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CLINICAL SIGNIFICANCE OF PULMONARY FUNCTION TESTS

Alterations in Pulmonary Function Following Respiratory Viral Infection*

William J. Hall, M.D., and Caroline B. Hall, M.D.

Respiratory viral illness is a major cause of morbidity in both adults and children. This report focuses on both the acute and chronic effects on respiratory function of these ubiquitous infections. Infant airways are particularly vulnerable due to the relatively low conductance in immature peripheral airways. Bronchiolitis, caused predominantly by respiratory syncytial virus, is the most important of these viral illnesses and is emerging as a major risk factor for the subsequent development of obstructive airway disease in adults, possibly by interference with normal alveolar proliferation. The basic pathogenic mechanism involved in adult respiratory viral infection is bronchial hyperreactivity, presumably secondary to epithelial damage and resultant sensitization of rapidly adapting airway receptors. In addition, there may be virus-related alterations in the autonomic and humoral regulation of airway tone. Viral infections may alter the effects of common air pollutants on respiratory function.

Acute respiratory illness, the majority of which is caused by viruses, is responsible annually in the United States for approximately 40 percent of illness-associated time lost from work by adults and for 60 percent of time lost from school by children. Major research advances over the last two decades have resulted in more precise characterization of the specific respiratory viruses responsible for clinical syndromes, rapid clinically applicable methods of virus identification, and the development of immunoprophylaxis and chemotherapy for some diseases. A parallel interest in the pathogenetic mechanisms of these common infections has been more recent.

In this article, we selectively review recent data concerning the acute and chronic effects of viral respiratory infection on pulmonary function and the proposed mechanisms of these alterations. Since these illnesses spare no age group, respiratory viral illness of both adults and children are considered.

ALTERED PULMONARY FUNCTION ASSOCIATED WITH RESPIRATORY VIRAL INFECTION IN INFANTS AND YOUNG CHILDREN

Surprisingly, similar data emerging from studies in several countries suggest that lower respiratory illness in childhood may be a major risk factor for the development of obstructive airway syndromes of adult life. An abnormally high prevalence of respiratory symptoms and ventilatory impairment has been noted even in such groups as highland New Guineans and Micronesians not subject to the usual Western risk factors of smoking and industrial pollution. A high prevalence of acute childhood respiratory illness emerges as a common denominator.

Physiologic confirmation of these epidemiologic observations has been possible recently. In the extensive population studies of Lebowitz, Burrows, et al., encompassing over 2,500 subjects over the age of 20, an antecedent history of childhood respiratory illness was significantly associated with chronic ventilatory impairment. Moreover, they documented an excessive age-related decline in ventilatory function in subjects with this history. An accelerated decline in forced flow rates was apparent even in life-long nonsmokers and suggested that respiratory illness in early life is an important independent risk factor for the development of obstructive airways diseases.

Which and how many of the specific respiratory infections of childhood might predispose to adult airway obstruction is unclear. However, in infancy and early childhood, respiratory syncytial virus (RSV) is the most important respiratory pathogen. This is an ubiquitous agent, producing the most severe illnesses in the first few months of life, although repeated infections throughout life are common. The RSV is the major cause of bronchiolitis, the syndrome characterized clinically by the acute onset of tachypnea and wheezing, and pathologically, by inflammation of the small airways or bronchioles.
A number of studies have examined the relationship of bronchiolitis to the development of subsequent wheezing in childhood. These studies have shown a surprisingly high incidence of recurrent wheezing occurring in 25 percent to 50 percent of the patients who had acute bronchiolitis in infancy.\textsuperscript{14-18} Although these retrospective studies have indicated that such children generally had a high incidence of asthma in first degree relatives, more recent prospective studies have suggested that bronchiolitis may be an important risk factor for obstructive airway disease independent of an atopic or asthmatic diathesis. Kattan and co-workers\textsuperscript{17} recalled 23 children who had had clinical evidence of bronchiolitis before the age of 18 months and who had remained symptom free for ten years thereafter. Careful pulmonary function testing revealed that the majority of these children had abnormal PaOs, elevated volume of isoflow, and an elevated ratio of residual volume to total lung capacity. Sims and co-workers\textsuperscript{18} reported follow-up studies of ventilatory function on 35 eight-year-old children known to have RSV bronchiolitis in infancy. They found lower flow rates and greater exercise-induced bronchial lability in these children relative to matched controls. Furthermore, there was no substantial relationship of these ventilatory abnormalities to atopic history. It was concluded that the observed ventilatory impairment was independent of an allergic or asthmatic diathesis.

These observations have prompted more careful epidemiologic and pathophysiologic evaluations of specific respiratory viral infections in infancy and childhood.\textsuperscript{19} Particular attention has been focused on bronchiolitis caused by RSV.

Pathology specimens have demonstrated a remarkable pattern of respiratory bronchiolar epithelial destruction and intraluminal plugging, often with sparing of surrounding alveoli\textsuperscript{20} (Fig 1). The corresponding physiologic manifestations of this often life-threatening illness include marked elevations of pulmonary flow resistance,\textsuperscript{21} abnormally high thoracic gas volume,\textsuperscript{22} and marked hypoxemia.\textsuperscript{23} In one recent series of 32 infants hospitalized with proven RSV infection, marked hypoxemia was a consistent finding, often persisting for up to six weeks following hospital discharge.\textsuperscript{24}

Both the severity of the acute illness and the potential permanent effect on pulmonary function associated with RSV infection may relate to the singular vulnerability of the young lung. Studies of Hogg et al\textsuperscript{25} have demonstrated that peripheral airways are disproportionately narrow prior to age five, and thus, are especially subject to obstruction from any inflammation. In addition, primary infection with lower respiratory tract involvement from a number of the respiratory viruses, such as RSV and the parainfluenza viruses, is most likely to occur at this age. Hence, although these small airways have been labeled the “silent zone” in adults, in infancy, the converse is more appropriate.

As has been pointed out by Reid,\textsuperscript{26} the infant lung is not the adult in miniature. Extensive remodeling characterizes the growth and maturation of the lung. For example, at birth, the infant lung has about 20 million terminal alveolar sacs, and it is not until age eight that the 300 million mature alveoli characteristic of the adult lung are achieved. Infection of the airway during this vulnerable stage may impair normal anatomic development, and may explain some of the apparent long-term effects of these infections on pulmonary function.

\begin{figure}
\centering
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\caption{Cross-section through terminal bronchiole from an infant who died with culturally documented RSV bronchiolitis. There is abundant epithelial destruction and intraluminal plugging with relative sparing of surrounding alveoli.}
\end{figure}
EFFECT OF VIRAL INFECTION ON PULMONARY FUNCTION IN OLDER CHILDREN AND ADULTS

The role of viruses in causing exacerbations of wheezing in asthma has recently been well delineated. McIntosh demonstrated that 42 percent of all wheezing attacks in children hospitalized at the National Jewish Hospital in Denver were associated with an acute viral infection. Certain viruses seem to have a particular propensity to cause wheezing, RSV being most common, followed by the parainfluenza viruses and coronaviruses. Studies of exacerbations of asthma in adults suggests that approximately 20 percent of acute exacerbations of bronchospasm are associated with a definable viral agent, chiefly influenza and rhinovirus.

The relative importance of viral infection in exacerbations of bronchitis in patients with chronic obstructive lung disease is less clear. Smith et al recently reported an eight-year prospective study evaluating the effect of viral infections on symptoms and pulmonary mechanics in 84 patients with chronic obstructive lung disease. Overall, they were able to associate 20 percent of the exacerbations of chronic bronchitis with a virus, most commonly rhinovirus, followed by influenza. Most of these infections associated with viral infection produced an acute decline in FEV1 of 25 to 300 ml. In general, abnormalities were limited to a 90-day period following infection. Of perhaps even greater clinical significance has been the observation from the same long-term study that viral infections in patients with chronic obstructive lung disease are associated with increased rates of isolation of Streptococcus pneumoniae and Haemophilus influenzae, two of the most common bacterial organisms responsible for exacerbations of bronchitis.

Recent evidence suggests that even "uncomplicated" viral respiratory infection in adults, i.e., infection with clinical manifestations limited to the upper respiratory tract and normal chest roentgenograms, is commonly associated with prolonged physiologic abnormalities, suggestive of lower respiratory tract involvement.

The "common cold" may well be the most common of all mankind’s illnesses. Defined etiologic agents include rhinovirus, coronavirus, and parainfluenza virus, but in approximately 75 percent of the cases, no etiologic agent can be identified. In addition to the classic signs of coryza and pharyngitis, these illnesses are often associated with cough and decreased exercise tolerance more suggestive of lower respiratory tract involvement. A number of physiologic studies have demonstrated alterations in pulmonary function. Picken et al documented abnormal frequency dependent dynamic compliance suggestive of peripheral airway abnormalities following rhinovirus infections. In some instances, these abnormalities developed four to eight weeks after the acute onset of illness and did not return to normal for an additional six weeks. Cate et al demonstrated diminished steady state diffusing capacity measurements in subjects with rhinovirus infection, felt to be caused by transient bronchiolitis. Fridy and coworkers found abnormal closing volumes and diminished density dependent expiratory flow rates in smokers with predominantly rhinovirus disease studied prospectively. In a recent prospective study of young children 2.5 to 11 years of age, uncomplicated upper respiratory tract infections were uniformly associated with diminished forced expiratory flow rates. This study is of particular importance since other complicating risk factors such as smoking and long-term air pollution exposure would be obviated. A notable feature of virtually all these studies is the protracted duration of physiologic abnormalities, usually averaging from three to eight weeks.

More recent attention has focused on the pathophysiology of influenza virus infections. It has long
been appreciated that individuals with underlying chronic obstructive pulmonary disease are susceptible to serious, life-threatening pulmonary complications of influenza infection. Moreover, these cases represent only a small minority of the estimated 20 percent to 50 percent of the population at risk who are infected during a pandemic.

Previous studies have suggested that pulmonary function abnormalities frequently follow influenza infection, even in the absence of pneumonia. For several sequential years, we have studied airway mechanics in groups of otherwise healthy young adults with nonpneumonic naturally acquired influenza A (H3N2) infection.

In these studies, total pulmonary resistance was measured at 3, 5, 7, and 9 cycles per second by the oscillometric technique. This method permitted us to make repetitive measurements in subjects who had difficulty performing forced flow maneuvers because of upper respiratory symptoms. Figure 2 shows the typical findings in subjects with acute influenza A infection. During the initial three weeks following onset of symptoms, subjects demonstrated frequency dependence of total pulmonary resistance. This finding suggests the presence of uneven airway time constants, and we theorized that a generalized increase in flow resistance in peripheral airspaces could result in this degree of frequency dependence of resistance. As was noted with other viral infections, these mechanical abnormalities persisted beyond the period of symptomatic illness.

In a subsequent epidemic, we were able to further evaluate peripheral airway mechanics in uncomplicated influenza infection by demonstrating diminished density-dependent forced flow rates in volunteers with naturally acquired illness (Fig 3). Again, these abnormalities persisted for some three to five weeks following onset. Furthermore, when atopic subjects were compared to normals, no difference in density-dependent flow rates was observed, suggesting that these abnormalities were not related to pre-existing abnormal airway sensitivity.

Currently, there is much interest in the development of live vaccines against respiratory viruses, especially influenza. Since prolonged peripheral airway dysfunction is a common sequela to naturally acquired infection, evaluation of various candidate vaccines logically should include some physiologic testing. Several such studies have been done, and although results are somewhat variable, there is, at present, no evidence that live influenza virus vaccines have serious deleterious effect on lung function.

Pathophysiology of Virus-Lung Interaction

While these commonly observed abnormalities of
pulmonary function following viral infection could arise directly from viral replication and inflammation causing bronchiolar narrowing, several observations suggest that this is not the total explanation. First, the pulmonary function abnormalities are often most pronounced a week after onset of illness, when the clinical manifestations are improving. Secondly, the abnormalities are prolonged beyond the period of viral shedding. Full physiologic recovery generally occurs some three to five weeks following the onset of the illness. A continued "silent" replication of the virus in the lung for that period of time seems unlikely.

An alternative hypothesis has been advanced by the work of Empey et al. They demonstrated transient bronchial hyperreactivity to a histamine aerosol in presumed influenza A infection. In addition to observing marked enhancement in bronchial lability, they were able to demonstrate a lowered cough threshold to a citric acid aerosol during uncomplicated influenza A infection. Exaggerated responses to both histamine and citric acid were blocked by prior administration of an atropine aerosol suggesting the response was mediated via a vagal reflex. These authors postulated that epithelial damage associated with viral infections resulted in a sensitization of rapidly adapting airway epithelial receptors. These receptors are felt to be subepithelial in location and primarily distributed in larger airways. Extensive work in animals suggests that most, if not all, of the various stimuli known to cause bronchoconstriction and cough in human asthmatics do stimulate these receptors under experimental conditions, resulting in vagally mediated airway response (cough and bronchoconstriction). The most characteristic histologic hallmark of viral respiratory infection is some degree of bronchial epithelial destruction. Repair of this epithelial surface requires cellular regeneration. Walsh et al performed serial bronchial biopsies in patients with proven influenza A infection. Cellular repair took on the average of five weeks, which corresponds to the mean duration of hyperreactivity noted in these infections.

We have subsequently studied airway responses to cholinergic stimulation utilizing carbacholamine (Carbachol) aerosol challenge in subjects with culture proven influenza A infection. Transient bronchial hyperreactivity persisting for an average of three weeks following the onset of symptomatic illness was observed. Of interest is that no difference in the magnitude of hyperreactivity between atopic and nonatopic subjects was evident (Fig 4). It is likely that bronchial hyperreactivity is an extremely early phenomenon following influenza infection and largely independent of the magnitude of "inflammatory" manifestations of this illness. In one series of experiments, we administered the antiviral agent, amantadine, to a group of subjects with documented influenza A infection. In previous work, amantadine administration has been associated with accelerated improvement in symptoms in influenza A infection, presumably by inhibition of viral replication. In order to determine the effect of amantadine on physiologic abnormalities, we studied matched groups of young adults with naturally-acquired influenza A infection. Amantadine administration was associated with more rapid improvement in clinical scores compared to controls and an accelerated improvement in density-dependent flow rates, but had no effect on the rate of resolution of airway hyperreactivity to cholinergic aerosol inhalation. Amantadine administration, therefore, seemed to ameliorate the viral inflammatory response reflected in changes in density-dependent flow rates. However, the lack of effect on hyperreactivity would
suggest that the damage initiating this response occurred early before therapy or is unaffected by therapy.

Further evidence linking viral infection and bronchial reactivity may be drawn from several sources. Transient bronchial hyperreactivity has now also been observed in nonasthmatic, nonatopic individuals with respiratory illness caused by viruses other than influenza. Recently, we studied a naturally occurring outbreak of RSV infection in a group of young, nonatopic adults. The major abnormality noted in these subjects was enhanced bronchial reactivity to cholinergic stimulation (Fig 5). In some cases, hyperreactivity persisted for over eight weeks. This phenomenon was of particular interest, since of the respiratory viruses, RSV has been most associated with wheezing.

In addition to sensitization of local airway receptors, viral respiratory infection may alter the usual balance between the autonomic nervous system and humoral agents which together modulate airway muscular tone. Imbalance of the autonomic nervous system has been hypothesized as a mechanism of asthma characterized chiefly by a diminished beta-adrenergic response of bronchial smooth muscle. Recently Busse studied the effect of intercurrent viral infection on the beta-adrenergic sensitivity of asthmatic patients. He examined the granulocytic response to isoproterenol, which is known to inhibit release of lysosomal enzymes via the cyclic-adenosine monophosphate system. This isoproterenol inhibition was found to be diminished in asthmatic patients compared to normal subjects, and during intercurrent viral infection, the response was further diminished. They suggested that a similar change in beta-adrenergic tone of airways could partially explain the exaggerated bronchoconstrictor response observed during viral infections.

Infection may also play an important role in IgE-mediated histamine release. Ida and colleagues obtained leukocytes from patients with ragweed allergy, incubated them with respiratory viruses, and then challenged them with a ragweed antigen E. Leukocytes incubated with virus demonstrated a significant enhancement of histamine release. Moreover, interferon isolated from this cell system enhanced histamine release from fresh leukocyte cultures—a previously undescribed biologic role of interferon. These findings suggest that atopic patients would experience enhanced bronchial reactivity if specific antigen exposure occurred at the time of viral infection.

There is, therefore, growing evidence that a complex series of events surrounds host response to respiratory viral infection (Fig 6). In addition to the obvious inflammatory changes, viral infection may enhance the sensitivity of important airway reflexes. Furthermore, regulation of bronchial tone by the autonomic nervous system and locally mediated humoral bronchoactive agents, such as histamine, may be altered transiently following viral infection. In this setting, the characteristic prolonged alterations in pulmonary function observed following viral infection become more explicable.

These data indicating that viral infection is associated with hitherto unanticipated, sometimes protracted, alterations in pulmonary function raise many considerations. For example, interpretation of mild obstructive disease or airway reactivity should take into consideration the possibility of an antecedent upper respiratory tract infection. In addition, it is possible that seemingly unrelated airway irritants may be synergistic. For some years, epidemiologic studies have pointed out an association of acute respiratory infection and elevated levels of air pollution. Utell and co-workers have recently studied the effects on pulmonary function of short-term inhalation of particulate nitrates, a common air pollutant. They found no demonstrable effect either in

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**Figure 5. Effect of respiratory syncytial virus infection on change in total pulmonary resistance after carbacholamine aerosol (2 percent, 15 tidal breaths) in ten healthy subjects. Diagonal line is line of identity. Points above the line represent an increase in total pulmonary resistance after carbacholamine aerosol. Initial measurements at time of presentation represented by solid circles indicate bronchoconstriction following carbacholamine aerosol. Closed circles represent similar testing in same subjects 16 weeks later.**

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normal or asthmatic subjects after short-term inhalation. However, when subjects with uncomplicated influenza infection were exposed to an identical nitrate exposure, they uniformly demonstrated transient diminution in forced expiratory flow rates. If further studies confirm this observation, the effects of industrial and automotive emissions on lung function may have to be evaluated in the light of their potential synergism with viral infection. This may be of some import when one considers the frequency of colds and exposure to air pollution in our population.

Further work, especially in animal models, will be necessary to fully delineate the relationship of respiratory viral infection and the mechanical function of the lung. It is apparent, however, that viral respiratory illness may be an important risk factor in the pathogenesis of obstructive airway disease and in the interaction of the lung with an increasingly complex physical environment.

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