance phenomena are related to acoustic phenomena in infants [40] and thus contain information on airway wall mechanics, and that airway wall mechanics change dramatically during an inhaled methacholine challenge [38, 41]. Thus, demonstrating that not only airway narrowing but also changes in airway wall mechanics are important during flow limitation in infants. The high speed interrupter technique has subsequently been used to demonstrate, in a cross-sectional study, that the anti-resonance frequency is significantly reduced in asymptomatic infants with a history of wheezing disorders when compared to healthy infants [42]. Since the boundary conditions and the effective mean airway path-length are likely to be similar in age matched groups of infants, these data support the hypothesis that airway wall mechanics are different in these groups of infants. Differences in airway wall mechanics can either be due to inborn developmental differences in wall structure or due to acquired

post-inflammatory changes in wall structure and mechanics. To resolve the latter point a future prospective study is needed, commencing shortly

after birth before environmental or inflammatory injury occurs.

Summary and hypothetical model of wheezing in infants

There is growing evidence that *not only airway diameter but also airway wall function and lung volume* may be altered in wheezing disorders in infants. All these components act in a complex dynamic equilibrium in health and may be disturbed in disease. Figure 1 represents this complex system in disease. It can be seen that most structural changes in wheezing disorders not only influence airway diameter but also act on airway wall mechanics.

Furthermore, while in adults inflammation and remodelling alone may explain structural and functional changes in wheezing disorders, in infants inflammation, remodelling and airway development have to be considered as a *continuously interacting system*. Airway resistance, airway wall compliance and airway tissue interaction change with age. These components (Figure 1 bold arrow), however, are also part of the functional changes in wheezing disorders. Thus, there must

Figure 1

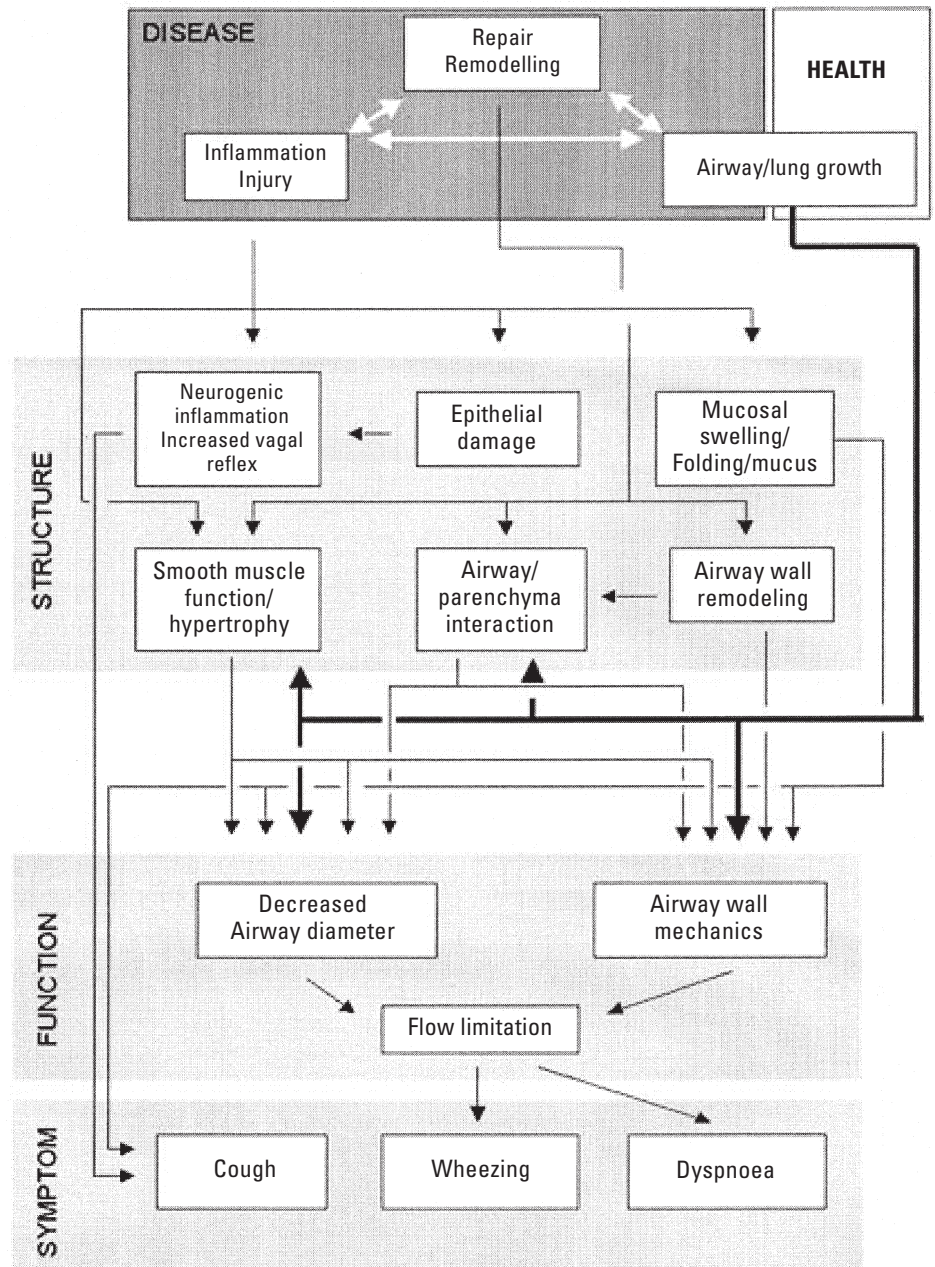
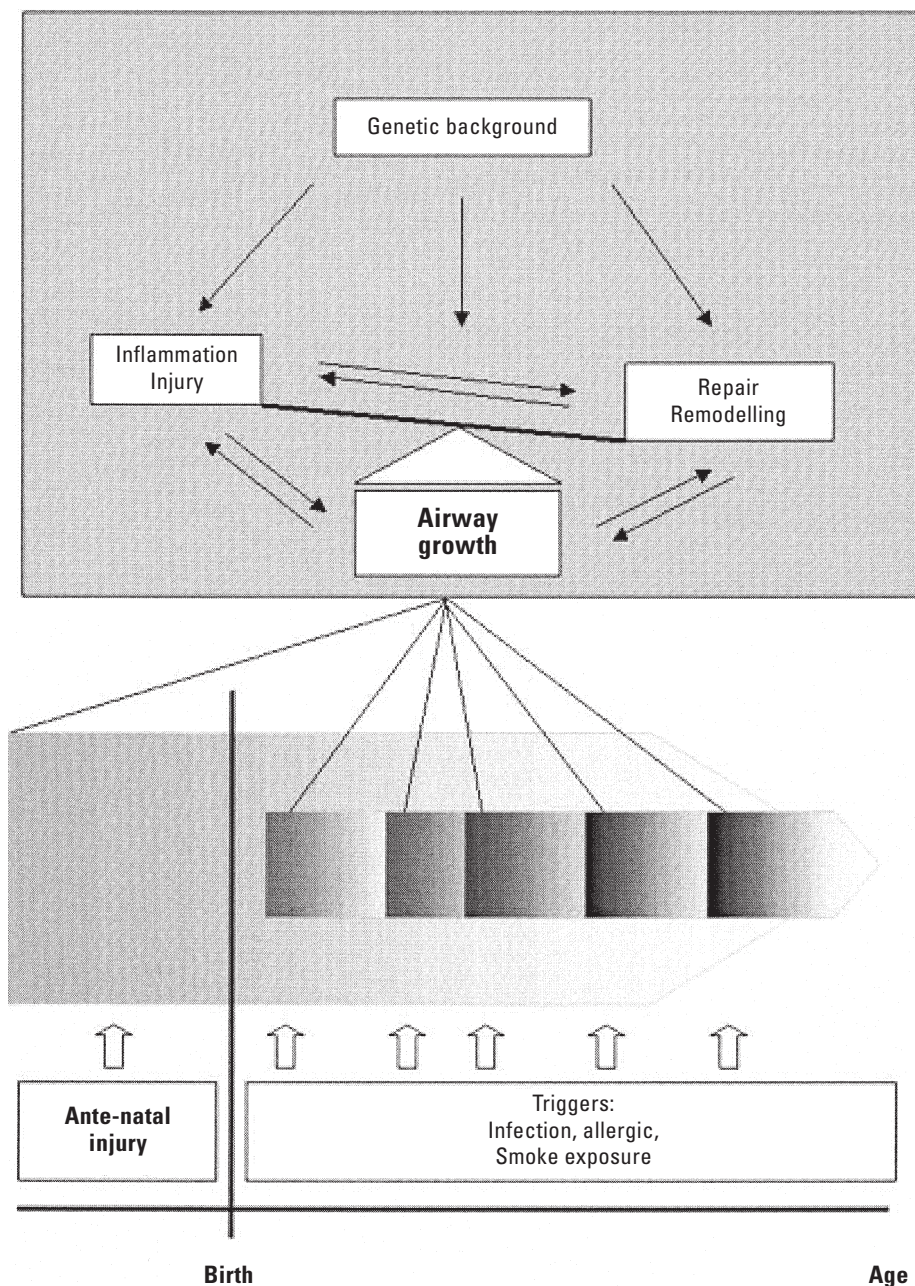


Figure 2



be a close interaction between inflammation, remodelling and normal lung development (Figure 2 upper part). Combining epidemiological and physiological evidence, one could hypothesise, that this triangular interaction behaves in a dynamic manner during growth. This dynamic behaviour may be determined by the programmers and the genetic background regulating this system as well as the nature and frequency of the triggers disturbing this system. Whether or not wheezing is transient or persistent may be understood as a function of this dynamic system.

Correspondence:
 Urs Frey, MD, PhD
 Paediatric Respiratory Medicine
 Dept. of Paediatrics
 University Hospital of Berne
 Inselspital
 CH-4010 Berne
 E-mail: urs.frey@insel.ch

References

- 1 Shaheen SO, Barker DJP, Shiell AW, Crocker FJ, Wield GA, Holgate ST. The relationship between pneumonia in early childhood and impaired lung function in late adult life. *Am J Respir Crit Care Med* 1994;149:616-9.
- 2 Silverman M. Asthma and wheezing disorders in young children. *N Engl J Med* 1995;332:181-182.
- 3 Dezateux C, Stocks J. Lung development and early origins of childhood respiratory illness. *Br Med Bull* 1997;53: 40-57.
- 4 Barker DJP, Godfrey ILM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 1991;303:671-5.
- 5 Schwartz J, Gold D, Dockery DW, Weiss ST, Speizer FE. Predictors of asthma and persistent wheeze in a national sample of children in the United States. Association with social class, perinatal events and race. *Am Rev Respir Dis* 1990;142: 555-62.
- 6 Rona RJ, Gulliford MC, Chinn S. Effects of prematurity and intrauterine growth on respiratory health and lung function in childhood. *BMJ* 1993;306:817-20.
- 7 Lewis S, Richards D, Bynner J, Butler N, Britton J. Prospective study of risk factors for early and persistent wheezing in childhood. *Eur Respir J* 1995;8:349-55.
- 8 Tager IB, Hanrahan JP, Tosteson TD, Castile RG, Brown RW, Weiss ST, Speizer FE. Lung function, pre- and post-natal smoke exposure, and wheezing in the first year of life. *Am Rev Resp Dis* 1993;147:811-7.
- 9 Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house-dust mite allergen Der p1 and the development of asthma in childhood. A prospective study. *N Engl J Med* 1990;323:502-7.
- 10 Strachan DP. Is allergic disease programmed in early life? *Clin Exp Allerg* 1994;24:603-5.
- 11 Martinez FD. Role of viral infections in the inception of asthma and allergies during childhood: could they be protective? *Thorax* 1994;49:1189-91.
- 12 Holt PG. Environmental factors and primary T-cell sensitisation to inhalant allergens in infancy: reappraisal of the role of infections and air pollution. *Pediatr Allergy Immunol* 1995: 6:1-10.
- 13 Strachan DP, Seagroatt V, Cook DG. Chest illness in infancy and chronic respiratory disease in later life: an analysis by month of birth. *Int J Epidemiol* 1994;23:106-8.
- 14 Martinez FD. Role of viral infections in the inception of asthma and allergies during childhood: could they be protective? *Thorax* 1994;49:1189-91.
- 15 Martinez F, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illnesses in infants. *N Engl J Med* 1988;319:1112-7.
- 16 Stocks J. Developmental physiology and methodology. In Silverman M, Taussig LM. (Eds) *Early Childhood Asthma: What are the Questions?* *Am J Respir And Care Med* 1995;151: S11-3.
- 17 Hislop A. Developmental anatomy and cell biology. In: Silverman M. (Ed) *Childhood Asthma and other Wheezing Disorders*. London: Chapman & Hall, 1995;215-30.
- 18 Prendiville A, Green S, Silverman M.. Paradoxical response to nebulized salbutamol in wheezy infants, assessed by partial expiratory flow volume curves. *Thorax* 1987;42:86-91.
- 19 Silverman M. On the effect of smooth muscle tone in patients with tracheomalacia. *Pediatr Pulmonol* 1991;10:261-4.
- 20 Webster PM, Sawatzky RP, Hoffstein V, et al. Wall motion in expiratory flow limitation: choke and flutter. *J Appl Physiol* 1985;59:1304-12.
- 21 Gavriely N, Kelly KB, Grothberg JB, Loring SH. Forced expiratory wheezes are a manifestation of airway flow limitation. *J Appl Physiol* 1987;62:2398-403.
- 22 Dawson SV, Elliot EA. Wave speed limitation expiratory flow – a unifying concept. *J Appl Physiol* 1977;43:498-515.
- 23 Bhutani VK, Rubenstein D, Shaffer TH. Pressure-induced deformation in immature airways. *Pediatr Res* 1981;15:829-32.
- 24 Deoras KS, Wolfson MR, Searls RL, Hilfer SR, Shaffer TH. Developmental changes in tracheal structure. *Pediatr Res* 1991;30:170-5.
- 25 Koslo RJ, Bhutani VK, Shaffer TH. The role of tracheal smooth muscle contraction on neonatal tracheal mechanics. *Pediatr Res* 1986;20:1216-20.
- 26 Panitch HB, Allen JL, Ryan JP, Wolfson MR, Shaffer TH. A comparison of preterm and adult airway smooth muscle mechanics. *J Appl Physiol* 1989;66:1760-5.
- 27 Panitch HB, Deoras KS, Wolfson MR, Shaffer TH. Maturation changes in airway smooth muscle structure-function relationships. *Pediatr Res* 1992;31:151-6.
- 28 Penn RB, Wolfson MR, Shaffer TH. Effect of tracheal smooth muscle tone on collapsibility of immature airways. *J Appl Physiol* 1988;65:863-9.
- 29 Shaffer TH, Bhutani VK, Wolfson MR, Penn RB, Tran NN. In vivo mechanical properties of the developing airway. *Pediatr Res* 1989;25:143-6.
- 30 Van der Velden VH, Hulsmann AR. Autonomic innervation of human airways: structure, function, and pathophysiology in asthma. *Neuroimmunomodulation* 1999;6:145-59.
- 31 Hakonarson H, Maskeri N, Carter C, Chuang S, Grunstein MM. Autocrine interaction between IL-5 and IL-1beta mediates altered responsiveness of atopic asthmatic sensitized airway smooth muscle. *J Clin Invest* 1999;104:657-67.
- 32 Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma, from bronchoconstriction to airway inflammation and remodelling. *Am J Resp. Crit Care Med* 2000;161:1720-45.
- 33 Sly P, Tepper R, Henschen M, Gappa M, Stocks J. Standards for infant respiratory function testing: Tidal forced expirations. *Eur Respir J* 2000;16:741-8.
- 34 The Joint American Thoracic Society/European Respiratory Society Working Group on Infant Lung Function. The raised volume rapid thoracoabdominal compression technique. *Am J Respir Crit Care Med* 2000;161:1760-2.
- 35 Panitch HB, Talmaciu I, Heckman J, Wolfson MR, Shaffer TH. Quantitative bronchoscopic assessment of airway collapsibility in newborn lamb tracheae. *Pediatr Res* 1998;43:832-9.
- 36 Jackson AC, Giurdanella CA, Dorkin HL. Density dependence of respiratory system impedances between 5 and 320 Hz in humans. *J Appl Physiol* 1989;67:2323-30.
- 37 Jackson AC, Neff KM, Lutchen KR, Dorkin HR. Interpretation of respiratory system impedances (4-256 Hz) in healthy infants. *Ped Pulmonol* 1996;226:364-75.
- 38 Frey U, Silverman M, Kraemer R, Jackson AC. High frequency respiratory impedance in infants by forced oscillations. *Am J Respir Crit Care Med* 1998;158:363-370.
- 39 Frey U, Suki B, Kraemer R, Jackson AC. Human respiratory input impedance between 32 and 800 Hz measured by high speed interrupter technique. *J Appl Physiol* 1997;82:1018-23.
- 40 Frey U, Silverman M, Kraemer R, Jackson AC. High frequency input impedance in infants assessed with the high speed interrupter technique. *Eur Resp J* 1998;12:148-58.
- 41 Frey U, Jackson AC, Silverman M. Differences in airway wall compliance as a possible mechanism for wheezing disorders in infants. *Eur Resp J* 1998;12:136-42.
- 42 Frey U, Makkonnen K, Wellman T, Beardsmore C, Silverman M. Alterations in airway wall properties in infants with a history of wheezing disorders. *Am J Respir Crit Care Med* 2000;161: 1825-9.

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website <http://www.smw.ch> (direct link from each SMW record in PubMed)
- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

Editorial Board

Prof. Jean-Michel Dayer, Geneva
 Prof. Peter Gehr, Berne
 Prof. André P. Perruchoud, Basel
 Prof. Andreas Schaffner, Zurich
 (Editor in chief)
 Prof. Werner Straub, Berne
 Prof. Ludwig von Segesser, Lausanne

International Advisory Committee

Prof. K. E. Juhani Airaksinen, Turku, Finland
 Prof. Anthony Bayes de Luna, Barcelona, Spain
 Prof. Hubert E. Blum, Freiburg, Germany
 Prof. Walter E. Haefeli, Heidelberg, Germany
 Prof. Nino Kuenzli, Los Angeles, USA
 Prof. René Lutter, Amsterdam, The Netherlands
 Prof. Claude Martin, Marseille, France
 Prof. Josef Patsch, Innsbruck, Austria
 Prof. Luigi Tavazzi, Pavia, Italy

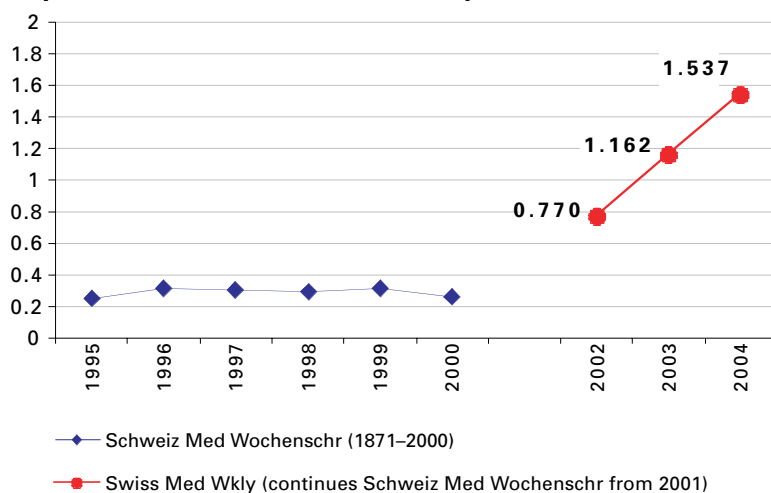
We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:

http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
 SMW Editorial Secretariat
 Farnsburgerstrasse 8
 CH-4132 Muttenz

Manuscripts: submission@smw.ch
 Letters to the editor: letters@smw.ch
 Editorial Board: red@smw.ch
 Internet: <http://www.smw.ch>