[4] Wennergren G, Kristjánsson. Relationship between respiratory syncytial virus bronchiolitis and future obstructive airway diseases. Eur Respir J 2001; 18: 1044–1058.
[5] Gern JE et al, The role of viral infections in the natural history of asthma. J Allergy Clin Immunol 2000; 106: 201–212.
[6] Sigurs N et al, Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am Respir Crit Care Med 2000; 161: 1501–1507.
[7] Stein RT et al, Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 1999; 354: 541–545.
[8] Simões EAF et al, The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children. J Allergy Clin Inmunol 2010; 126: 256–62.
[9] McBride JT. Pulmonary function changes in children after respiratory syncytial virus infection in infancy. J Pediatr 1999; 135: S28–32.
[10] Daley D et al. Associations and interactions of genetic polymorphisms in innate immunity genes with early viral infections and susceptibility to asthma and asthma-related phenotypes. J Allergy Clin Immunol. 2012 Dec; 130(6): 1284–93.
[11] Smith Cm et al. Ciliary dyskinesia is an early feature of respiratory syncytial virus infection. Eur Respir J 2013 Mar 21 [Epub Ahead of print].
[12] Régnier S, Huels J. Association between Respiratory Syncytial Virus Hospitalizations in Infants and Respiratory Sequelae: Systematic Review and Meta-Analysis. Pediatr Infect Dis J. 2013 Mar 20 [Epub ahead of print].
[13] Manzoni P et al, High risk for RSV bronchiolitis in late preterms and selected infants affected by rare disorders: a dilemma of specific prevention. Early Hum Dev 2012; 88(Suppl 2): S34–41.
[14] Simon A et al. Respiratory syncytial virus infection in children with neuromuscular impairment. Open Microbiol J 2011; 5: 155–8.
[15] Kristensen K et al. Chronic diseases chromosomal abnormalities and congenital malformations as risk factors for respiratory syncytial virus hospitalization: a population-based cohort study. Clin Infect Dis 2012; 54: 810–817.
[16] Sommer C et al., Risk factors for severe respiratory syncytial virus lower respiratory tract infection. Open Microbiol J 2011; 5: 144–154.
[17] Thorburn K. Preexisting disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. Arch Dis Child 2009; 94: 99–103.
[18] Figueras-Aloy J, et al. Spanish multidisciplinary consensus on the prevention of respiratory syncityal virus infection in children. An Pediatr (Barc) 2008; 69: 63–71.
[19] Medrano López C, et al., Clinical consensus on respiratory syncytial virus (RSV) infection prophylaxis and the use of palivizumab in paediatric cardiology. An Pediatr (Barc) 2010; 7: 432.e1–432.e13.
[20] Committee on Infectious Diseases. From the American Academy of Pediatrics: Policy statements – Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. Pediatrics 2009; 124: 1694–1701.
[21] Winterstein AG, et al., Palivizumab Immunoprophylaxis Effectiveness in Children With Cystic Fibrosis. Pediatr Pulmonol 2012. DOI: 10.1002/ppul.22711 [Epub ahead of print].
[22] Robinson KA, et al., Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis (Review). Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD007743.
[23] Wang D, et al., Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses. Health Technol Assess. 2011; 15: iii–iv, 1–124.

SPA-6
New treatments in childhood asthma

A. Escribano. *University of Valencia, Spain*

A reduction in mortality and hospitalization rates caused by asthma has been observed in the last 15 years. This comforting data should incentivize the development of new strategies to reduce, even more, the significant burden that this disease poses.

Current therapy for asthma with inhaled corticosteroids and long-acting inhaled β_2-agonists is highly effective, safe, and relatively inexpensive, but many patients remain poorly controlled and, in children with severe asthma, the response to them is very variable. Moreover, inhaled corticosteroids control the symptoms while being used, but they quickly appear again when administration is stopped. This is because, until now, any of the available treatments for asthma have long term effect on inflammation or airway remodeling, so that they do not modify or cure the disease, not prevent its establishment and neither control some forms of severe asthma. Until the molecular and genetic causes of asthma can be understood, healing prospects seem remote.

Little progress has been made in the introduction of new drugs, despite the intense efforts and investments carried out in recent years. Furthermore, animal models have proved to be misleading, thus it is necessary to count on human trials. Several new treatments are under development, although many of them are so specific, targeted to a single mediator or receptor, that although they may be effective in specific phenotypes of asthma (endotypes), is unlikely that they have a major clinical impact. The complexity and heterogeneity of asthma requires acting against multiple pathogenic mechanisms. While corticosteroids are effective due to their great anti-inflammatory potential, the use of drugs with more widespread effects, such as kinase inhibitors, may be more effective but have a greater risk of side effects.

It is possible that drugs that could act on key points at the beginning of the inflammatory process, controlled the disease. In the future it would be important if pediatric patients could take part of multicenter clinical trials with promising therapies, such as new anticholinergic agents, antileukinas and, even, bronchial thermoplasty.

It is hoped that in the coming years, improved understanding of molecular and epigenetic mechanisms of asthma, enhanced knowledge of pharmacogenomics, the use of specific biomarkers to define the type of asthma, its severity and response to certain treatments, early intervention linked to an individualized monitoring of the course of the disease and the availability of personalized medicines, will allow for the design of individualized therapies that achieve the complete control of such a variable and heterogeneous disease as the asthma.

References

Barnes PJ. Severe asthma: advances in current management and future therapy. *J Allergy Clin Immunol* 2012; 129: 48–59.
Fitzpatrick AM, Baena-Cagnani CE, Bacharier LB, Severe Asthma in Childhood: Recent Advances in Phenotyping and Pathogenesis Curr Opin Allergy Clin Immunol. 2012 April; 12(2): 193–201.
Lötvall J, Akdis CA, Bacharier LB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol 2011; 127 (2):355–360.
Sayers I. A tailored approach to asthma management: Arg (16) holds the key? Clin Science (2013) 124, 517–519.

SPA-7
Lung function in infants

M. Sánchez-Solís, L. García Marcos. *University of Murcia, Spain*

From the 1980's the development of new devices has allowed us to learn about the role of infant lung function in respiratory diseases. The knowledge of lung function in newborn and infants, should help us to understand the physiology of the illness in wheezing infants, evolution of lung disease from prematurity and bronchopulmonary dysplasia, and in cystic fibrosis which are the most frequent chronic respiratory diseases in the first two years of life.

Wheeze infants: In infants with recurrent wheeze it has been shown a worse lung function compared with healthy matched infant; by mean of the rapid compression technique, it has been possible to show that the maximal flow at functional residual capacity (V'_{maxFRC}) is already diminished in wheeze infants in the first year of life [1,2], suggesting airway obstruction in those infants. Recently, by mean of raised-volume rapid thoraco-abdominal

compression technique (RVRTC), after adjustment for sex, age, body length at test and maternal smoking, significant reductions in z-scores for forced expiratory flow at 0.5 seconds ($FEV_{0.5}$), in forced expiratory flow at 75% of forced vital capacity (FEF_{75}) and in forced expiratory flow at 25 to 75% of forced vital capacity (FEF_{25-75}) were observed in infants with recurrent wheeze when compared with controls, but not in forced vital capacity (FVC) showing an obvious obstructive airway pattern in recurrent wheeze infants [3]. So the conclusion is that, with different methods of assessment, lung function is reduced in patients suffered recurrent lower respiratory illness (LRI), compared with healthy infants. The first study designed to determine whether early childhood respiratory illness led to decreases in lung function or a low lung function previous to the first airway infection led to an increased risk for wheezing, was the Tucson Children's Respiratory Study. In this prospective study of 124 infants enrolled as newborns, was shown that the risk of having a wheezing illness was 3.7 times higher (95% CI, 0.9–15.5; p = 0.06) among infants whose values for total respiratory conductance (the reciprocal of the resistance to air flow of the entire respiratory system) were in the lowest third, as compared with infants with values in the upper two thirds of the range of values for the group [4]. Seven more cohort studies [5–12], by means of different methods of assessment of lung function, demonstrated consistently a premorbid lower lung function in wheeze infants compared with healthy ones. Majority of these studies were developed assessing lung function with V'_{maxFRC}, however the recent data published from the Southamptom cohort (ALSPAC study) [12] shown that reduction in forced expiratory volume at 0.4 seg ($FEV_{0.4}$), measured before the 14 weeks of age, is a risk factor to wheeze. This study, for the first time, demostrated too that lower lung function in early infancy is a risk factor for non-atopic wheeze rather than atopic wheeze. The conclusion can only be that some children were born with an obstructive airway pattern and they are in risk to suffer LRI.

The Tucson Children's Respiratory Study concludes that diminished initial airway function may be a predisposing factor, not only for the first episode of wheezing, but also for recurrent wheezing respiratory illnesses starting in the first year of life [5]. As it is known, they described three phenotypes based in having recurrent wheezing during first three years of life, evaluated at 6 years of age; transient wheeze (these patients had had at least one wheeze lower respiratory illness during the first 3 years of life but had no wheezing at 6 years), persistent wheeze (they had wheezing both before 3 years of age and at 6 years) and late wheeze (had no wheezing in the first 3 years but had wheezing at 6 years of age), and the most important difference between transient and persistent wheeze infants was that the transient wheeze group had diminished lung function, evaluated by mean of V'_{maxFRC}, both in infancy (previously to the first episode) and at 6 years of age when compared to children who never wheezed. But the persistent wheeze group had V'_{maxFRC} values in infancy that were no different from those of the children who never wheezed and by age 6 years, however, had the lowest lung function with a significant reduction in V'_{maxFRC} [13]. In contrast with the Tucson's study, the cohort of Perth [14] demostrated a relationship between reduction in V'_{maxFRC} at 1 month of age and persistence of wheeze at 4–6 years and even at 11 years of age. Those children with no wheeze from 3 years of age (transient wheeze) have normal V'_{maxFRC} when neonate. As in Tucson's study, a lower infant lung function (V'_{maxFRC}) was seen in transient group from the cohort of Southampton (ALSPAC). But furthermore, in the ALSPAC study, V'_{maxFRC} was reduced in persistent wheeze group. Although there is a clear tendency in a reduction of $FEV_{0.4}$ in persistent wheeze group, no association was seen between infant $FEV_{0.4}$ and any phenotype, probably because the limited number of lung function test performed in infant of this group [12]. Recently has been published the results of the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) [15], a cohort of 411 high risk infants whose mothers were asthmatic. In this study the authors found that children who developed asthma by age 7 had reduced airflow when neonate: forced expiratory flow at 50% of vital capacity (FEF_{50}) (p = 0.03) and $FEV_{0.5}$ very close of the statistical significance (p = 0.07). An increased bronchial responsiveness as neonates is related with asthma at 7 years of age, too. This airflow deficit progressed in the first 7 years of life suggesting that disease mechanisms are operating before and after birth. Some risk factors have been described to explain this, very early in life, worse lung function:

- *Prenatal tobacco exposure*. A very recent and large pooled analysis of eight birth cohorts with data on more than 21,000 children showed that maternal smoking during pregnancy is associated with wheeze and asthma in preschool children. The likelihood to develop wheeze and asthma increased statistically significantly in a linear dose-dependent manner in relation to maternal daily cigarette consumption during the first trimester of pregnancy [16]. There is accumulating evidence that exposure to parental smoking is associated with impaired lung function during infancy, which is likely to persist. Maternal smoking during pregnancy and in the early months of life remains the most significant source of such exposure. The most consistent finding, from all studies of infant lung function, is of reduced flows at low lung volumes, which may reflect more extensive underlying pathological and functional alterations in the distal airways [17]. Most of the studies, describes a lose in expiratory flows (V'_{maxFRC} [18–24], $FEV_{0.5}$ [26], FEF_{50} and FEF_{25-75} [27]); but at least, a study described a reduction in FRC_{He} [19] too.
- *Gene polymorphisms*. Recently, from the Southampton Women's Survey Study [23] has been published that five single nucleotide polymorphisms (SNPs), relating to four genes, showed significant associations with infant lung function: Hedgehog interacting protein (HHIP) was associated with compliance; Retinoic acid receptor b (RARB) was associated with V'_{maxFRC}; the Natural cytotoxicity triggering receptor 3 (NCR3) respiratory rate and the histone deacetylase 4 (HDAC4) was associated with both compliance and V'_{maxFRC}. On the other hand, different SNPs in Glutathione S-Transferase gens (GSTT1, GSTP1) both in mothers and in infants were associated with a diminished V'_{maxFRC} and bronchial hyperreactivity in infant exposed to tobacco smoke in utero [25]. Neonatal V'_{maxFRC} was reduced in those possessing Gln27 or Arg16 alleles, however there was no effect of beta-2 adrenoceptor gen polymorphisms on FEV1 at 10 years [26]. Conversely, the study from Zhang et al. [27] found no association of haplotypes of β2-adrenoceptor polymorphisms with infant lung function (V'_{maxFRC}), although they found that some SNPs are associated with lung function and bronchial hyperreactivity later in life (6 and 11 years of age).
- *Atopy and inflammation*. Atopy has been studied as another risk factor for diminishing lung function in the first years of life. The article published by Håland et al. [11] shows that children (less than 2 years of age) with both recurrent LRI and atopic eczema had significantly lower t_{PTEF}/t_E at 2 yr and at birth, compared with children with no recurrent LRI or atopic eczema. The study conducted by Debley et al. [28] found no correlation between enrollment single breath exhaled nitric oxide and enrollment lung function, but was associated with a decline in $FEV_{0.5}$, FEF_{25-75} and FEF_{75} over 6 months; a 10 ppb increase in single breath exhaled nitric oxide was associated with a 0.4 z-score decline in $FEV_{0.5}$, a 0.4 z-score decline in FEF_{25-75}, and a 0.42 z-score decline in FEF_{75}, suggesting a loss of expiratory flows as a consequence of eosinophilic inflammation. In a study from Malmström et al. [29], lung function and endobronchial biopsy were obtained; the study failed to show relationship between lung function and histological findings, perhaps because of the small sample. In another, similar study [30] developed in 23 infants who had failed empiric antiasthma and/or antireflux therapy and underwent flexible bronchoscopy, the authors found that, compared to subjects without neutrophilic inflammation, subjects with neutrophilic inflammation had significantly higher