LUNG FUNCTION AND BRONCHIAL RESPONSIVENESS IN PRESCHOOL CHILDREN

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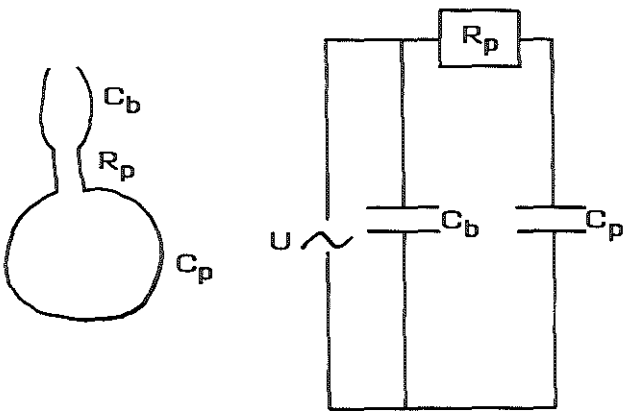
ERRATA

- page 15: line 6 from under: ...early life influences...
- page 24: paragraph 2; line 1: assumed
- page 25: figure 2.11



- page 30: table 2.2 upper part: NAME: EJD
- page 32: line 8: whole body plethysmography
- page 35: line 8: significantly
- page 45: paragraph 2; line 6: $H_2O.l^{-1}.s$
- page 63: figure 3.a (- - - = median value)
- page 102: last paragraph: ... 8 children who had a ND accident (32%) had a 1^{st} or 2^{nd} degree relative...
- page 112: line 2: Cdyn = $-1/2\pi fx_{rs}$
- page 122: paragraph 4: line 3: hoofdstuk 8.

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(Longfunctie en bronchiale prikkelbaarheid
bij peuters en kleuters)

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CONTENTS

(TABLE OF SYMBOLS, ABBREVIATIONS AND UNITS

I	=	current (A)
U	=	potential difference (Volt)
R	=	resistance (Ohm)
Z	=	impedance i.e. complex resistance of a.c. circuit
a.c.	=	alternating current
d.c.	=	direct current
I_t	=	current I at time t
I_o	=	maximum current
ω	=	$2\pi f$
f	=	frequency of a.c. (Herz; Hz; cycles s^{-1})
C	=	capacitance
U_C	=	potential difference over C
L	=	inductance
U_L	=	potential difference over L
reference vector	=	that quantity in an a.c. wiring that is equal for all the components in the circuit
X_C	=	capacitive reactance
X_L	=	inductive reactance
f_o	=	resonance frequency (Hz)
FOT	=	forced pseudo-random noise oscillation technique
γ^2	=	coherence function; all measurements with $\gamma^2 < 0.95$ are rejected because of inappropriate signal-noise ratio
V	=	flow ($l.s^{-1}$)
$\triangle P$	=	pressure change ($cm.H_2O$)
Z_{rs}	=	impedance of the respiratory system ($cm\ H_2O.l^{-1}.s$)
R_{rs}	=	resistance of the respiratory system measured by means of FOT ($cm\ H_2O.l^{-1}.s$)
$\overline{R_{rs}}$	=	mean value of R_{rs} measured at frequencies of 2-26 Hz ($cm.H_2O.l^{-1}.s$)
R_{rs6}	=	R_{rs} measured at 6 Hz oscillation frequency ($cm.H_2O.l^{-1}.s$)
dR_{rs}/df	=	measure of frequency dependence of R_{rs}
$\overline{dR_{rs}/df}$	=	frequency dependence of R_{rs} calculated over the complete frequency spectrum ($cm.H_2O.l^{-1}.s^2$)
X_{rs}	=	reactance of the respiratory system (i.e. inertial and elastic properties of the respiratory system) ($cm\ H_2O.l^{-1}.s$)
$\overline{X_{rs}}$	=	mean value of X_{rs} measured at frequencies of 2-26 Hz ($cm.H_2O.l^{-1}.s$)
R_{aw}	=	airway resistance measured by means of whole body plethysmography ($cm\ H_2O.l^{-1}.s$).
FEV_1	=	forced expiratory volume in 1 s. ($l.s^{-1}$)
$MEFV_{25}$	=	maximum expiratory flow at 25% FVC measured by maximum flow-volume registration ($l.s^{-1}$)

$PEFV_{25}$	=	maximum expiratory flow at 25% FVC measured by partial flow-volume registration ($l.s^{-1}$)
PD	=	provocative dose; dose of an agonist which causes a predetermined percentage change from mean baseline lung function
TD	=	threshold dose; dose of an agonist which causes a 2 SD change from mean baseline lung function

CHAPTER 1. INTRODUCTION

1. Introduction

In the Netherlands the term chronic obstructive lung disease (COLD) is used for a group of related conditons with a common constitutional basis and common clinical features such as bronchoconstriction, increased mucus secretion and airway inflammation (i.e. asthma, asthmatic bronchitis, chronic bronchitis and emphysema). Approximately 30% of Dutch men and women between the ages of 40 and 64 years have symptoms of COLD to a larger or smaller extent. 8% require regular treatment and 1 to 2% are disabled to a considerable degree (van der Lende, 1979).

Bronchial asthma refers to a condition characterized by recurrent reversible narrowing of the airway lumen in response to stimuli of a level or intensity not inducing such narrowing in most individuals. Clinically it is characterized by wheezing, laboured breathing, an irritative cough and the production of tenacious sputum. Asthmatic bronchitis is a condition of asthma combined with hypersecretion with wheezing and productive cough. In practice it is difficult to separate asthma and asthmatic bronchitis. In this thesis they will be taken together under the term "asthma".

The natural history of childhood asthma is not well defined. Many studies have been retrospective and rely on questionnaires about events in the past. Burrows et al. (1977) found that adults with symptoms of chronic bronchitis or who had impaired lung function had a history of significantly more childhood respiratory disease than subjects free of symptoms. However it is unlikely that the recall of childhood illness by adults is particularly reliable. Patients with current respiratory symptoms will probably recall past respiratory symptoms better than those free of current problems (Phelan, 1984).

A study by Rackemann and Edwards (1952) over a 20 years follow-up period in subjects with onset of asthma before age 13 showed that half of the patients became symptom-free and were leading normal lives while another 25% were free of symptoms if they avoided known adverse factors such as animals or dust. Nonatopic individuals were more likely to have a complete remission than were atopic subjects.

The importance of long-term follow-up was shown by Blair (1977) who showed that about half of his patients with childhood asthma were symptom-free by the end of a 20-24 years follow-up study. However it appeared in 27% of his patients that after as many as 3 years without symptoms a relapse occurred.

Martin et al. (1980) have shown that although the chance of "outgrowing" is better in the milder forms of asthma than in the severe cases, individual predictions cannot be made. Most subjects improved during adolescence and 55% of those in whom wheezing had started before 7 years of age and stopped before

adolescence remained symptom-free. However 45% of the subjects who had apparently ceased to wheeze at age 14 had minor recurrences before the age of 21. Less than 20% of those with persistent symptoms in childhood had become completely free of symptoms during adolescence.

These results indicate that studies that do not go beyond early adolescence will give a false impression of the natural history of childhood asthma. Some patients who appear to have "outgrown their childhood asthma" will have relapses as adults. They have only "outgrown their pediatrician" (Martin et al., 1980).

2. Mechanisms in asthma

Asthma is characterized by bronchial smooth muscle spasm, mucus plugging of the airways and airway inflammation. The regulation of bronchial smooth muscle tone is a complex process which is mediated by various receptors on the cell membrane. There is a balance between the bronchoconstrictive action of the parasympathetic system on the one hand and the bronchodilatatory action of the beta-adrenergic system on the other.

Although the results of studies on the effect of the adrenergic system on the resting bronchial smooth muscle tone differ, (Simonsson et al., 1967; Szentivanyi, 1968) most investigators assume that it is mainly dependent on the basal parasympathetic tone (Nadel, 1973; Widdicombe, 1977). Stimulation of the cholinergic (muscarine) receptors of the muscle cell by acetylcholine will lead to an influx of calcium ions, release of intracellular calcium ions and stimulation of contractile proteins (Barnes and Cuss, 1985).
This results in an increase in bronchial smooth muscle tone (Schulz, 1977).

Stimulation of alpha-adrenergic receptors by catecholamines has the same effect as stimulation of cholinergic receptors. Alpha-adrenergic hyperresponsiveness of vascular and pupillary responses was found in asthma (Henderson et al., 1979). The role of alpha-receptors in asthma is not established (Paterson et al., 1979) although recent findings indicate that stimulation of alpha receptors on parasympathetic ganglia or nerve endings may relase acetylcholine and thus result in contractile responses (Black, 1985). The role of the non-adrenergic bronchodilatatory system found in animals (Richardson, 1977) is not established in humans as well. The mechanisms involved in the regulation of bronchial patency consist of stimulation of afferent vagal nerve endings in the bronchial mucosa which are called irritant receptors, direct stimulation of various smooth muscle receptors, mucus secretion, mediators derived from mast cells and inflammatory cells and inflammation of the bronchial wall (Kerrebijn, 1984). Irritant receptors (Hogg, 1982) are sensitive to inhaled substances such as pollutants (SO_2, NO_x, ozone), smoke and dust, as well as to cold air, infections, mucosal oedema and histamine (Boushey et al., 1980). They send their signals through afferent nerves to the central nervous system, from where they are transmitted through efferent fibres to the parasympathetic ganglia in the bronchial wall and through postganglionic fibres to smooth muscle cells and mucosal glands, causing bronchoconstriction and mucus secretion.

Mast cells and leukocytes (Newball and Lichtenstein, 1981) have the ability to generate mediators which are involved in the acute and late allergic reaction, in the subacute and chronic stages of the inflammatory process and possibly in the acute reaction after exercise and hyperventilation with cold dry air.

Most mast cells are predominantly found in the submucosa, but they are also present in the bronchial lumen. Their number increases towards the peripheral airways. The most widely studied mediator is histamine. Histamine stimulates irritant receptors and probably also directly triggers H_1 receptors on smooth muscle cell membranes, especially in the peripheral airways and, when it is produced in excessive amounts, in the central airways.

Other mediators involved in the mechanism of bronchoconstriction are leukotriens, prostaglandines, tromboxane, bradykinin and possibly platelet activating factor. Their precise site and mode of action are as yet unclear.

The quantity of mediators released is closely correlated to the number of mast cells and hence maximal in the peripheral airways (Gold et al., 1973).

The inflammatory reaction is associated with mucosal oedema, an increased mucosal permeability and tissue damage due to products from eosinophils (Dahl and Venge, 1982), polymorphonuclear leukocytes and macrophages. This makes the irritant receptors more readily accessible to environmental stimuli and increases the amount of mediators released. This enlarges the sensitivity of the airways to irritants from the inhaled air, viral infections and osmotic changes of the bronchial mucosa. This increased sensitivity to irritants is called bronchial hyperresponsiveness (Boushey et al., 1980).

3. Bronchial responsiveness (BR)

Increased BR is generally regarded as a genetically determined characteristic of asthma which can be influenced by various environmental factors (Boushey et al., 1980; Neijens, 1981).

It has been suggested that an intrinsic dysregulation of cellular responses contributes to increased BR in asthma. Enhanced releasibility of mediators and oxygen radicals, both spontaneously and after stimulation, was found in vitro in mast cells (Schulman, 1983) and in leukocytes of asthmatic patients (Neijens et al., 1984).

An increased responsiveness of bronchial smooth muscle cells after receptor stimulation might play a role in bronchial hyperresponsiveness. Although an increase in in-vitro airway responsiveness to a variety of stimuli has been demonstrated in several animal models of asthma (Anthonissen et al., 1979; Anthonissen et al., 1980; Souhrada and Souhrada, 1982; Morcillo et al., 1984; McKay and Brooks, 1984) there is no conclusive evidence that exaggerated responses of airway smooth muscle cells are present in human asthma. Several authors did not find a relationship between in-vivo and in-vitro bronchial responsiveness (Vincenc et al., 1983; Armour et al., 1984a; Armour et al., 1984b; Roberts et al., 1984). However, others found a markedly increased in-vitro contractility of

bronchial smooth muscle in relation to asthma or chronic bronchitis (Simonsson et al., 1973; Schellenberg and Foster, 1984; de Jongste et al., 1985).

Increased BR can be produced experimentally by neutrophil influx into the airway mucosa (Fabbri et al., 1984; O'Byrne et al., 1984). Especially late type asthmatic reactions induce increased BR (Murphy et al., 1985).

Increased BR may last for several weeks after airway inflammation due to allergens (Cartier et al., 1980), viral infections (Empey et al., 1976; de Jongste et al., 1984) or chemical irritants (i.e. NO_x, ozone, SO_2) (Orehek et al., 1976; Golden et al., 1978; Holtzman et al., 1979; Sheppard et al., 1980). During that time the subject is more sensitive to allergic and environmental provocations than in periods of low BR.

The so-called circadian rhythm influences BR. BR is highest around 4.00 a.m. and lowest about 4.00 p.m. (de Vries et al., 1962).

In the laboratory BR is usually determined by measurement of the bronchoconstrictive response to inhaled substances such as histamine, methacholine and fog or to exercise or hyperventilation with cold dry air (McFadden and Ingram, 1979; Boushey et al., 1980; Chatham et al., 1982; Neijens et al., 1982; Eiser et al., 1983; Anderson et al., 1984).

Clinically increased BR can be recognized as episodes of cough, dyspnoea, or wheezing after exposure to inhaled dust, vapours, cold air, or exercise. Nocturnal respiratory symptoms seem to be related to the circadian rhythm. Several investigators showed that the degree of BR relates to the overall severity of asthma (Makino, 1966; Townley et al., 1975; Cockcroft et al., 1977; Juniper et al., 1978).

Airway reactions to inhaled allergens in atopic patients are not only dependent on the degree of sensitization but also on the level of BR (Neijens et al., 1979; Neijens and Kerrebijn, 1983).

Increased BR may be a risk factor for the development of progressive lung disease. Barter and Campbell (1976) showed that adults with increased BR had a more rapid deterioration in lung function than in those with normal reactivity. Britt et al. (1980) found that the sons of subjects with chronic obstructive lung disease who themselves had hyperresponsive bronchi, showed a more rapid deterioration in lung function than those sons without increased BR.

4. Aims of the study

It is hypothesized that childhood asthma, especially when not well controlled, may constitute a risk factor for the development of COLD in adulthood (Cropp, 1985). It is unknown whether lung injury during early life is a risk factor for the development of COLD in adulthood. Asthma often starts before school-age (Cropp, 1985). Except for the disturbing symptoms, a reason for paying

attention to asthma in preschool children is the hypothesis that adequate intervention may reduce the risk of COLD in adult life (Kerrebijn, 1982). To detect lung function abnormalities at as young as possible ages suitable methods should be available. Most lung function methods can only be performed in children over 6 years of age.

Lung function was measured with the forced pseudo-random noise oscillation technique (FOT) (Lándsér et al., 1976a) because only passive cooperation is needed. Resistance (R_{rs}) and reactance (X_{rs}) of the respiratory system are simultaneously measured over a frequency spectrum of 2 to 26 Hz. R_{rs} is mainly determined by the patency of the upper and large airways. X_{rs} is influenced by mass-inertial and elastic properties of the respiratory system.

The applicability of FOT in preschool children was investigated. The method is now suitable for use in clinical practice to measure lung function and BR in children from about 2½ years of age.

We measured airway patency, bronchial smooth muscle tone and BR in preschool asthmatic children. Secondly, we investigated whether lung injury during early influences the development of lung function and bronchial responsiveness in children who do not have a genetic predisposition of asthma.

This was investigated in children who had infant bronchiolitis, in subjects who survived infant bronchopulmonary dysplasia after neonatal respiratory distress syndrome and in individuals who experienced a near-drowning accident. The results are compared to data found in healthy controls.

Table 2.1. Analogy between physiological and electrical variables used to explain forced oscillometry.

physiological variables	electrical variables
$\triangle P$; Pressure difference ($cm.H_2O$)	U; potential difference (V)
$\dot{V}$; flow ($l.s^{-1}$)	I ; current (A)
Z_{rs} ; impedance of respiratory system ($cm.H_2O.l^{-1}.s$) ($= R_{rs} + iX_{rs}$)	Z; impedance (i.e. a complex resistance) of a.c. circuit (Ohm)
X_{rs} ; reactance of respiratory system ($cm\ H_2O.l^{-1}.s$)	X; reactance of a.c. circuit (Ohm)
elastic properties	X_C capacitive reactance $\frac{1}{\omega C}$ (Ohm)
mass-inertial properties	X_L inductive reactance ωL (Ohm)
R_{rs} ; resistance of respiratory system ($cm\ H_2O.l^{-1}.s$)	R; real resistance (Ohm)

Two types of currents are known in electricity:
a direct current (d.c.) and a sinusoidal alternating current (a.c.). In a d.c. the drift velocity superimposed on the random motion of the charge carriers (e.g. electrons) is in one direction only. In an a.c. the direction of the drift velocity reverses, usually many times a second. So an a.c. varies mostly periodically with time in magnitude and direction. One complete alternation is called a cycle and the number of cycles per second is the frequency (f). The unit of frequency is the hertz (Hz).

For a sinusoidal waveform (figure 2.1) we may write $I_t = I_o \sin\omega t$, where I_t is the current at time t, I_o is the maximum current and ω is a constant which equals $2\pi f$, where f is the frequency of the a.c.

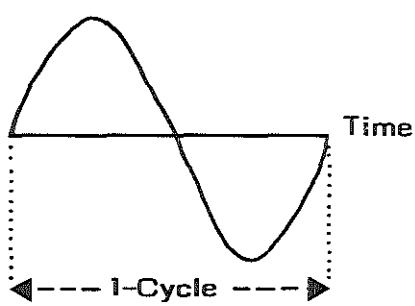


Figure 2.1

In a real resistance signals of I and U are in phase and in a simple a.c. circuit according to Ohm's Law, the resistance is defined as

$$R = \frac{U}{I}$$

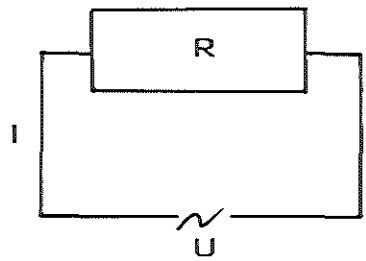


Figure 2.2

In a compex a.c. circuit the total impedance is defined as

$$Z = \frac{U}{I}$$

Hence when applied to the respiratory system the impedance (Z_{rs}) can be calculated from $\triangle$ P and $\dot{V}$:

$$Z_{rs} = \frac{\triangle P}{\dot{V}}$$

$\triangle P$ and $\dot{V}$ can be measured at the mouth (see figure 2.12; page 27).

However, this model is only valid if the total respiratory system can be considered as a simple electrical circuit (figure 2.2) with only one real resistance.

If there is a potential difference (U) over a capacitance (C) U_C is 90° out of phase with I. The vector diagram for a pure capacitance in an a.c. circuit is shown in figure 2.3; the current I leads the applied potential difference U by 90°.

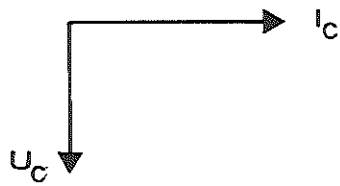


Figure 2.3

The vector diagram for an inductance is given in figure 2.4; in this case the current I lags the applied potential difference by 90°.

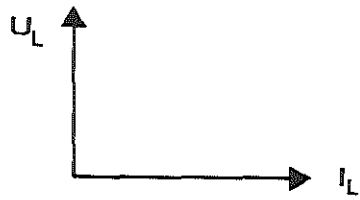


Figure 2.4

It is obvious that the respiratory system is far more complicated than a simple wiring circuit with only one real resistance, which can be represented by Ohm's law. For the description of a more complicated model we consider a series circuit with resistance R, capacitance C and inductance L.

a. Resistance and capacitance

Suppose an alternating potential difference U is applied across a resistance R and a capacitance C in series (figure 2.5a).

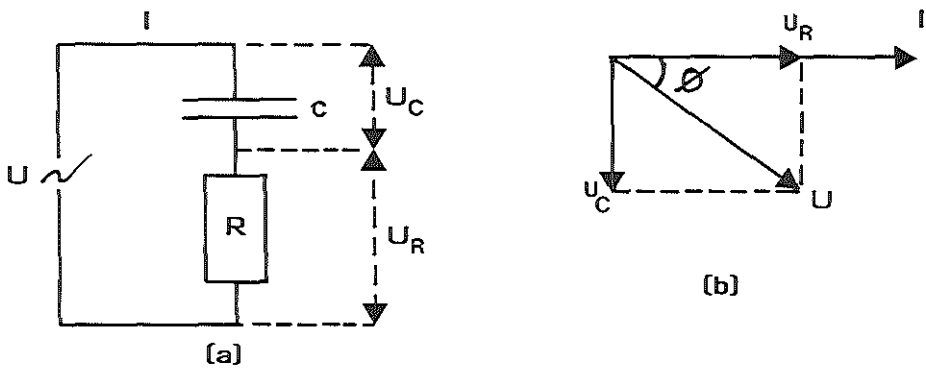


Figure 2.5

The same current I flows through each component and so the reference vector will be that representing I. Drawing the vector diagram (figure 2.5b) I is drawn first. U_R across R is in phase with I and U_C across C, lags I by 90°. The vector sum of U_R and U_C equals the applied potential difference U, hence

$$U^2 = U_R^2 + U_C^2$$

But $U_R = I\,R$ and $U_C = I\,X_C$, where X_C is the reactance of C and equals

$$\frac{I}{\omega C} \quad (\omega = 2\pi f)$$

Hence $U^2 = I^2.(R^2 + X_C^2)$

So $U = I\sqrt{R^2 + X_C^2}$

The quantity $\sqrt{R^2 + X_C^2}$ is called the impedance Z of the circuit. It has a resistive and a capacitive component (R and X_C respectively):

$$|Z| = \left|\frac{U}{I}\right| = \sqrt{R^2 + X_C^2}$$

In the forced oscillation model the impedance of the respiratory system

$Z_{rs} = \frac{\Delta P}{\dot{V}}$ (see table 2.1; figure 2.1)

Also, from the vector diagram we see that the current I leads U by a phase angle Ø which is less than 90° and is given by

$$\tan Ø = \frac{U_C}{U_R} = \frac{IX_C}{IR} = \frac{X_C}{R}$$

b. Resistance and inductance (L)

In this case U_L across L leads on the current I and the potential difference U_R across R is again in phase with I (figure 2.6a).

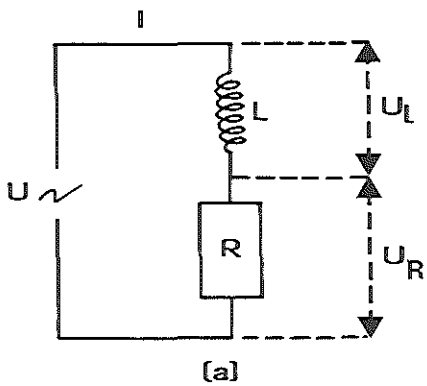


Figure 2.6a

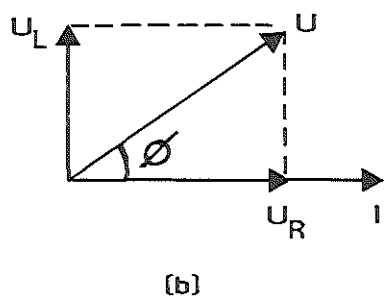


Figure 2.6b

The applied potential difference U equals the vector sum of U_L and U_R (figure 2.6b) and so

$U^2 = U_R^2 + U_L^2$

$U_R = IR$ and $U_L = IX_L$, where X_L is the reactance of L and equals ωL.

Hence $U^2 = I^2.(R^2 + X_L^2)$

So $U = I\sqrt{R^2 + X_L^2}$

Here the impedance Z is given by:

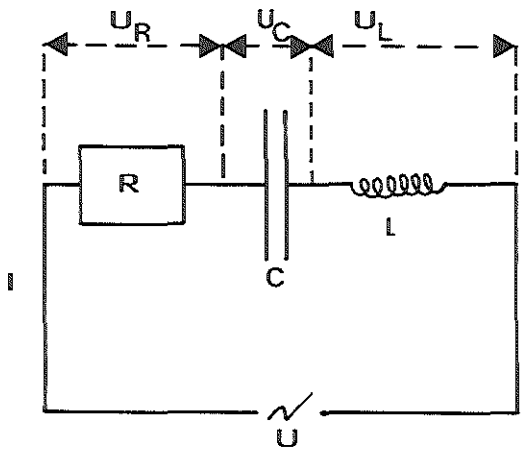
$$|Z| = \left|\frac{U}{I}\right| = \sqrt{R^2 + X_L^2}$$

The phase angle Ø by which I lays on U is given by:

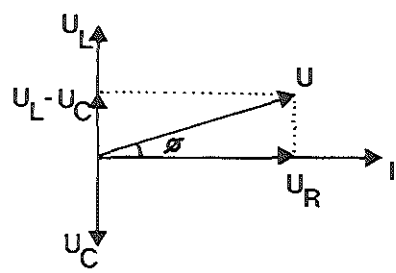
$$\tan Ø = \frac{U_L}{U_R} = \frac{IX_L}{IR} = \frac{X_L}{R}$$

c. Resistance, capacitance and inductance

An R-C-L circuit is shown in figure 2.7a



(a)



(b)

Figure 2.7a

Figuur 2.7b

U_R is in phase with I, U_L leads I by 90° and U_C lags it by 90°. U_L and U_C are 180° out of phase. The vector sum of $(U_L - U_C)$ and U_R equals the applied potential difference U (figure 2.7b).

Therefore, $U^2 = U_R^2 + (U_L - U_C)^2$

But $U_R = IR$, $U_L = IX_L$ and $U_C = IX_C$,

hence $U^2 = I^2.(R^2 + (X_L - X_C)^2)$,

so $U = I\sqrt{R^2 + (X_L - X_C)^2}$.

The impedance Z is given by

$$|Z| = \left|\frac{U}{I}\right| = \sqrt{R^2 + (X_L - X_C)^2}$$

The phase angle Ø by which I lags U is given by:

$$\tan Ø = \frac{U_L - U_C}{U_R} = \frac{X_L - X_C}{R}$$

Impedance Z of the a.c. wiring consists of a real resistance R, a resistance of the capacitance X_C and one of the inductance X_L. X_C and X_L are opposite in direction. If the absolute values of X_L and X_C are identical the signals cancel each other. This is called electrical resonance.

d. Electrical resonance

As $X_L = 2\pi fL$ and $X_C = \frac{1}{2\pi fC}$ the summed impedance Z of R, X_L and X_C varies with the frequency f of the applied potential difference of the a.c. $|X_L|$ increases with f, $|X_C|$ decreases with f. R is assumed to be independent of f (figure 2.8).

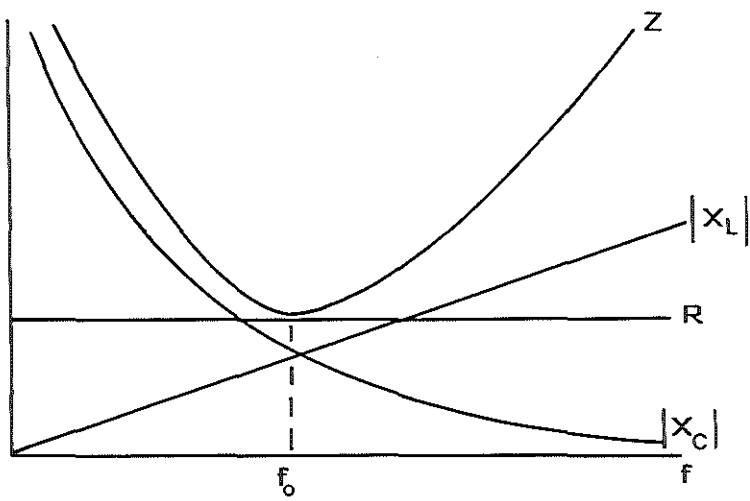


Figure 2.8

At a certain frequency f_o, called the resonance frequency, X_L and X_C are equal but opposite in direction, Z has its minimum value and is equal to R. The circuit behaves as a pure resistance and the current I has its maximum value ($I = \frac{U}{R}$) (figure 2.9).

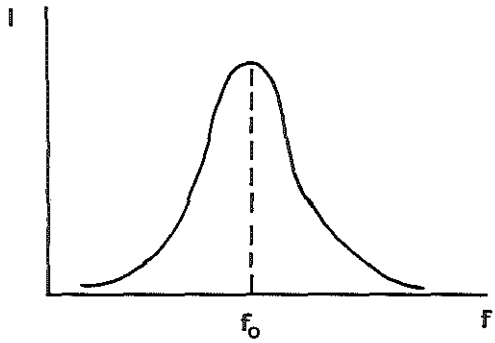


Figure 2.9

The impedance of the respiratory system (Z_{rs}) (in the electrical model the impedance Z) is the resultant of the resistance R_{rs} (in electrical model the real resistance R) and the reactance X_{rs}. The reactance X_{rs} is mainly determined by elastic (capacitance X_C) properties of lung tissue and thorax and by inertial (inductance X_L) properties of air within the airways. X_{rs} can alternatively be expressed as a "dynamic compliance" (Cdyn) by the transformation
$Cdyn = -1/(2 \pi f X_{rs})$ (Lándsér et al., 1979).

It is generally asumed that the application of electrical analysis to the respiratory system is justified (Grimby et al. 1968; Franetzki et al. 1979; Korn et al. 1979; Holle et al. 1979; Holle et al. 1981). However, considering the lungs to be a system which is characterized by a simple serial circuit is far too simple.

Otis et al. (1956) considered the lung as a system consisting of an indefinite number of parallel units subjected to the same driving pressure (pleural pressure), and analyzed its behaviour on the basis of a simple model with two parallel units, each unit consisting of a flow-resistive element and a volume-elastic element in series (figure 2.10); the mechanical characteristics of this model, when subjected to a sinusoidally varying pressure wave, can be defined using equations developed to describe the behaviour of analogous electrical circuits (see table 2.1). On the basis of these equations, it can be shown that the behaviour of the model as a function of frequency is determined by the time constants of the two parallel units (time constant = compliance x resistance).

If the time constants of the parallel units are equal, the compliance and resistance of the model do not vary with the frequency; if the time constants of the separate units are unequal compliance and resistance decrease with increasing frequency. According to the theoretical analysis of Otis et al., the time constants of the parallel lung units represent an important determinant of the intrapulmonary distribution of ventilation. However, the frequency dependence of compliance and resistance will also appear without time-constant inequalities between parallel parenchymal lung units.

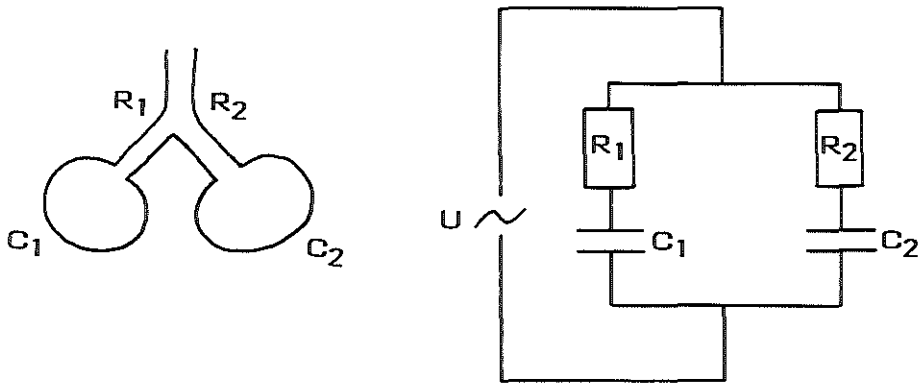


Figure 2.10. Two-compartment lung model of Otis et al. (1956) and electrical analogue of the model: R_1 and R_2, C_1 and C_2 = resistances and compliances of the two parallel units. The resistance of the common pathway is assumed to be zero.

Mead (1969) has analyzed the contribution of compliance of airways to the frequency-dependent behaviour of the lung (figure 2.11).

In this analysis the role of an increased resistance of the peripheral airways as a major determinant of the frequency dependence of compliance and resistance was studied. Mead stated that airways are more than simply conduits; they are also compliant structures. As conduits, they are mechanically in series with the airspaces which they supply. As expanding structures they are mechanically in parallel with the airspaces; their expansion makes a separate contribution to the total expansion of the lungs. Under static conditions this contribution to overall expansion is small. But under dynamic conditions this contribution can become appreciable. This is the case when airspace filling is slowed by increases in airway resistance.

If this increase is in the peripheral airways a marked discrepancy can develop between the speed of filling of the airways and airspaces. The contribution of

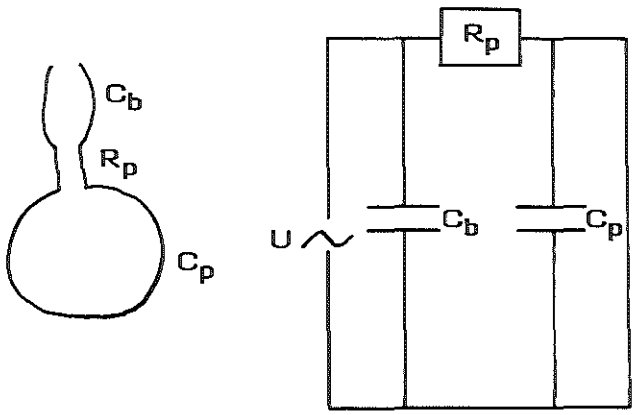


Figure 2.11. Lung model of Mead (1969) and electrical analogue; C_b = distensible airway compartment ($R_b = 0$); C_p = airspace compartment; R_p = resistance of the airspace compartment (peripheral resistance).

airspace expansion to total lung expansion will decrease during rapid, shallow breathing. In other words there is frequency dependence of the resistance and compliance. As compliance and X_{rs} are inversely related a decrease in compliance corresponds to an increase in X_{rs}.

Modifications of the model of Mead and the model of Otis were made and mathemetical analysis was performed by others. Cutillo and Renzetti (1983) gave an extensive review of the several models representing the respiratory system.

Inertial properties of the lungs were not taken into account in both the analysis of Otis as well as that of Mead. At low frequencies inertial properties have only minimal influence on total respiratory impedance (see also electrical model figure 2.8). At higher frequencies (9 Hz or more) explored by the forced oscillation technique, inertial forces on the mechanical behaviour of the respiratory system are far more important.

The frequency dependence of resistance and compliance during bronchial obstruction is a sensitive parameter of bronchial obstruction, especially of peripheral airways disease (Otis et al., 1956; Albright and Bondurant, 1965; Mead, 1969; Woolcock et al., 1969; Cutillo and Renzetti, 1983).

Kjeldgaard et al. (1976) investigated frequency dependence of lung compliance and resistance of the respiratory system (R_{rs}) by means of forced oscillations at 3 and 9 Hz. They found a close correlation between frequency dependence of lung compliance and R_{rs} during bronchial obstruction. As the frequency dependence (dR_{rs}/df) is a sensitive parameter in early detection of uneveness of ventilation multiple frequency oscillation methods must be considered superior to single frequency equipments in detecting this phenomenon.

3. Historical review of forced oscillometry

DuBois et al. (1956) introduced the forced oscillation technique. Measurements were performed during breath-holding, at one oscillation frequency only.

Ferris et al. (1964) started measurements during spontaneous breathing. Originally, these were made at relatively high oscillation frequencies compared to natural breathing to separate superimposed and breathing signals.

The method of Grimby et al. (1968) is still the basis of the present techniques. The method is based on the following measuring device as shown in figure 2.12.

The flow produced by a generator which develops the oscillating pressure can be separated from the flow produced by the respiratory system during breathing, because of the differences in frequency of the imposed flow oscillation (3 Hz) and the respiratory flows (0,2- 0,4 Hz). Flow and pressure changes are measured simultaneously at the mouth. From these signals the impedance of the respiratory system can be calculated.

The method of Goldman et al. (1970), which is based on the technique of Grimby et al. (1968), is commercially applied in the Astrograph^{R}. Cogswell et al. (1973, 1975) and Lenney and Milner (1978a, 1978b, 1978c) perform their

measurement at a frequency of 6 Hz. In the Siemens Siregnost FD 5 a fixed frequency of 10 Hz is applied (Förster et al., 1978; Franetzki et al., 1979; Korn et al., 1979; Holle et al., 1979; Holle et al., 1981). However, with a single fre-

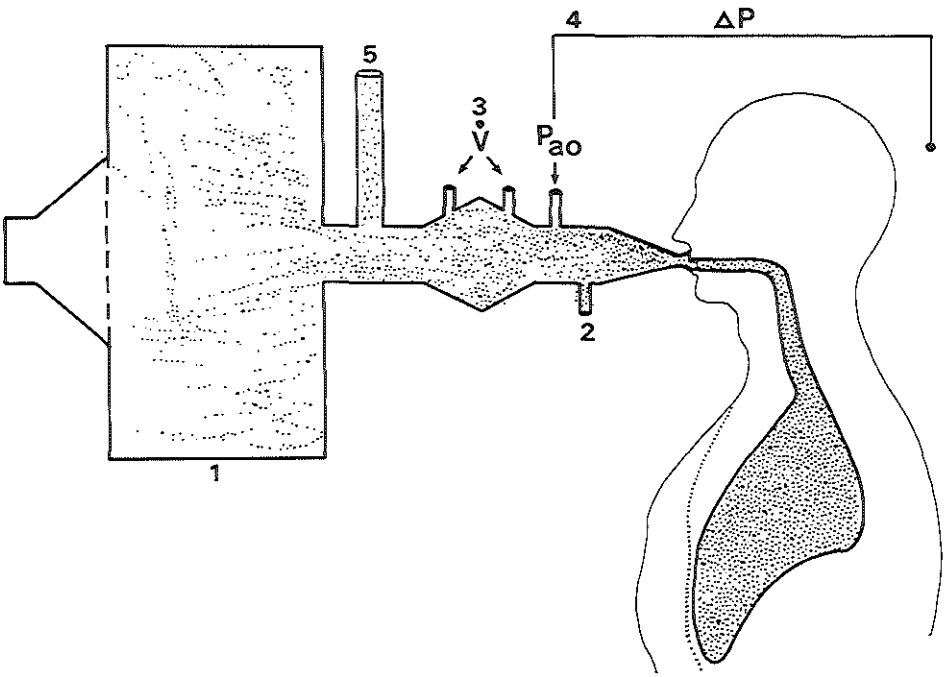


Figure 2.12. Forced oscillation technique according to Grimby et al. (1968).

1. Signal generator and loudspeaker
2. Bias flow; constant flow (0.3 $l.s^{-1}$) produced by a pump, reducing the dead space effect of the device
3. Pneumotachograph measuring mouth flow (V)
4. Pressure measurement to detect pressure changes at the mouth (P_{ao})
5. Side tubing, permitting the subject to breath outside air

quency it is not possible to measure the frequency dependence of resistance which is a sensitive indicator of bronchial obstruction. To detect frequency dependence it is necessary to perform measurements at more than one oscillation frequency.

The use of effective filtering procedures is necessary to improve the unfavourable signal to noise ratio at the lower oscillation frequencies.

Although frequency dependence of R_{rs} can be determined with the single frequency method of Aronsson and co-workers (Aronsson et al., 1977; Solymár, 1982), measurements at the three frequencies (i.e. 2, 4 and 12 Hz) cannot be performed simultaneously but only at intervals of minutes.

Michaelson et al. (1975) introduced the random noise oscillation technique. The magnitude (Z_{rs}) and frequency dependence of the impedance of the respiratory system (Z_{rs}) at frequencies from 3 to 45 Hz are obtained by a modification,

in which a random noise pressure wave is imposed on the respiratory system at the mouth and compared to the induced flow using a Fourier analysis (Zoledziowski and Cropp, 1979). Williams et al. (1979) introduced the random noise technique in children aged 3-5 years. The random noise technique has a great disadvantage. If all frequencies (3-45 Hz) start and stop at the same moment, the amplitude at the beginning and end of the measurement is positive respectively negative while the amplitudes in the middle parts are so small that they can easily be disturbed by the noise due to spontaneous breathing (figure 2.13). This is caused by the fact that the amplitudes of the different frequencies may be abolished in the middle part because the frequencies are out of phase with each other.

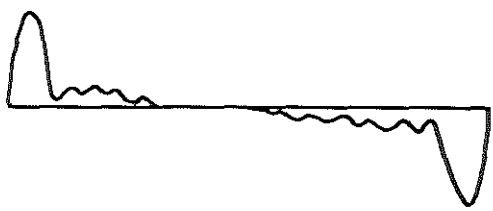


Figure 2.13

These differences in signal to noise ratio at various moments during the measurements make calculation of R_{rs} and frequency dependence complicated.

The method of Lándsér et al. is called a pseudo-random noise technique (Lándsér et al., 1976a; Lándsér et al., 1979; Holle et al., 1981; Lándsér et al., 1982; Clément et al., 1983; Duiverman et al., 1985a). Multiple known frequencies are applied and each frequency is started at a different randomly selected moment (see figure 2.14). This abolishes the disadvantage of the technique according to Michaelson because of a more favourable signal noise ratio at various moments during the measurement.

Figure 2.14

The term pseudo-random noise has been chosen because the composition of the signal is not random, but the succession of appearances of the frequencies is random though repeated every 2 seconds. Analysis of the pseudo-random noise signal is performed by fast Fourier transformation (Hewlett-Packard Fourier Analyzer System) yielding a resistance and reactance value for each of the harmonics of 2 Hz up to 26 Hz (i.e. 2,4,6,8,10,12,14,16,18,20,22,24,26 Hz).

4. Forced pseudo-random noise oscillation technique

With the forced oscillation technique according to Lándsér both resistance and reactance values are measured over a frequency spectrum of 2-26 Hz. R_{rs} values are mainly determined by the patency of the central airways. As R_{rs} values are simultaneously measured over a frequency spectrum of 2-26 Hz the so-called frequency dependence of R_{rs} ($\overline{dR_{rs}/df}$), can be calculated as well. It is defined as the slope of R_{rs} vs. frequency curve calculated over the complete frequency spectrum. $\overline{dR_{rs}/df}$ is defined as the mean slope of the curve. $\overline{dR_{rs}/df}$ is a a measure of unevenness of ventilation. X_{rs} values are mainly determined by the elastic properties of lung tissue and chest wall and by the inertance of air within the central airways.

As can be seen in the electrical model the influence of X_C dominates over X_L at frequencies below f_o (figure 2.8, 2.9). In the respiratory system reactance (X_{rs}) will be negative at frequencies below f_o. At frequencies above f_o the influence of X_I dominates over X_c; hence X_{rs} will be positive. As a consequence of bronchial obstruction X_{rs} values will decrease.

During measurements the child is seated behind the apparatus with a mouthpiece in the mouth. The nose is clipped and mouth and cheeks are fixed to eliminate shunting of airflow to the upper airways. One measurement series takes 16 seconds. A pseudo-random noise signal (2-26 Hz) is superimposed on the spontaneous quiet breathing. All measurements are performed in triplicate and the values averaged afterwards.

Figure 2.15 shows R_{rs} and X_{rs} vs. f curves in a 9 years old girl before and after methacholine-induced bronchoconstriction (see chapter 5). Before challenge there was no frequency dependence of the resistance. After challenge R_{rs} values were increased and frequency dependent. X_{rs} values were more negative. The resonance frequency (f_o) increased.

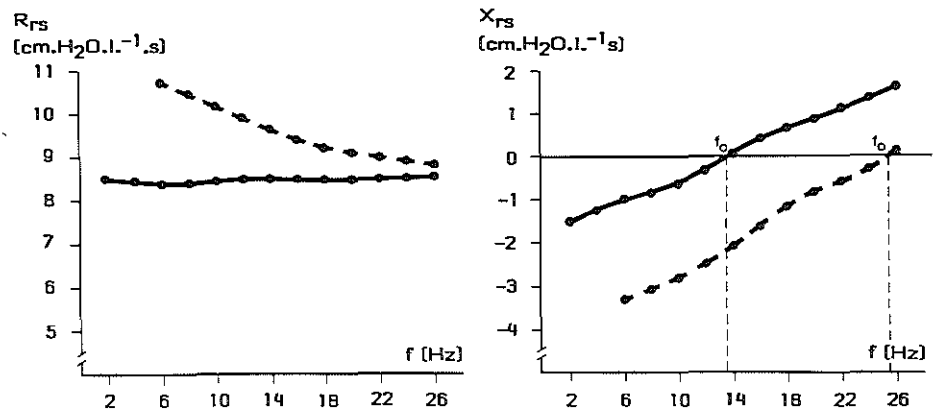


Figure 2.15. Example plots of R_{rs} and X_{rs} vs. frequency (f) before (—) and during (---) methacholine-induced bronchoconstriction (f_o = resonance frequency).

Table 2.2. Print-out of measurements with the FOT according to Lándsér before and during methacholine challenge; (FR. = frequency; RES. = R_{rs}; REACT. = X_{rs}; COH. = coherence function γ^2; RS. FR. = resonance frequency; RE.(06) = R_{rs6}; AVR. RE. = $\overline{R_{rs}}$; 1000*R1 = $d\overline{R_{rs}}/df$; AVR. RA. = $\overline{X_{rs}}$).

RESULT OF 3 MEASUREMENTS

NAME: BASELINE DATE OF BIRTH: 030951 HEIGHT: 1.82 WEIGHT: 71 SEX: M
AGE: 32 DATE OF EXAMINATION: 180684

FR.	RES.	REACT.	COH.	RE+	1	2	3	4	5	6	7	8
HZ.	(CM.H2O/l/S)			RA*–4	–3	–2	–1	0	1	2	3	4
02	2.79	–1.23	.98				*+					
04	2.84	– .74	2.96				+*					
06	2.89	– .30	2.99				+ *					
08	2.92	.10	2.98				+ *					
10	2.95	.46	3.00				+ *					
12	2.97	.77	2.97				+ *					
14	2.97	1.04	2.99				+ *					
16	2.97	1.27	2.99				+ *					
18	2.96	1.45	3.00				+ *					
20	2.94	1.59	2.98				+ *					
22	2.91	1.68	2.99				+ *					
24	2.87	1.74	2.99				+ *					
26	2.82	1.75	2.98				+ *					

	RS.FR.	RE.(06)	AVR.RE	1000*R1	AVR.RA
MEAS.	6.681	2.89	2.941	.030	–.837
PRED.	8.409	2.24	2.236	3.517	.505

RESULT OF 3 MEASUREMENTS

NAME: EJD 128 METHA DATE OF BIRTH: 030951 HEIGHT: 1.82 WEIGHT: 71 SEX: M
AGE: 32 DATE OF EXAMINATION: 180684

FR.	RES.	REACT.	COH.	RE+	1	2	3	4	5	6	7	8
HZ.	(CM.H2O/l/S)			RA*–4	–3	–2	–1	0	1	2	3	4
02	8.77	–2.17	0.00 C									
04	7.86	–2.26	.96			*						+
06	7.04	–2.31	.98			*					+	
08	6.29	–2.30	2.92			*				+		
10	5.63	–2.26	2.95			*			+			
12	5.05	–2.16	2.95			*			+			
14	4.56	–2.02	2.94			*		+				
16	4.15	–1.82	2.98			*		+				
18	3.82	–1.59	2.97			*	+					
20	3.57	–1.30	2.98				* +					
22	3.41	– .97	2.98				*+					
24	3.33	– .59	2.99				+*					
26	3.33	– .17	2.99				+ *					

	RS.FR.	RE.(06)	AVR.RE	1000*R1	AVR.RA
MEAS.	26.564	7.04	4.982	–224.107	–1.778
PRED.	8.409	2.24	2.236	3.517	.505

Table 2.2 shows the print-out of measurements with the Lándsér device before and after methacholine challenge (128×10^{-5} g) applicated in a healthy adult. The figures shown are the regression functions of the mean values of 3 measurements. Coherence function values are higher than 1.00 because they represent the sum of the coherence factors of the individual measurements. Baseline R_{rs} (RES.) and X_{rs} (REACT.) values are normal. There is no frequency dependence of resistance (1000*R1) and the resonance frequency (RS.FR.) is normal. After histamine challenge R_{rs} values increase and a marked frequency dependence exists. X_{rs} values decrease; as a consequence the resonance frequency increases.

For each frequency a coherence factor (γ^2) (Ferris et al., 1964; Michaelson et al., 1975; Lándsér et al., 1976a) is calculated to assess the interference of the noise of the signal with the signal of breathing. A perfect coherence is indicated by 1; its value decreases in the presence of noise and of alinearities of the pneumotachograph signal. Only those values with a coherence function equal to or larger than 0.95 are retained. To improve the reproducibility of the measurements a 16 second period is analyzed; the R_{rs} and X_{rs} values being averaged. Before each investigation the equipment is calibrated by means of a mechanical resistance of known magnitude.

The on-line use of a microprocessor system facilates the calculations. In addition measured values can be compared instantly with predicted values.

5. Correlation of R_{rs} values (FOT) with other measurements of respiratory resistance

Measurements of respiratory resistance can be performed by several techniques as is shown in figure 2.16.

	Extrathoracic airways	*Intrathoracic airways*	*Lung tissue*	*Chest wall*
R_{aw}	<..whole body plethysmography..>			
R_l	<.....oesophageal balloon.....>			
R_{rs}	<.....forced oscillation technique.....>			

Figure 2.16. Components of respiratory resistance measured by different methods.

By the forced oscillation technique the impedance of the total respiratory system is measured. With the body plethysmograph and oesophageal balloon technique resistance values will be a somewhat smaller than with forced oscillometry. These differences must be taken into account if different methods are compared.

CHAPTER 3. INFLUENCE OF POSITIONS OF THE HEAD AND TONGUE AND OF THE MUSCULAR TONE OF THE MOUTH FLOOR AND PHARYNX ON R_{rs} and X_{rs} VS. FREQUENCY

1. Introduction

By forced pseudo-random noise oscillometry (FOT) resistance (R_{rs}) and reactance (X_{rs}) of the respiratory system are measured during quiet spontaneous breathing. The child is seated upright behind the apparatus while its nose is clipped and its cheeks are well fixed by the hands of the investigator. Inappropriate fixation leads to shunting of the oscillation signals in the upper airways (Michaelson et al., 1975; Solymár, 1982). In young children and in case of bronchoconstriction this gives rise to a decrease in R_{rs} values.

We investigated whether alterations of the position of the head, as well as positions of the tongue and increased muscular tone of the mouth floor would influence the results of FOT measurements. In other words how important it is that the child is seated with its head in upright position and is relaxed during the measurement.

2. Subjects and methods

15 healthy subjects who were experienced in lung function testing were investigated. After FOT measurements with the head in an upright position (nose-clipped, cheeks and mouth-floor well fixed) the effect of the following changes was investigated.

1. maximal flexion of the neck
2. maximal extension of the neck
3. tongue put against the hard palate.
4. increased tone of the mouth-floor and pharyngeal musculature

All measurements were performed in five fold. Mean values and standard deviations were calculated for each measurement.

3. Statistical analysis

Wilcoxon's paired signed rank test was used to compare the mean individual R_{rs6}, $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$ values (see abbreviations on table of symbols, abbreviations and units) in the various measuring positions. Differences were considered significant with p values less than 5 percent.

4. Results

Data are shown in figure 3.1. Maximal flexion of the neck gave rise to an increase in R_{rs6} ($p < 0.01$) and $\overline{X_{rs}}$ ($p < 0.05$), while $\overline{dR_{rs}/df}$ was not influenced ($p > 0.05$)
Maximal extension of the neck caused a decrease of R_{rs6} ($p < 0.02$) and $\overline{X_{rs}}$ ($p < 0.01$) and again no effect on $\overline{dR_{rs}/df}$. In most subjects positioning of the tongue against the hard palate and an increased tone of the mouth floor and pharyngeal musculature did not influence R_{rs6}, $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$, but in some the change was significant different from values obtained in baseline position (> 1.65 standard score* (ss). They are indicated in figure 3.1 as *.

5. Discussion

R_{rs} is mainly determined by the diameter of the central airways. Resistance of the upper airways (i.e. the glottis) determines approximately one-half of the total airway resistance (Schiratzki, 1964). Hence relatively small changes in upper airway resistance may influence total respiratory resistance considerably. Maximal flexion of the head gives rise to an increase in upper airway resistance and can therefore explain the increase in R_{rs}. Extension of the head has an opposite effect. X_{rs} is not only influenced by mass-inertial losses of air within the central airways (X_I) but also by elastic properties of lung tissue and chest wall (X_c). X_I has a positive and X_c a negative sign (figure 2.7, page 22). In case of maximal flexion of the head X_I increases. The relative influence of X_I dominates over X_c, hence $\overline{X_{rs}}$ will increase. In case of maximal extension of the head upper airway resistance will decrease, the mass-inertial losses of air within the central airways will be less and thus the relative influence of X_c dominates that of X_I. Hence $\overline{X_{rs}}$ will be lower.

dR_{rs}/df is considered to be a measure of unevenness of ventilation due to peripheral airways obstruction. Hence changes in upper airway resistance do not influence $\overline{dR_{rs}/df}$ values to the same degree as they affect R_{rs6} and $\overline{X_{rs}}$.

The Wilcoxon paired signed rank test showed a significant trend in the effect of flexion and extension on R_{rs6} and $\overline{X_{rs}}$. However if the values were expressed as a change in ss from values obtained in baseline position, differences were less than + or – 1.65 ss (95% confidence limits) in most cases. In the ss the within-subject variability of the measurement is taken into account. Hence more than 1.65 ss change from baseline implies that there is only a 5% chance that this is due to the method instead of the change in measuring position. In only a few subjects this was the case.

* Standard score is defined as the mean measured value minus the mean baseline value divided by the standard deviation of baseline value.

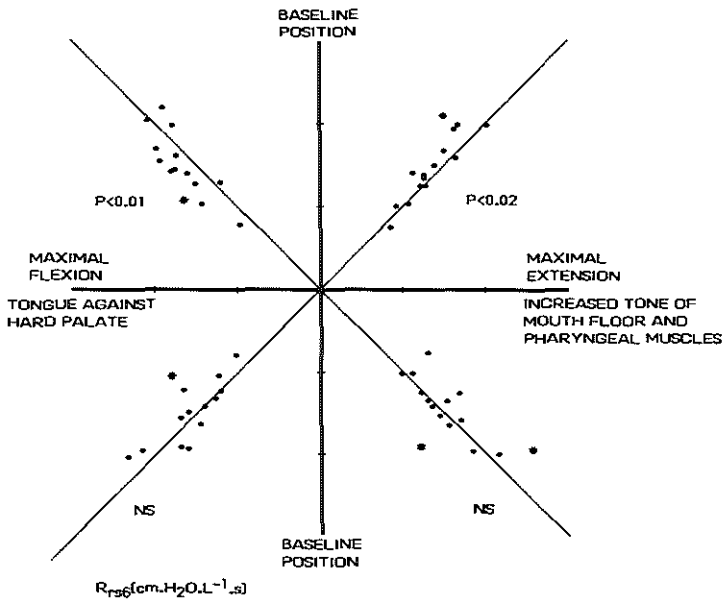


Figure 3.1.a Influence of positions of the head and tongue and of the muscular tone of the mouth floor and pharynx on R_{rs6} values.
More than 1.65 standard score change from values obtained in baseline position are indicated by *.

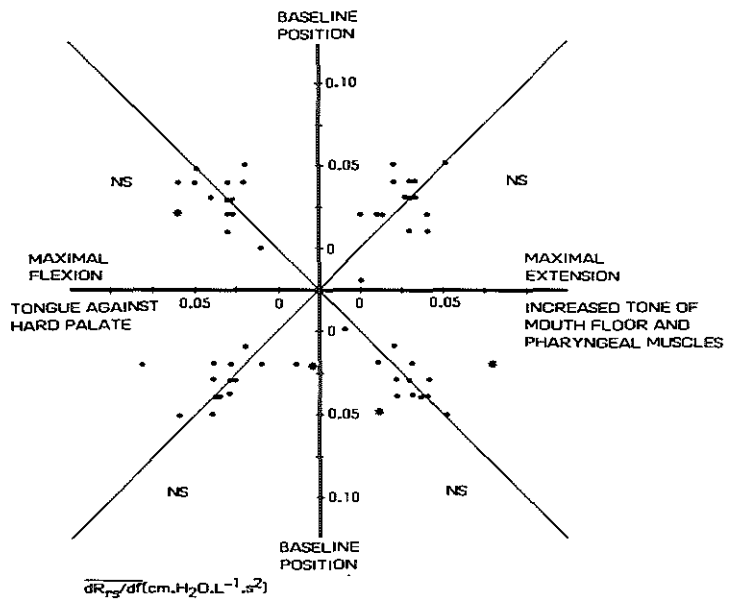


Figure 3.1.b Influence of positions of the head and tongue and of the muscular tone of the mouth floor and pharynx on $\overline{dR_{rs}/df}$ values.
More than 1.65 standard score change from values obtained in baseline position are indicated by *.

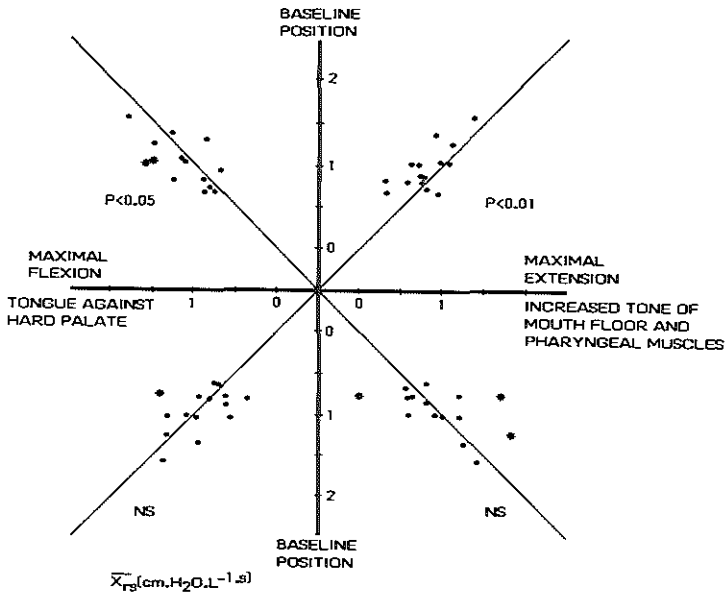


Figure 3.1.c Influence of positions of the head and tongue and of the muscular tone of the mouth floor and pharynx on $\overline{X}_{rs}$ values.
More than 1.65 standard score change from values obtained in baseline position are indicated by *.

6. Conclusion

Proper fixation of cheeks and mouth-floor (Michaelson et al., 1975; Solymár, 1982) seems to be of more importance than small deviations from baseline measuring position, position of the tongue and the tone of the mouth floor and pharyngeal musculature. Our data indicate that these have little influence on the results of FOT. However, as significant changes may occur, we advise to keep the head in an upright position and the tongue against the mouth floor while fixating the cheeks and the mouth-floor. This can best be done by the investigator and not by the child itself.

CHAPTER 4. FORCED OSCILLATION TECHNIQUE; REFERENCE VALUES FOR RESISTANCE AND REACTANCE OVER A FREQUENCY SPECTRUM OF 2-26 Hz IN HEALTHY CHILDREN AGED 2.3 - 12.5 YEARS.

La technique des oscillations forcées, valeurs de référence pour la résistance et la réactance aux fréquences 2-26 HZ chez des enfants sains agés de 2,3 a 12,5 ans.

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Abstract

The forced pseudo-random noise oscillation technique is a method by which total respiratory resistance (R_{rs}) and reactance (X_{rs}) can be measured simultaneously at various frequencies by means of complex oscillations, superimposed at the mouth during spontaneous quiet breathing. Reference values were obtained in 255 healthy Caucasian children of Dutch descent aged 2.3-12.5 years. R_{rs} and X_{rs} vs. frequency (f) curves are mainly determined by the child's sex, age, height and weight. Taking complete R_{rs} and X_{rs}-f curves into account, we found that R_{rs} values were significantly higher in young boys than in young girls. They were equal at about 8 years, but at about 12 years of age R_{rs} values were again significantly higher in boys than in girls. Frequency dependence of R_{rs} was found in healthy boys up to about 5 years of age but not in girls of the same age or in older children. These data suggest differences in airway diameter between boys and girls. At all ages X_{rs} was significantly lower in boys than in girls. This suggests differences in bronchial patency of peripheral airways, boys being at a disadvantage. It is concluded that multiple frequency oscillometry is a method which is ideal for children from the age of about 3. The possibility of measuring R_{rs} as well as frequency dependence of R_{rs} and X_{rs} simultaneously is the major advantage over other oscillation devices.

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List of abbrevations

R_{rs}	: total respiratory resistance ($cm.H_2O.l^{-1}.s$)
X_{rs}	: total respiratory reactance ($cm.H_2O.l^{-1}.s$)
$\overline{R_{rs}}$	: mean R_{rs} of R_{rs} values measured at different oscillation frequencies
$\overline{X_{rs}}$	: mean X_{rs} of X_{rs} values measured at different oscillation frequenc
R_{rs6}	: R_{rs} at 6 Hz oscillation frequency
$\overline{dR_{rs}/df}$	: frequency dependence of R_{rs} vs frequency ($cm.H_2O.l^{-1}.s^2$)
γ^2	: coherence function; if γ^2 is <0.95 an unfavourable signal-noise ratio exists; the measurement is rejected automatically.

1. Introduction

The forced pseudo-random noise oscillation technique according to Lándsér is a method by which the resistance (R_{rs}) and reactance (X_{rs}) of the respiratory system can be measured simultaneously at various frequencies by means of complex oscillations superimposed at the mouth during spontaneous quiet breathing. Many of the techniques for the measurement of airways obstruction which were developed for the investigation of adults, have been successfully applied to children. However, even the most simple test, such as the peak expiratory flow or forced expiratory volume in 1 second, requires the cooperation of the patient. Since these tests are effort dependent, their usefulness in preschool children is limited. Direct measurements of airflow resistance have been made in children with a pneumotachograph at the mouth and a balloon in the oesophagus to record transpulmonary pressure changes (12,20). These techniques require the passage of an oesophageal balloon and in young children sedation, and are therefore not suitable for routine use. Airways resistance measurements by whole body plethysmography are only possible in cooperative children or in children below 5-7 years of age under sedation (9,10,21). They are not easy to perform in preschool children and in sick patients.

In 1956 DuBois et al. introduced the forced oscillation technique (11). As this demands only passive cooperation it has been successfully applied to measure total respiratory resistance in animals (1,14), human adults (13,15), schoolchildren (42,45) and preschool children (3,4,17,18,22,30).

If, instead of a single frequency, a composite signal is applied, the impedance of the respiratory system can be measured simultaneously over a wide range of frequencies (27,32,46). The impedance of a network made up of resistive and reactive elements is composed of two parts: a real part or resistance R_{rs} and an imaginary part or reactance X_{rs}. The first is mainly determined by the frictional losses of the airflow within the airways. Hence it is largely dependent on the diameter of the airways. The second is mainly determined by the compliant properties of the chest-lung system and by the inertance of lung tissue, chest wall and air within the bronchi. It is of interest to examine how resistance and reactance change with frequency (7,16,19,26,31,46,47).

However, it would require a time consuming succession of different measurements performed at different frequencies if a technique is used in which only

monosinusoidal signals are applied. The possibility of measuring the impedance simultaneously at different frequencies (i.e. 2,4,6,8, ...26Hz) by the use of pseudo-random noise signals is the most important advantage of multiple frequency oscillometry compared to other methods (24,41).
To determine reference values for R_{rs} and X_{rs} over the frequency spectrum of 2-26 Hz, 387 children aged 2.3-12.5 years were examined by the forced pseudo-random noise oscillation technique.

2. Methods

The forced pseudo-random noise oscillation technique has been described in detail elsewhere (27,28,34).
The cheeks of the seated child are held by the investigator. The child breathes quietly through a pneumotachograph. A pseudo-random noise pressure signal, containing all harmonics of 2-26 Hz (peak-to peak amplitude smaller than 0.2 kPa) is applied at the mouth by means of a loudspeaker. Mouth pressure and flow signals, recorded by two identical differential transducers (Validyne MP 445), are fed into a Fourier analyzer. The latter performs a ensemble averaging over a time interval of 16 seconds and calculates the impedance of the respiratory system at 2,4,6 .24,26 Hz. The impedance is partitioned into a real and an imaginary part. The real part is computed as the ratio of the in phase components of pressure and flow. It reflects the total resistance of airways, lung tissue and chest wall. The imaginary part is computed as the ratio of the components of pressure and flow, which are 90° out of phase. It reflects the total reactance due to the compliances of lung tissue, chest wall and airway-walls, and to the inertances of lung tissue, chest wall and air within the bronchi. It can alternatively be expressed as a "dynamic compliance" C_{dyn} by the transformation
$C_{dyn} = {}^{1}/(2\pi\, fX_{rs})$ (28).
A coherence function (γ^2) is obtained to evaluate the accuracy of the computations. The coherence function evaluates the amount of noise or alinearity present in the measured signals. Only values of R_{rs} and X_{rs} with coherence functions exceeding or equal to 0.95 are retained. Empirically it was found that the relative error of the estimations of R_{rs} and X_{rs} did not exceed 10 percent when the coherence values was $\geqslant 0.95$ (27).

3. Study design

387 randomly selected Caucasian children of Dutch descent aged 2.3-12.5 years were examined. They were recruited from two primary schools and two infant classes, in a small town near Rotterdam (Nieuwerkerk a/d IJssel), which has inhabitants from rural and urban origin. They can be considered representative of Dutch schoolchildren. 255 children, 129 of whom were boys, without any past or present symptoms of wheezing or recurrent cough were selected by means of a interviewer administered questionnaire.

They can be considered to represent healthy Dutch children aged 2.3-12.5 years.

They showed a normal height and weight distribution for age (38). All children were examined by means of the forced pseudo-random noise oscillation technique. Five consecutive measurements were performed in each child. A 20% random sample of the healthy children was investigated for a second time after 4-6 weeks. Spirometry was also performed by children who were old enough to cooperate ($\geq$ 6 years of age).

All children had a physical examination prior to the measurements. Written informed consent was obtained from the parents of each child. The project was approved by the local medical ethics committee.

4. Statistical analysis

The analysis of R_{rs} and X_{rs} data is complicated because R_{rs} or X_{rs} vs. frequency (intraindividual functions) may vary with sex (S), age (A), height (H) and weight (W) (interindividual functions). The statistical analysis applied is described in detail by Lándsér et al. (29) and Clément et al. (2). Since age, height and weight are highly correlated in children, difficulties arise in the computation of the regression functions. Therefore a method was used where A, H and W were transformed into mutually uncorrelated variables. The procedure is described in the appendix. To separate healthy children from patients with symptoms of bronchial obstruction by means of the measured R_{rs} and X_{rs} vs. frequency curves it is necessary to find the factors that discriminate best between normal and abnormal. Previously it was shown that the respiratory impedance of patients with a mild degree of obstructive lung disease, is characterized by an increase of the R_{rs} respectively a decrease of the X_{rs} values averaged over the frequency interval from 4-26 Hz, and by an increased frequency dependence of R_{rs}. The latter can be quantified as the mean value of the first derivative of R_{rs} vs. frequency computed over the investigated 4-26 Hz interval $(\overline{dR_{rs}/df})$. We estimated in each child the observed arithmetic mean of the R_{rs} and of its successive derivates with respect to frequency, up to the fourth, according to a method outlined previously (2,29). These individual mean values were next compared with the corresponding values predicted by the regression equations estimated from the data of the whole sample in function of S, A, H and W.

If the observed mean of either R_{rs} or frequency dependence of R_{rs} or X_{rs} deviated too much from predicted, i.e. exceeded the 95% unilateral confidence limits the subject was qualified conventionally as "abnormal".

5. Results

Results of 255 children aged 2.3-12.5 years who answered negative to questions on recurrent respiratory disease and had no past or present history of asthma are presented.

Inspiratory VC and FEV_1 values obtained in children who were old enough to cooperate fitted well with reference values by Zapletal et al. (48) (fig. 1).

R_{rs} values at 6 Hz oscillation frequency (R_{rs6}) decreased as a function of height (fig. 2). Our data correlate well with values obtained with a single frequency device (6 Hz) in healthy children aged 3-12 years (3).

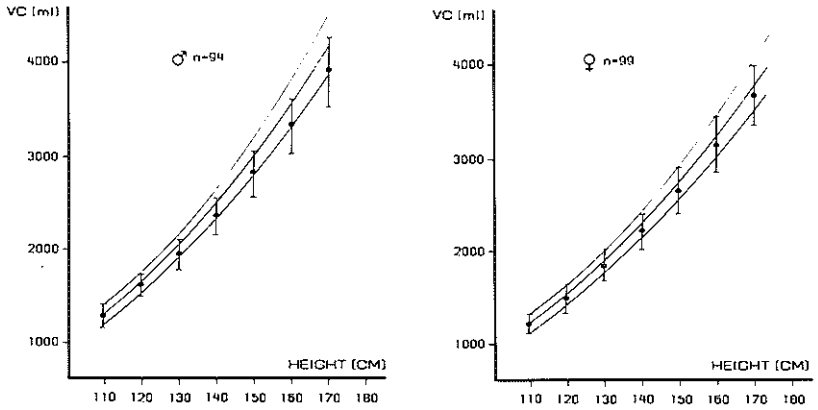

Figure 1a: Inspiratory VC, mean ± 1 SD for boys and girls; reference values (mean ± 1 SD) from Zapletal et al. (47).

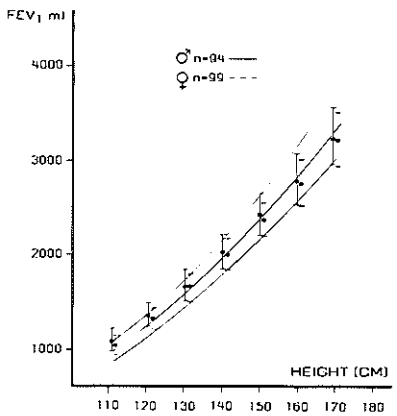

Figure 1b: FEV_1; mean ± 1 SD for boys and girls; reference values (mean ± SD) from Zapletal et al. (47).

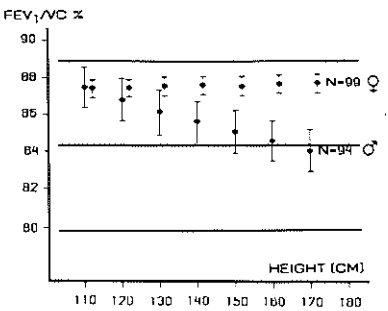

Figure 1c: $FEV_1/VC\%$; mean ± SD for boys and girls; reference values (mean ± 1 SD) from Zapletal et al. (47).

We studied how sex, age, height and weight contributed to the relationship between the frequency spectrum and R_{rs} respectively X_{rs}. Regression coefficients for normal values of $\overline{R_{rs}}$, $\overline{dR_{rs}/df}$, and $\overline{X_{rs}}$ are given in table 1. R_{rs} and X_{rs} were influenced by sex (S), age (A), height (H) and weight (W). If the child's height was less than the mean height for age, R_{rs} values were higher and X_{rs} values were lower (i.e. more negative); the reverse was true for heights greater than the mean for age (fig. 3 and 4). Overweight was associated with higher values of R_{rs} but

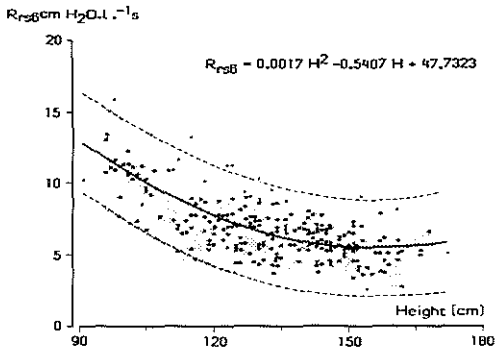

Figure 2: R_{rs6} (cm.$H_2O.l^{-1}$.s) vs. height for boys and girls (-- mean ± 2 SD; 1 SD = ± 1.75); reference values from Cogswell et al. (3).

virtually no change in X_{rs}; underweight gave lower R_{rs} values (fig. 5 and 6). The influence of weight was quantitatively smaller than that of height. $R_{rs}$and X_{rs} vs. frequency curves were mainly determined by $\overline{R_{rs}}$, $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$. In children at 4 years of age $\overline{R_{rs}}$ was significantly ($p < 0.01$) higher in boys than in girls. At about 8 years of age $\overline{R_{rs}}$ values did not differ significantly in the two sexes. At about 12 years however $\overline{R_{rs}}$ was again significantly ($p < 0.01$) higher in boys than in girls.

In contrast to girls, young boys showed frequency dependence of R_{rs} up to the age of approximately 5 years (fig. 3 and 5).
At all ages X_{rs} values in boys were significantly ($p < 0.01$) lower than in girls (fig. 4 and 6).

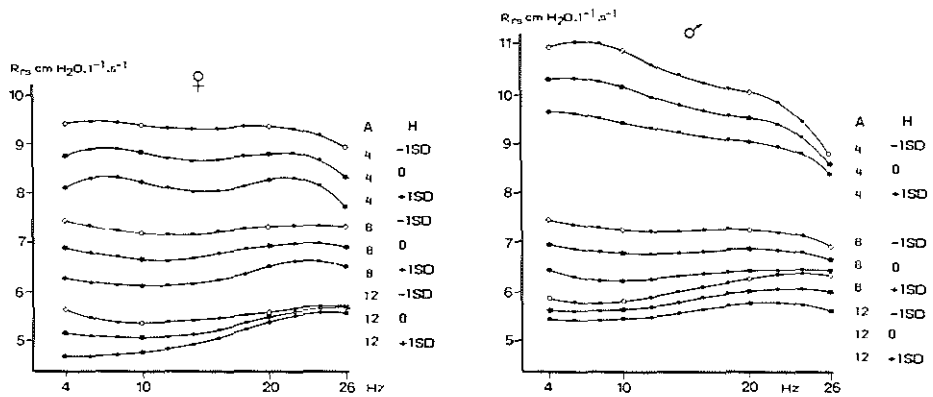

Figure 3: Influence of sex, age and height on R_{rs} vs. frequency in healthy children. In all regressions mean weight for age was used. A = age, (yr); H = mean height for age in cm. ± 1 SD.

The between subject standard deviation of the measured R_{rs} and X_{rs} vs. frequency changes with age and sex (table 2). It is greater in the younger age groups, especially in boys and at lower frequencies. Since it appeared impractical to use 95% unilateral confidence limits varying with age, we calculated means of SD values at all ages and used these to define confidence limits over the

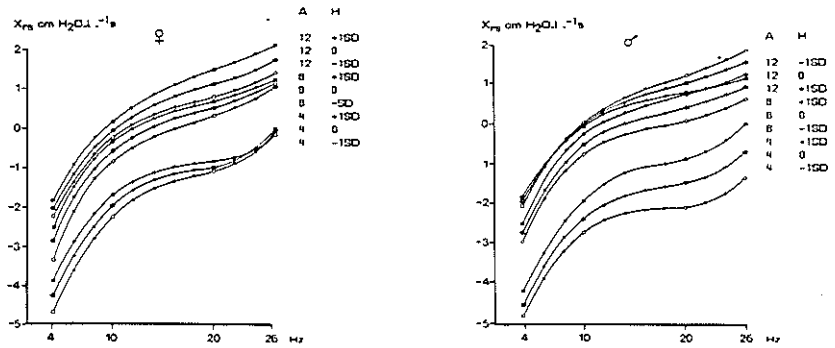

Figure 4: Influence of sex, age and height on X_{rs} vs. frequency in healthy children. In all regressions mean weight for age was used. A = age (yr); H = mean height for age in cm. ± 1 SD.

complete age range (table 3). The figures thus obtained are somewhat too low at ages 6 and less. However it turned out that in 244 out of 255 healthy children R_{rs} values were within these limits. For X_{rs} values this was the case in 246 and for frequency dependence in 243 (table 4).

The mean within-subject standard deviation of 5 consecutive measurements performed during the same session was for $\overline{R_{rs}}$ 0.84 cm $H_2O.l^{-1}.s.$ (< 9 years of age) and 0.59 cm $H_2O.l^{-1}.s.$ (> 9 years of age); for $\overline{X_{rs}}$ 0.59 cm $H_2O.l^{-1}.s.$ and 0.38 cm $H_2O.l^{-1}.s.$ respectively. The mean within-subject standard deviation of two sessions of 5 consecutive measurements each, and separated by an interval of 4-6 weeks, increases to 1.17 cm $H_2O.l^{-1}.s.$ (< 9 years) and 0.96 cm $H_{2O}.l^{-1}.s.$ (> 9 years) for $\overline{R_{rs}}$, and to 0.73 cm $H_2O.l^{-1}.s.$ and 0.52 cm $H_2O.l^{-1}.s.$ respectively for $\overline{X_{rs}}$. This increase can be attributed to the additional variability induced by time-changes of the respiratory impedance.

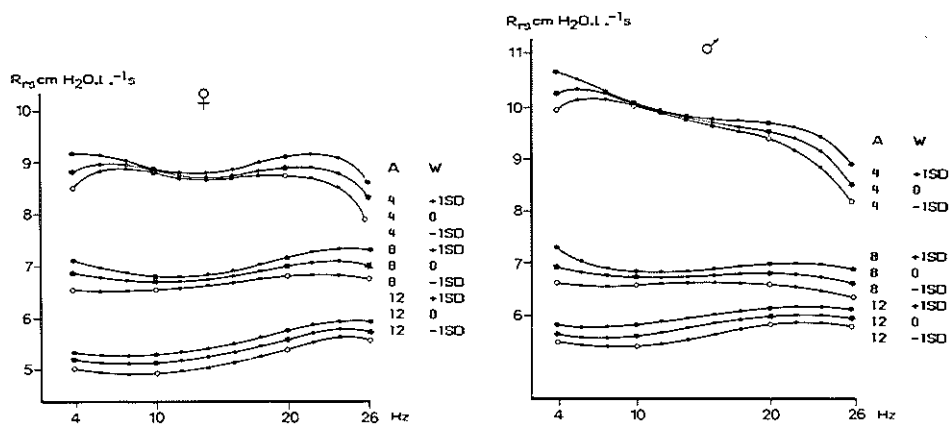

Figure 5: Influence of sex, age and weight on R_{rs} vs. frequency in healthy children. In all regressions mean height for age was used.
A = age (yr); W = mean weight for age in kg. ± 1 SD.

Table 1: Regression coefficients for normal values of $\overline{R_{rs}}$, $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$ in function of age in years (A), height in cm (H) and weight in kg (W).

	BOYS	GIRLS		BOYS	GIRLS		BOYS	GIRLS
$\overline{R_{rs}}$ (cm $H_2O.l^{-1}.s$)			$\overline{dR_{rs}/df}$ (cm $H_2O.l^{-1}.s^2$)			$\overline{X_{rs}}$ (cm $H_2O.l^{-1}.s$)		
A	−4.5326	−3.7173	A	4.6096×10^{-2}	-8.12×10^{-3}	A	1.2384	0.4121
A^2	0.40251	0.3555	A^2	3.621×10^{-3}	-1.394×10^{-3}	A^2	7.157×10^{-2}	-2.136×10^{-2}
A^3	-1.7658×10^{-2}	-1.7658×10^{-2}	H	8.738×10^{-3}	1.579×10^{-4}	H	0.20319	0.05177
H	−0.23728	−0.23728	AH	-8.142×10^{-4}	1.970×10^{-4}	AH	-1.8566×10^{-2}	-7.21×10^{-4}
W	5.03×10^{-2}	5.03×10^{-2}	constant	−0.8972	-6.5×10^{-2}	constant	−21.72	−7.99
HA	1.4166×10^{-2}	1.4166×10^{-2}						
constant	40.978	37.404						

Table 2: Mean values of $\overline{R_{rs}}$ and $\overline{X_{rs}}$ ± 1 SD (cm. $H_2O.l^{-1}.s$) at 6, 16, 24 Hz oscillation frequencies of boys and girls at three different ages (4, 8, 12 years). f = oscillation frequency (Hz); A = age in years; s = sex, F = female, M = male.

f (Hz)	A	S	mean $\overline{R_{rs}}$ ± 1 SD at 6-16-24 Hz	mean $\overline{X_{rs}}$ ± 1 SD at 6-16-24 Hz
6	4	M	10.39 ± 3.03	−3.56 ± 1.06
		F	8.92 ± 1.66*	−3.22 ± 0.85*
	8	M	6.86 ± 1.88	−1.86 ± 0.94
		F	6.75 ± 1.24^{NS}	−1.76 ± 0.57*
	12	M	5.62 ± 1.14	−1.03 ± 0.39
		F	5.11 ± 1.02*	−1.11 ± 0.61*
16	4	M	9.79 ± 2.03	−1.60 ± 1.28
		F	8.71 ± 1.67*	−1.12 ± 0.87*
	8	M	6.86 ± 1.80	0.20 ± 0.78
		F	6.74 ± 1.17^{NS}	0.26 ± 0.67*
	12	M	5.91 ± 1.06	0.77 ± 0.61
		F	5.29 ± 1.01*	0.83 ± 0.76*
24	4	M	9.20 ± 1.99	−1.04 ± 1.31
		F	8.72 ± 2.02*	−0.44 ± 1.05*
	8	M	6.86 ± 1.75	0.79 ± 1.10
		F	7.01 ± 1.24 ^{NS}	0.97 ± 0.79*
	12	M	6.13 ± 1.20	1.40 ± 0.74
		F	5.69 ± 1.10*	1.57 ± 0.89*

*$p<0.01$

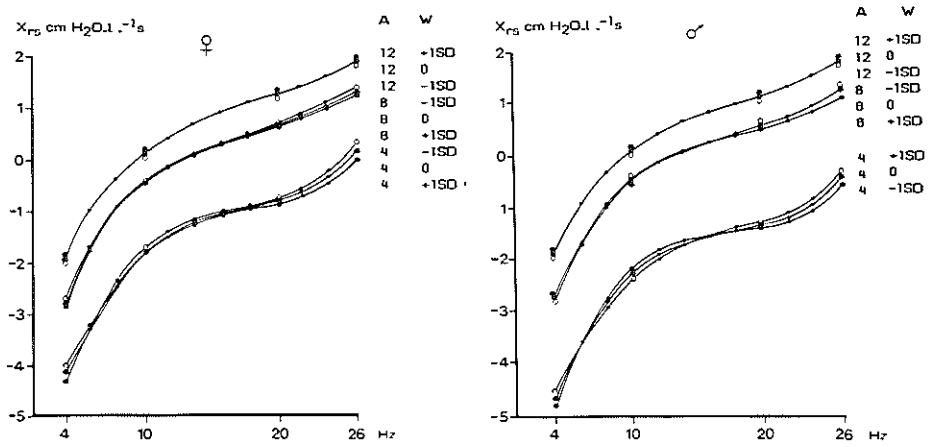

Figure 6: Influence of sex, age and weight on X_{rs} vs. frequency in healthy children. In all regressions mean height for age was used.
A = age (yr); W = mean weight for age in kg. ± 1 SD.

Table 3: Unilateral 95% confidence limits of $\overline{R_{rs}}$, $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$. SD values shown are means of SD values at ages 2.3 - 12.5 years.

	Measured value normal value & 1.65 SD
Upper limit $\overline{R_{rs}}$	mean $\overline{R_{rs}}$ + 2.54 ($cm\,H_2O.l^{-1}.s$)*
Lower limit $\overline{dR_{rs}/df}$	mean $\overline{dR_{rs}/df}$ − 0.10* ($cm.H_2O.l^{-1}.s^2$)*
Lower limit $\overline{X_{rs}}$	mean $\overline{X_{rs}}$ − 1.27 ($cm\,H_2O.l^{-1}.s$)*

* see table 1

$\overline{R_{rs}}$, $\overline{dR_{rs}/df}$, $\overline{X_{rs}}$: see list of abbreviations

Table 4: $\overline{R_{rs}}$, $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$ values of 255 healthy children defined as normal or Table 4 $\overline{R_{rs}}$, $\overline{dR_{rs}/df}$ and X_{rs} values of 255 healthy children defined as normal or abnormal based on unilateral 95% confidence limits.

$\overline{X_{rs}}$ normal, $\overline{dR_{rs}/df}$ normal	$\overline{X_{rs}}$ normal, $\overline{dR_{rs}/df}$ abnormal	$\overline{X_{rs}}$ abnormal, $\overline{dR_{rs}/df}$ normal	$\overline{X_{rs}}$ abnormal, $\overline{dR_{rs}/df}$ abnormal
$\overline{R_{rs}}$ normal			
233	4	6	1
$\overline{R_{rs}}$ abnormal			
4	5	0	2

* see list of abbreviations

Discussion

The forced oscillation techniqe offers the possibility of performing lung function tests in preschool children since only passive cooperation of the child is needed. The method can be applied in most children over the age of 3. When oscillation data are analysed on-line with a microprocessor mean values of R_{rs} and X_{rs} over the complete frequency spectrum as well as frequency dependence of R_{rs} and their differences from the mean reference values as obtained in this study (table 1) are rapidly available. The possibility of measuring simultaneously R_{rs} as well as frequency dependence of R_{rs} and X_{rs}, is the major advantage over other oscillation techniques. R_{rs} and X_{rs} values are related to the child's sex, age, height and weight. Height and age are the most important determinants.

The selected children can be considered to be a representative sample of healthy Dutch children. They live in a town near Rotterdam with low levels of air-pollution; inhabitants are of rural and urban origin. All children had a negative past or present history of recurrent respiratory disease or asthma and revealed no abnormalities on physical examination. Hence the children who form the reference population can be considered to be healthy based on their parents answers to the questionnaire and on the physical examination. Even if some of them had a lower respiratory tract infection in infancy resulting in mild persistent lung function abnormalities, a different outcome is unlikely. Spirometric values (fig. 1a, 1b, 1c) also support the claim that the children investigated can be taken as a reference population for reference values. The children were examined in March and April. This period was chosen to minimise the risk of complicating factors such as viral infections or allergic reactions. Our R_{rs} data at 6 Hz fitted well with the reference values of Cogswell et al. (3). However, by single frequency oscillometry boys and girls cannot be distinguished. For the analysis of the R_{rs} respectively X_{rs} curve over the 4-26 Hz frequency spectrum we used the method developed by Clément et al. (2,29). They found that in adults R_{rs} and X_{rs} were mainly determined by age and weight, but measurements were only performed in men and not in women. Hence it is not known whether sex influences the prediciton equations.

Although there is overlap between boys and girls when taking the complete R_{rs} or X_{rs}-f curves into account, we found three marked differences between boys and girls:

1. $\overline{R_{rs}}$ values are significantly higher in boys than in girls at the age of 4 and 12 years. At about age 8 differences are not significant (table 2).
2. Frequency dependence of R_{rs} $\overline{(dRrs/df)}$ exists in healthy boys up to about 5 years of age and not in girls of the same age or in older children (fig. 3 and 5).
3. X_{rs} values are significantly more negative in boys than in girls (table 2).

R_{rs} values are higher and X_{rs} values lower in young children due to smaller lung volumes and airway diameters. In adults Fisher et al. (13) and Jiemsripong et al. (25) found a higher respiratory resistance in women than in men. This may be due to the smaller lung volume in women, which goes along with a smaller airway diameter (5). Since Polgar and Promadhat (36) found TLC to be higher in boys than in girls over 110 cm tall (approximately 5-6 years), differences in lung size cannot explain the higher resistance in boys found in our study. Various studies indicate that airways are relatively wider in girls than in boys (8,37). Healthy girls aged 3 to 6 years have larger expiratory flow rates when corrected for lung size than boys of the same age (43,44). The FEV_1/FVC ratio in girls aged 6 to 11 years was found to be higher than in boys of the same age (8). We could confirm this in our study (fig. 1). The differences in R_{rs} found between boys and girls below the age of about 8 are compatible with differences in airway diameter (6,23). Also in boys aged 12 R_{rs} values are higher than in girls of the same age. This may be explained by the fact that at age 12, many girls but not boys have reached their puberty, and the growth spurt is accompanied by an increase in airway diameter. At 8 years of age differences are not significant.

We found frequency dependence of R_{rs} in healthy boys under the age of five, but not in girls of the same age or in older children. X_{rs} values were significantly lower in boys than in girls. Frequency dependence of resistance and compliance is a sensitive measure of peripheral airways obstruction (7,26,46,47). It is a consequence of different time constants between lung units ventilated in parallel which will cause uneven ventilation resulting in frequency dependence of R_{rs} and X_{rs} (7,26,31,42). Lower X_{rs} values may be explained by lower capacitive and inertial properties of the lungs. Frequency dependence and more negative X_{rs} values both support the hypothesis that peripheral airway diameter is smaller in young boys than in young girls.

Our findings are compatible with studies on airways, parenchymal and thoracic growth that suggest a dysanaptic growth pattern of different parts of the respiratory system (6,23,35,39,40). The lag between growth of lung and stature is related to the growth pattern of the thorax (39).

The lower R_{rs} and higher X_{rs} values in children with an increased height for age indicate that this is associated with a larger airway diameter for age. The reverse is also true (fig. 3,4).

In adults extreme overweight gives rise to a decreased lung volume for age and height and to a higher airways resistance (23). In children the influence of weight on R_{rs} is small (fig. 5). This results in minimally increased values of R_{rs} in children with overweight and practically no influence on X_{rs} (fig 6).

Analysis of the R_{rs} and X_{rs} vs. frequency curves was performed by means of the statistical technique described in the appendix. An accurate description of the curves and their variations with sex, age, height and weight, as shown in the figures 4,5,6 and 7, required the use of 59 and 45 (statistically significant) coefficients for the R_{rs} vs. f and X_{rs} vs. f curves respectively. However, for diagnostic purposes, and to decide if results obtained in a given subject are within the normal range, it is not necessary to compute exactly its expected R_{rs} and X_{rs}

values. Generally, a satisfactory separation between healthy and diseased children can be realized by investigating only a few characteristics of the data. Previous work in adults showed that three parameters contained most information allowing a discrimination between healthy subjects and patients with incipient or advanced obstructive lung disease (2,29). These parameters are the mean values of R_{rs} and X_{rs}, $\overline{R_{rs}}$ and $\overline{X_{rs}}$, and the frequency dependence of R_{rs}, $\overline{dR_{rs}/df}$. Preliminary data suggest that obstructive lung disease in children is also characterized by an increase of $\overline{R_{rs}}$ and a decrease of $\overline{X_{rs}}$ and of $\overline{dR_{rs}/df}$ (unpublished observations).

Therefore, it is likely that these changes are diagnostic for this disease. In table 1 the mean values of $\overline{R_{rs}}$, $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$ obtained in our healthy girls and boys are expressed as a function of age, height and weight. The 95% unilateral confidence limits given in table 3, set at 1.65 times the mean interindividual standard deviations of the regressions of $\overline{R_{rs}}$, $\overline{dR_{rs}/df}$ or $\overline{X_{rs}}$ on age, height and weight, can then be used to discriminate normal from "abnormal" or diseased subjects (table 4). One should realize that this procedure may yield more false abnormal results in the age groups below 6 years, because in the latter the interindividual standard deviation tends to be higher than in the older groups. Nevertheless, the number of "abnormals" is small (table 4) and we did not observe a higher proportion of "abnormals" below the age of 6 years than above.

Acknowledgements

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Appendix

Transformation of the predictors age (A), height (H) and weight (W) into mutually uncorrelated variables.

The purpose is to express the reference values of the successive derivatives of R_{rs}, X_{rs} versus frequency (32) as functions of the predictors S (sex), A (age), H (height), W (weight) and of the powers and cross-products HA, HW, A^2, A^3.

However, the anthropometric and age variables are so highly correlated in children that their simultaneous introduction as predictors in regression functions is precluded. Indeed, the computation of the regression coefficients either leads

to undetermined solutions of equations, or results in serious sampling errors. These difficulties can be overcome by preliminary transformation of A, H and W into new mutually uncorrelated variables. The following procudure was followed.

We first computed the linear regression of H on A:

$H = h_1A + h_2$ (eq. 1) by the classical least-squares method. The measured height in each child i, (H_i), was then replaced by its difference ($\triangle H_i$) with respect to the value predicted by (eq.1): $\triangle H_i = H_i - h_i A_i - h_2$, where A_i is the age of child i. The ensemble of all $\triangle H_i$ values within the sample evidently represents the residual around equation (eq. 1). According to a classical least squares theorem $\triangle H$ is uncorrelated with A, i.e. $\Sigma A_i \triangle H_i = 0$. Thus $\triangle H$ and A may simultaneously be used as predictors in regression equations without the problems of computation quoted above. In particular, the linear regression of W on A and $\triangle H$ may be calculated:

$W = w_1A + w_2\triangle H + w_3$ (eq. 2).

The individual W_i values will similarly be replaced by their difference $\triangle W_i$ with respect to equation 2:

$\triangle W_i = w_1A_i + w_2 H_i + w_3 - w_i$.

Finally, all powers of A were replaced by mutually indepent orthogonal polynomials P(A), $P(A^2)$, $P(A^3)$, following a classical procedure (33). The calculations of the regression functions of the successive derivatives of R_{rs}, X_{rs} (31) were now performed on the variables P(A), $\triangle H$, $\triangle W$, the power functions $P(A^2)$, $P(A^3)$ and the cross-products $\triangle HP(A)$, etc.

Since the predictors are no longer mutually correlated the difficulties quoted above are eliminated. The final results, obtained after removal of the nonsignificant coefficients, allow the prediction of the "normal" curves R_{rs} and X_{rs}, vs. frequency as functions of A, H and W. They can be re-expressed in terms of the original variables A, H and W by simple substitution, using eq. (1) and (2).

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RÉSUMÉ: La technique des oscillations forcées par bruits pseudo-fortuits est une méthode qui permet la mesure simultanée à fréquences variables des résistance (R_{rs}) et réactance (X_{rs}) respiratoires totales, au moyen d'oscillations complexes imposées à la bouche pendant la respiration calme spontanée. Les valeurs de référence sont obtenues chez 255 enfants caucasiens en bonne santé, de souche hollandaise, âgés de 2,3 à 12,5 ans. Les R_{rs} et X_{rs} vs fréquence (f) sont essentiellement déterminées par le sexe, l'âge, la taille et le poids de l'enfant. L'examens des courbes complètes R_{rs}-f et X_{rs}-f montre que les valeurs de R_{rs} sont significativement plus élevées chez les garçons jeunes que chez les filles jeunes; elles sont ensuite égales vers huit ans, puis vers 12 ans redeviennent significativement plus élevées chez les garçons que chez les filles. R_{rs} dépend de la fréquence chez les garçons jusqu'à 5 ans, mais pas chez les filles du même âge ni chez les enfants plus âgés. Ces résultats suggèrent une différence de diamètre des voies aériennes entre garçons et filles. A tous les âges, X_{rs} est significativement plus basse chez les garçons que chez les filles, ce qui suggère des différences dans la perméabilité bronchique des voies aériennes périphériques, et ce au désavantage des garçons. On peut en conclure que l'oscillométrie à fréquences multiples est la méthode idéale pour les enfants d'environ trois ans. La possibilité de mesurer R_{rs} et simultanément la dépendance en fréquence de R_{rs} et X_{rs} est l'avantage majeur de cette méthode par rapport aux autres systèmes d'oscillation.

APPENDIX

Prediction equations for healthy children aged 2¼–12½ years.

Equations for R_{rs} or X_{rs} (cm $H_2O.l^{-1}.s.$) as a function of the oscillatory frequency f (between 4 and 26 Hz) and sex (S), age (A, yr), height (H, cm), and weight (W, kg). (S = O for boys and 1 for girls).

$$R_{rs}\,(\text{or}\,X_{rs}) = af^4 + bf^3 + cf^2 + df + e$$

For R_{rs}:

$$\begin{aligned}
a = {} & 5.045414 && \times 10^{-5} \times A + 0.3971755 \times 10^{-5} \times A^2 \\
& + 0.9453067 && \times 10^{-5} \times H - 0.9253904 \times 10^{-6} \times A \times H \\
& + 0.14148124 && \times 10^{-2} \times S + 0.14732291 \times 10^{-5} \times S \times A \times H \\
& - 0.17377789 && \times 10^{-4} \times S \times H - 0.1787675 \times 10^{-4} \times S \times A \\
& - 0.8737829 && \times 10^{-5} \times S \times A^2 - 0.9252740 \times 10^{-3}
\end{aligned}$$

$$\begin{aligned}
b = {} & - 0.26869068 && \times 10^{-2} \times A - 0.23382050 \times 10^{-3} \times A^2 \\
& - 0.51362997 && \times 10^{-3} \times H - 0.7957439 \times 10^{-4} \times W \\
& + 0.7350647 && \times 10^{-5} \times A \times W + 0.50576396 \times 10^{-4} \times A \times H \\
& - 0.84888747 && \times 10^{-1} \times S + 0.88393748 \times 10^{-4} \times S \times A \times H \\
& + 0.104266735 && \times 10^{-2} \times S \times H + 0.10726051 \times 10^{-2} \times S \times A \\
& + 0.52426979 && \times 10^{-3} \times S \times A^2 + 0.51090878 \times 10^{-1}
\end{aligned}$$

$$\begin{aligned}
c = {} & 0.4353378 && \times 10^{-1} \times A + 0.4800834 \times 10^{-2} \times A^2 \\
& + 0.8706587 && \times 10^{-2} \times H + 0.5053944 \times 10^{-2} \times W \\
& - 0.4583984 && \times 10^{-3} \times A \times W - 0.8766591 \times 10^{-3} \times A \times H \\
& + 0.17785212 && \times 10^{1} \times S + 0.18545060 \times 10^{-2} \times S \times A \times H \\
& - 0.21823656 && \times 10^{-1} \times S \times H - 0.2280916 \times 10^{-1} \times S \times A \\
& - 0.10999211 && \times 10^{-1} \times S \times A^2 - 0.9081400
\end{aligned}$$

$$\begin{aligned}
d = {} & - 0.1685686 && \times A - 0.3673689 \times 10^{-1} \times A^2 \\
& - 0.3985621 && \times 10^{-1} \times H - 0.8827712 \times 10^{-1} \times W \\
& + 0.7900840 && \times 10^{-2} \times A \times W + 0.44379252 \times 10^{-2} \times H \times W \\
& - 0.14323557 && \times 10^{2} \times S - 0.14846887 \times 10^{-1} \times S \times A \times H \\
& + 0.17692979 && \times S \times H + 0.1473881 \times S \times A \\
& + 0.8904023 && \times 10^{-1} \times S \times A^2 + 4.887398
\end{aligned}$$

$$\begin{aligned}
e = {} & - 0.505919 && \times 10^{1} \times A + 0.464310 \times A^2 \\
& - 0.176577 && \times 10^{-1} \times A^3 - 0.304810 \times H \\
& + 0.446470 && \times W - 0.350341 \times 10^{-1} \times A \times W \\
& + 0.176577 && \times 10^{-1} \times A \times H + 0.271567 \times 10^{2} \times S \\
& + 0.302912 && \times 10^{-1} \times S \times A \times H - 0.397992 \times S \times H \\
& + 0.102044 && \times 10^{-1} S \times A - 0.241405 \times S \times A^2 \\
& + 43.3879
\end{aligned}$$

For X_{rs}

$$
\begin{aligned}
a = {} & 0.1061255 && \times 10^{-5} \times A + 0.1630728 \times 10^{-5} \times A^2 \\
& + 0.4763713 && \times 10^{-5} \times H - 0.7078263 \times 10^{-5} \times W \\
& + 0.55233095 && \times 10^{-6} \times A \times W - 0.37172204 \times 10^{-6} \times A \times H \\
& - 0.2917428 \times 10^{-3}
\end{aligned}
$$

$$
\begin{aligned}
b = {} & - 0.4082738 && \times 10^{-3} \times A - 0.10254032 \times 10^{-3} \times A^2 \\
& - 0.35454253 && \times 10^{-3} \times H + 0.51379344 \times 10^{-3} \times W \\
& - 0.40837582 && \times 10^{-4} \times A \times W + 0.27483938 \times 10^{-4} \times A \times H \\
& + 0.24051736 \times 10^{-1}
\end{aligned}
$$

$$
\begin{aligned}
c = {} & 0.1859810 && \times 10^{-1} \times A + 0.2298437 \times 10^{-2} \times A^2 \\
& + 0.9374096 && \times 10^{-2} \times H - 0.13343203 \times 10^{-1} \times W \\
& + 0.10795219 && \times 10^{-2} \times A \times W - 0.7265247 \times 10^{-3} \times A \times H \\
& - 0.6923861
\end{aligned}
$$

$$
\begin{aligned}
d = {} & - 0.2271071 && \times A - 0.1553496 \times 10^{-1} \times A^2 \\
& - 0.8981851 && \times 10^{-1} \times H + 0.13826138 \times W \\
& - 0.11345343 && \times 10^{-1} \times A \times W + 0.6682869 \times 10^{-2} \times A \times H \\
& + 0.1407810 && \times 10^{1} \times S + 0.1752111 \times 10^{-2} \times S \times A \times H \\
& - 0.169759754 && \times 10^{1} \times S \times H \, 0.431550 \times 10^{-1} \times S \times A \\
& - 0.1039190 && \times 10^{-1} \times S \times A^2 + 7.206603
\end{aligned}
$$

$$
\begin{aligned}
e = {} & 1.71462 && \times A + 0.50802 \times 10^{-1} \times A^2 \\
& + 0.388785 && \times H - 0.435638 \times W \\
& + 0.360406 && \times 10^{-1} \times A \times W - 0.285320 \times 10^{-1} \times A \times H \\
& - 7.3866 && \times S - 0.84369 \times 10^{-2} \times S \times A \times H \\
& + 0.103220 && \times S \times H - 0.17892 \times S \times A \\
& + 0.62951 && \times 10^{-1} \times S \times A^2 - 39.4254
\end{aligned}
$$

CHAPTER 5. COMPARISON OF DIFFERENT INDICES FROM DOSE-RESPONSE CURVES TO INHALED METHACHOLINE DETERMINED BY FORCED PSEUDO-RANDOM NOISE OSCILLOMETRY AND FORCED EXPIRATORY FLOW-VOLUME CURVES

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Abstract

The forced pseudo-random noise oscillation technique (FOT) is a method by which resistance (R_{rs}) and reactance (X_{rs}) of the respiratory system can be measured simultaneously at various frequencies by means of complex oscillations, superimposed at the mouth during spontaneous quiet breathing. Methacholine inhalation challenges were performed in 20 asthmatic children, aged 9.1 to 16.2 years. The degree of bronchial responsiveness to methacholine was calculated from a dose-response curve. From this curve the following indices were derived:

1) threshold dose (TD); i.e. dose after which lung function differs 2 SD from baseline;
2) provocative dose (PD); i.e. dose causing a predetermined change of baseline lung function.

We defined indices obtained by FOT, to measure TD and PD, and compared these to indices derived from complete and partial expiratory flow-volume curves ($MEFV_{25}$, $PEFV_{25}$, FEV_1). Indices obtained by FOT proved to be at least as sensitive to detect methacholine-induced bronchoconstriction as indices derived from flow-volume curves. The within-patient reproducibility of FOT resistance and flow-volume indices is about equal. For clinical practice PD_{40} R_{rs6} proved to be a reproducible and sensitive FOT index to define BR. For research purposes TD $\overline{dR_{rs}/df}$ can be chosen as a sensitive index to detect induced bronchoconstriction after inhalation of methacholine.

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List of abbreviations

FOT	forced pseudo-random noise oscillation technique
R_{rs}	resistance of the respiratory system measured by FOT cm.H_2O.l^{-1}.s)
X_{rs}	reactance of the respiratory system measured by FOT cm.H_2O.l^{-1}.s)
$\overline{R_{rs}}$	mean R_{rs} measured at frequencies of 2-26 Hz cm.H_2O.l^{-1}.s)
R_{rs6}	R_{rs} measured at 6 Hz oscillation frequency (cm.H_2O.l^{-1}.s)
dR_{rs}/df	frequency dependence of R_{rs}
$\overline{dR_{rs}/df}$	mean slope of R_{rs} vs. frequency (cm.H_2O.l^{-1}.s^2)
$\overline{X_{rs}}$	mean X_{rs} measured at frequencies of 2-26 Hz (cm.H_2O.l^{-1}.s)
RV	residual volume (l)
FRC	functional residual capacity (l)
TLC	total lung capacity (l)
VC	vital capacity (l)
FEV_1	forced expiratory volume in one second ($l.s^{-1}$)
$MEFV_{25}$	maximum expiratory flow when 25% of FVC remains in the lung measured from flow-volume curves ($l.s^{-1}$)
$PEFV_{25}$	idem, measured from partial flow-volume curve ($l.s^{-1}$).
TD	threshold dose: dose which causes a 2 SD change from mean initial lung function value
PD	provocative dose: dose which causes an arbritrary percentage change from mean initial lung function value

Introduction

Increased bronchial responsiveness (BR) to nonspecific bronchoconstricting agents is generally regarded as a characteristic of asthma (2). The degree of BR is calculated from a dose-response curve to a bronchoconstricting agent. From this curve the following indices can be derived: 1. threshold dose (TD): lowest dose which causes a significant change (2SD) of baseline airway calibre; 2. provocative dose (PD), dose which causes a predetermined change of baseline airway calibre. TD and PD depend on the methods used to measure airway calibre (14).

With the forced pseudo-random noise oscillation technique (FOT) the impedance of the respiratory system can be measured over a frequency spectrum of 2-26 Hz.

The impedance of a network made up of resistive and reactive elements, such as occurs in the respiratory system, is composed of two parts: a real part or resistance R_{rs} and an imaginary part or reactance X_{rs}. In the lung the first is mainly determined by the frictional pressure losses due to airflow within the airways. Hence it is largely dependent on the diameter of the airways and only to a limited degree on the resistance of the lungs and chest wall. The second is mainly determined by the compliant properties of the chest-lung system and by the inertance of lung tissue, chest wall and air within the bronchi (10,18). In this study we define indices obtained by multiple frequency oscillometry (3,4) which can be used to measure TD and PD in asthmatics and compare these to indices derived from maximum and partial expiratory flow-volume curves.

Patients and methods

Methacholine bromide in unbuffered saline was used as bronchoconstricting agent. It was administered with a DeVilbiss nebulizer type 646 to which a Rosenthal-French dosimeter was connected (3). This device delivers a constant amount of solution to the mouth. The dosimeter is triggered by inhalation from FRC level to TLC. Compressed air at 20 p.s.i. was connected to the input valve and the timing adjustment of the dosimeter was 0.6 seconds. Five microlitres were delivered per breath. Each provocation dose consisted of 4 consecutive inhalations. The administered doses of methacholine were 0.25, 0.50,1,2,4,8,16,32,64 and 128 x 10^{-5} gram. Physiological saline was inhaled before methacholine in order to exclude non-specific responses. The challenge was preceded by 5 consecutive FOT measurements and flow-volume recordings. Methacholine-induced bronchoconstriction was reversed by inhalation of 4 x 10^{-4} g fenoterol by metered dose inhaler.

Maximum (MEFV) and partial (PEFV) flow-volume curves were used. The maximum curves were computed from the best 3 out of 5 expirations by superimposing the breaths at TLC. Partial flow-volume curves were derived as follows: the subject slowly expired to RV and then slowly inspired to about 50% of the FVC as measured with the MEFV. The child then expired as fast as possible to RV. The PEFV manoeuvre was performed after about 30 seconds quiet breathing. PEFV curves were superimposed at RV. We assumed that RV did not differ between the two expiratory manoeuvres. FEV_1 was calculated by the computer from the MEFV curve as the difference in volume between the beginning of expiration and 1 second thereafter.
$MEFV_{25}$ and $PEFV_{25}$ are the flows derived from MEFV and PEFV curves respectively; they are determined at a lung volume when 25% of the largest control FVC remains to be exhaled. We report the largest flows.

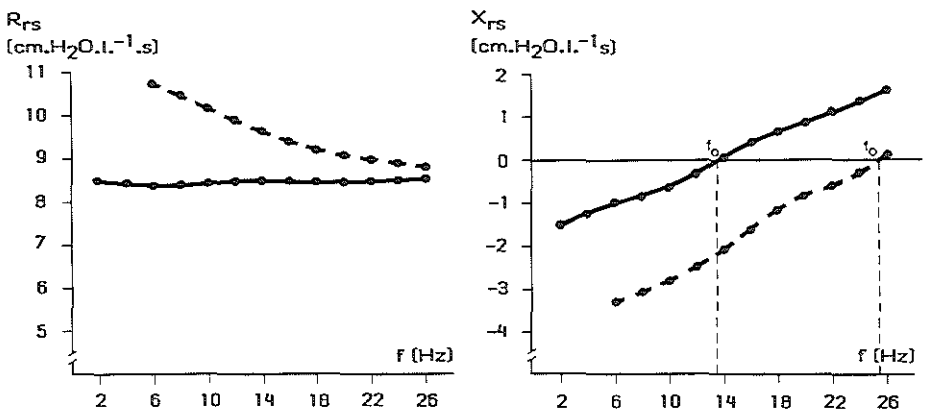
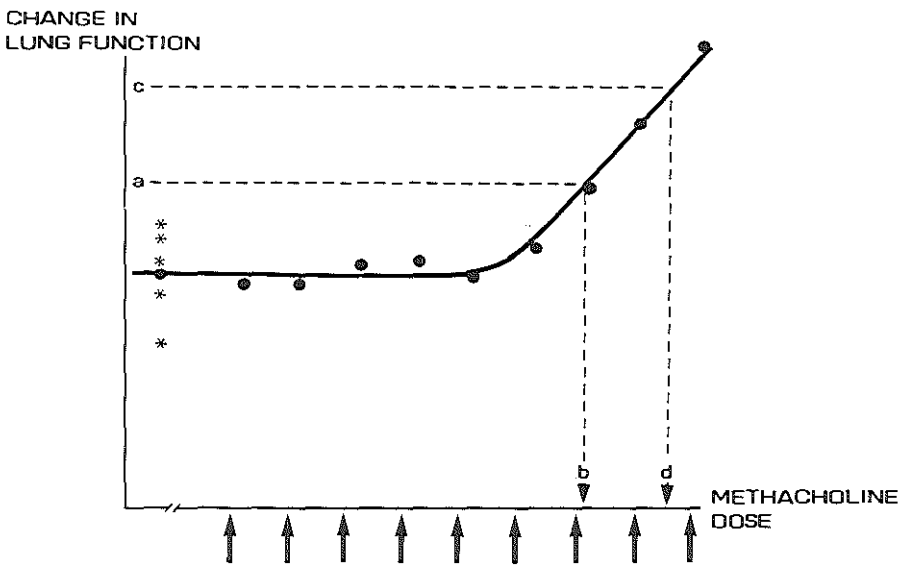


Figure 1. Example plot of R_{rs} and X_{rs} vs. frequency in baseline (——) and bronchoconstricted (----) condition (f_o = resonance frequency).

The forced pseudo-random noise oscillation technique (FOT) has been described in detail elsewhere (18,19).The cheeks and mouth floor of the seated child are held by the investigator. The child breathes quietly through a pneumotachograph. A pseudo-random noise pressure signal, containing all harmonics of 2-26 Hz (peak-to peak amplitude smaller than 0.2 kPa) is applied at the mouth by means of a loudspeaker. Mouth pressure and flow signals, recorded by two identical differential transducers (Validyne MP 445), are fed into a Fourier analyzer. The latter performs an ensemble averaging over a time interval of 16 seconds and calculates the impedance of the respiratory system at 2,4,6,.....24,26 Hz. From FOT $\overline{R_{rs}}$, R_{rs6}, $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$ (see list of abbreviations) were simultaneously obtained by on-line analysis of the oscillatory signals as described elsewhere (4,10). These indices were chosen because they can be considered to be the most characteristic of FOT (10).



a. 2 SD change in lungfunction
b. Methacholine threshold dose
c. Change in lung function which is the criterium for the methacholine provocative dose
d. Methacholine provocative dose

Figure 2. A smoothed dose-response curve reflecting the change in lung function (R_{rs6}) resulting from inhalations of sequential doses of methacholine bromide plotted on a log scale. (*consecutive baseline measurements; .• mean values).

In figure 1 an example plot of R_{rs} and X_{rs} versus oscillation frequency is shown. In normal conditions in adults R_{rs} values do not change with increasing oscillation frequencies. Following bronchoconstriction R_{rs} values increase mainly at low frequencies, resulting in a frequency dependence of R_{rs}. This means that R_{rs} values decrease with increasing oscillation frequency. Frequency dependence of R_{rs} ($\overline{dR_{rs}/df}$) can be quantified as the mean value of the first derivative of R_{rs} versus frequency computed over the investigated 4-26 Hz interval (10). All these frequencies are included in this calculation.

X_{rs} values are always frequency dependent, and decrease during bronchoconstriction. In order to anticipate possible bronchoconstriction caused by maximum inspiration, FOT always preceded MEFV and PEFV manoeuvres. Mean values of 3 technically satisfactory measurements were taken to construct dose-response curves. This was performed by plotting lung function data against log dose of methacholine and linear interpolation of data points (figure 2). From the 5 measurements which preceded the challenge (control measurements), mean baseline values and their SD were calculated for each lung function parameter. TD was defined as the calculated dose of methacholine which caused a 2 SD change from baseline lung function (8). PD_{20} FEV_1 was defined as the dose of methacholine which caused a 20 per cent fall in FEV_1 (2). PD_{40} $MEFV_{25}$ and PD_{40} $PEFV_{25}$ were defined as the doses of methacholine which caused a 40 percent fall in $MEFV_{25}$ and $PEFV_{25}$ respectively (8). PD_{40} $\overline{R_{rs}}$ and PD_{40} R_{rs6} were defined as the doses which caused a 40 per cent increase in $\overline{R_{rs}}$ and R_{rs6} respectively (9). PD $\overline{dR_{rs}/df}$ and PD $\overline{X_{rs}}$ could not be defined.

Patients were recruited from the outpatient clinic of the Sophia children's hospital Rotterdam. 20 asthmatics aged 9.1 to 16.2 years (mean 12.5 years) were investigated. They were in a stable clinical condition at the moment of the test. Medication, if any, was stopped one day before. Informed consent was obtained from all patients. The study was approved by the local medical ethics committee.

Statistical analysis

Analysis of variance (Signed rank test) was used to compare the differences of TD and PD values obtained by different lung function methods. Differences were considered significant if the p values were less than 5 per cent. Linear regression analysis was used to compare log TD and log PD for each lung function index.

Results

Within-patient mean baseline values and mean coefficients of variation of the different indices are shown in table 1.

TD and PD were closely correlated, with coefficients of correlation ranging from 0.79 to 0.97 ($p<0.01$) (table 2). TD was significantly more sensitive to measure methacholine-induced bronchoconstriction than PD.

Figure 3 shows the range and median values of all lung function indices. Median values of TD were lower than median values of PD with the exception of median TD $MEFV_{25}$ which was equal to median PD_{40} R_{rs6}. Median TD values ranged between 2 x 10^{-5} g histamine (TD $\overline{X_{rs}}$) and 4 x 10^{-5} g histamine (TD $MEFV_{25}$), with lower limits between 0.18 x 10^{-5} g histamine (TD $\overline{dR_{rs}/df}$, TD R_{rs6} and TD $\overline{R_{rs}}$) and 0.73 x 10^{-5} g histamine (TD FEV_1). Differences between TD expressed as p values of significance are shown in table 3. TD $\overline{X_{rs}}$ was significantly lower than TD R_{rs6}, TD $\overline{R_{rs}}$, TD $PEFV_{25}$ TD $MEFV_{25}$ and TD FEV_1. Although TD $\overline{X_{rs}}$ was also lower than TD $\overline{dR_{rs}/df}$ the difference was not significant.

PD_{40} R_{rs6} was significantly lower than PD_{40} $\overline{R_{rs}}$ to detect methacholine-induced bronchoconstriction ($p<0.05$). Although PD_{40} R_{rs6} was also lower than PD_{40} $MEFV_{25}$, PD_{40} $PEFV_{25}$ and PD_{20} FEV_1 differences between these indices were not significant.

Median PD values ranged between 4×10^{-5} g histamine (PD_{40} R_{rs6}) and 13×10^{-5} g histamine (PD_{40} $\overline{R_{rs}}$), with lower limits between 0.6×10^{-5} g histamine (PD_{40} R_{rs6}) and 2×10^{-5} g histamine (PD_{40} $\overline{R_{rs}}$).

The range of TD and PD values is large and there is considerable overlap between the various lung function indices.

Table 1. Mean baseline values and mean coefficients of variation of the measured lung function indices (n = 20). Coefficients of variation (standard deviation ÷ mean) of $\overline{X_{rs}}$ and $\overline{dR_{rs}/df}$ are high because their mean values approximate zero.

Baseline value	FEV_1 % predicted	$MEFV_{25}$ % predicted	$PEFV_{25}$ % predicted	$\overline{R_{rs}}$ $cm.H_2O.$ $l^{-1}.s$	R_{rs6} $cm.H_2O.$ $l^{-1}.s$	$\overline{dR_{rs}/df}$ $cm.H_2O.$ $l^{-1}.s^2$	$\overline{X_{rs}}$ $cm.H_2O.$ $l^{-1}.s$
Mean	85.6	74.9	67.8	5.24	5.81	–0.05	–0.34
SD	15.6	30.0	27.0	1.31	1.61	0.07	0.71
Coefficient of variation (%) within individuals	FEV_1	$MEFV_{25}$	$PEFV_{25}$	$\overline{R_{rs}}$	R_{rs6}	$\overline{dR_{rs}/df}$	$\overline{X_{rs}}$
Mean	4.2	11.2	14.6	9.7	11.1	69.5	83.8
SD	3.1	6.8	6.5	3.8	4.7	114.4	103.7

Table 2. Coefficients of correlation (r) and p values of linear regression analysis of TD on PD of various lung function indices to detect methacholine-induced bronchoconstriction.

	r*	p
FEV_1	0.79	< 0.01
$MEFV_{25}$	0.88	< 0.01
$PEFV_{25}$	0.93	< 0.05
$\overline{R_{rs}}$	0.86	< 0.01
R_{rs6}	0.97	< 0.01

*All r values are highly significant ($p < 0.001$)

Table 3. p values of analysis of variance (signed rank test) of various TD indices to detect methacholine-induced bronchoconstriction.

	TD $\overline{X_{rs}}$	TD $\overline{dR_{rs}/df}$	TD R_{rs6}	TD $\overline{R_{rs}}$	TD $PEFV_{25}$	TD $MEFV_{25}$	TD FEV_1
TD FEV_1	$p<0.02$	NS	NS	NS	NS	NS	
TD $MEFV_{25}$	$p<0.01$	NS	NS	NS	NS		
TD $PEFV_{25}$	$p=0.02$	NS	NS	NS			
TD $\overline{R_{rs}}$	$p<0.01$	$p=0.02$	$p<0.02$				
TD R_{rs6}	$p<0.01$	NS					
TD $\overline{dR_{rs}/df}$	NS						
TD $\overline{X_{rs}}$							

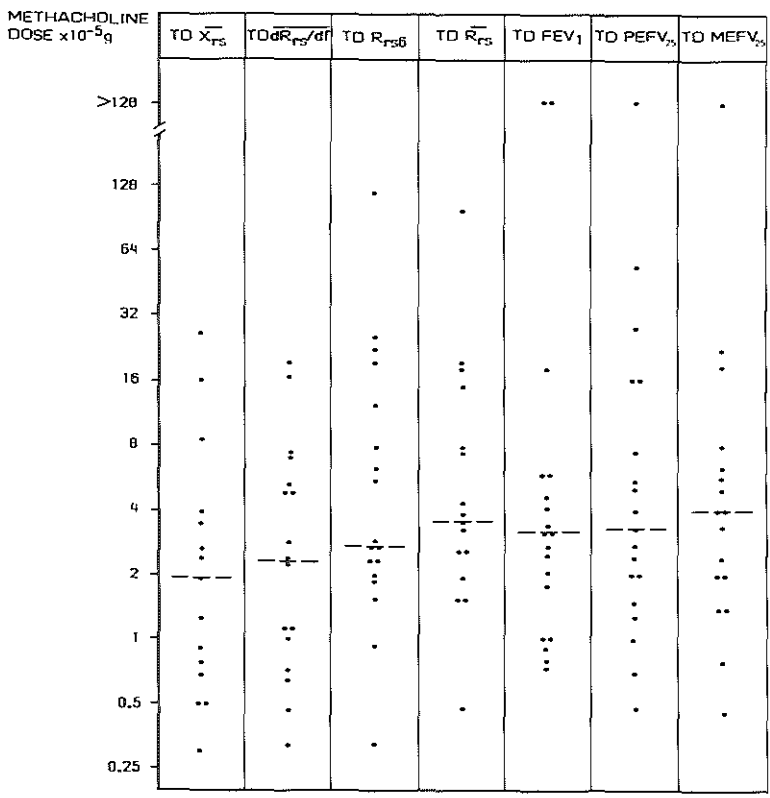


Figure 3.a Methacholine challenge measured by forced pseudo-random noise oscillometry ($\overline{X_{rs}}$, $\overline{dR_{rs}/df}$, R_{rs6}, $\overline{R_{rs}}$) and flow-volume curves ($MEFV_{25}$, $PEFV_{25}$, FEV_1). (--- meadian value) (TD values).

a decrease in X_{rs} will occur only in the presence of different time constants between the two alveolar compartments, i.e. in the periphery of the lungs. In Mead's model airways are regarded as more than simple conduits; they are mechanically in series with the airspaces they supply. As expanding structures they are mechanically in parallel with the airspaces; their expansion makes a separate contribution to the total expansion of the lungs. Under static conditions this contribution is small, but under dynamic conditions this can become appreciable. This is the case when airspace filling is slowed by increases of airway resistance. If this increase is in the peripheral airways a marked discrepancy between the speed of filling of the airways and airspaces can develop due to different time constants of the airways. This will cause frequency dependence of resistance and compliance. We assume that frequency dependence of R_{rs} indicates peripheral airways obstruction. As compliance and X_{rs} are inversely related (18) a decrease in compliance is the same as an increase in X_{rs}. The theoretical model of Mead was confirmed by Kjeldgaard et al. (17) who found a good correlation between frequency dependence of compliance and frequency dependence of total respiratory resistance measured by forced oscillations.

$PEFV_{25}$ and $MEFV_{25}$ are generally regarded as sensitive indices of airways obstruction (24). TD indices obtained by FOT proved to be equally or even more sensitive than TD indices derived from flow-volume curves. The same applies to PD_{40} R_{rs6}. Recently, Solymár et al. (23) came to the same conclusion using a different oscillation technique.

We found no differences between $MEFV_{25}$ and $PEFV_{25}$ to detect methacholine-induced bronchoconstriction in asthmatic children. In many adult asthmatics deep inspiration induces transient bronchoconstriction (15,21). Partial flow-volume curves, which do not require a previous deep inspiration (1), do not influence bronchomotor tone. In asthmatic children deep inspiration does not seem to influence bronchial smooth muscle tone so often as it does in asthmatic adults.

FOT measurements are performed during quiet spontaneous breathing; hence indices obtained by FOT can be compared in this sense with indices derived from PEFV curves. FOT proved to be even more sensitive to detect induced bronchoconstriction than $PEFV_{25}$.

With FOT, bronchial responsiveness to non-specific bronchoconstricting agents and allergens can be assessed in children from the age of about 3 (10), as well as in subjects in whom forced expirations cannot be obtained in a reproducible way (21). Calculation of TD with FOT necessitates the use of an on-line microprocessor to facilitate the calculation of the results since analysis of individual R_{rs} and X_{rs} vs frequency curves by hand is time consuming. If a microprocessor is not available, calculation of PD_{40} R_{rs6} is a good alternative. This correlates well with PD_{20} FEV_1. The sensitivity of PD_{40} R_{rs6} to detect induced bronchoconstriction is at least as good as that of PD_{20} FEV_1, PD_{40} $MEFV_{25}$ and PD_{40} $PEFV_{25}$.

In a study on a limited number of healthy children, 5.5 - 8.5 years of age, without a family history of asthma or atopic disease we found median TD values ranging between 32 and 64 x 10^{-5} g histamine with lower limits between 8 and 16 x 10^{-5} g. Median PD values were higher than 128 x 10^{-5} g histamine with lower limits of 64 x 10^{-5} g histamine (12, 13).

Conclusion

For clinical practice PD_{40} R_{rs6} has proven to be a reproducible and sensitive FOT index to define BR. It is highly correlated with PD_{20} FEV_1, which is generally accepted as an index to define BR. TD $\overline{dR_{rs}/df}$ detects bronchoconstriction after inhalation of a lower dose of methacholine than TD R_{rs6} or TD $\overline{R_{rs}}$. R_{rs} values are mainly determined by the diameter of the central airways. It is assumed that $\overline{dR_{rs}/df}$ is determined by the diameter of the peripheral airways. Although TD $\overline{X_{rs}}$ proved to be the most sensitive index to detect induced bronchoconstriction we prefer the use of TD $\overline{dR_{rs}/df}$, because X_{rs} is not only influenced by elastic properties of lung tissue and chest wall but also by mass-inertial properties of air within the central airways, while $\overline{dR_{rs}/df}$ is a measure of peripheral airways obstruction only. FOT is a suitable lung function method that can easely be performed in children from about 2 years age, who are not yet able to perform forced expiratory manoeuvres in a reproducible way. The possibility of measuring R_{rs} as well as frequency dependence of R_{rs} and X_{rs} simultaneously is the major advantage over other oscillation devices.

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CHAPTER 6. BRONCHIAL RESPONSIVENESS IN ASTHMATIC CHILDREN AGED 3 TO 8 MEASURED BY FORCED PSEUDO-RANDOM NOISE OSCILLOMETRY

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Abstract

With the forced pseudo-random noise oscillation technique (FOT) resistance (R_{rs}) and reactance (X_{rs}) of the respiratory system can be measured simultaneously over a frequency spectrum of 2-26 Hz. As only passive cooperation of the child is needed FOT is suitable for lung function measurements from the age of 2½. Hence bronchial responsiveness (BR) can be measured in children who are not yet able to perform spirometry or flow-volume curves. We compared BR to histamine and methacholine obtained with FOT. Threshold dose (TD) or provocative dose (PD) to histamine and methacholine showed a close correlation in asthmatic children aged 3.6 to 7.8 years. The 24 hour interval within-subject reproducibility of TD and PD to histamine in asthmatic children aged 3.9 to 8.5 years proved to be good. BR to histamine or methacholine measured by FOT was not influenced by baseline lung function or by bronchial smooth muscle tone.

List of abbreviations

BR	bronchial responsiveness
BHR	bronchial hyperresponsiveness
FRC	functional residual capacity (l)
TLC	total lung capacity (l)
MEFV	maximum flow-volume curve; $MEFV_{25}$: flow when 25% of the FVC remains to be exhaled ($l.s^{-1}$)
PEFV	partial flow-volume curve; $PEFV_{25}$: flow when 25% of the FVC remains to be exhaled ($l.s^{-1}$)
FOT	forced pseudo-random noise oscillation technique
$\overline{R_{rs}}$	mean value of resistance of the respiratory system (R_{rs}) measured at frequencies of 2-26 Hz ($cm.H_2O.l^{-1}.s$)
R_{rs6}	R_{rs} measured at 6 Hz oscillation frequency ($cm.H_2O.l^{-1}.s$)
dR_{rs}/df	frequency dependence of R_{rs}
$\overline{dR_{rs}/df}$	mean slope of R_{rs} vs. frequency; ($cm.H_2O.l^{-1}.s^2$)
$\overline{X_{rs}}$	mean value of reactance of the respiratory system (X_{rs}) measured at frequencies of 2-26 Hz ($cm.H_2O.l^{-1}.s$)

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TD	threshold dose; dose which causes a 2 SD change from mean baseline lung function value
PD	provocative dose; dose which causes a predetermined percentage change from mean baseline lung function value.

Introduction

Increased bronchial responsiveness (BR) to a variety of stimuli is a characteristic of asthma (1,12,16,25). Bronchial inhalation challenge is therefore used as a laboratory test for the diagnosis and assessment of patients with asthma, to study risk factors in lung disease, and as a guideline for treatment (12,16,19). Nonspecific responsiveness can be quantified by the inhalation of histamine or methacholine. The results are influenced by a variety of technical factors that require standardization (15,26,28,34). To measure BR in young children a suitable lung function method must be available. The forced pseudo-random noise oscillation technique (FOT) is a suitable method for preschool children as only passive cooperation is needed (13).

We compared the effect of bronchial challenge with histamine and methacholine delivered by a dosimeter (4,7) on lung function measured by FOT (13,21) in asthmatic children aged 3.6 to 7.8.

The 24 hours within-subject reproducibility of BR to histamine was investigated in another group of asthmatic children aged 3.9 to 8.5.

Patients and methods

- group 1. Histamine and methacholine challenges were performed in a randomised sequence on 2 consecutive days at the same time in the morning (9.00 a.m.) in 19 asthmatic children aged 3.6 to 7.8 (mean 5.4 years).
- group 2. The 24 hours within-subject reproducibility of BR to histamine was investigated in 21 asthmatic children aged 3.9 to 8.5 (mean 6.0 years).

Patients studied were recruited from the outpatient clinic of the Sophia Children's Hospital Rotterdam. They were in a stable clinical condition at the time of the measurements. Medication, if any, was stopped at least 1 day before. Informed consent was obtained for all patients.

Histamine and methacholine were delivered to the mouth by a Rosenthal-French dosimeter (4) which was connected to a DeVilbiss nebulizer type 646. The nebulizer was operated by compressed air at 20 p.s.i. The timing adjustment of the dosimeter was 0.6 seconds. Each provocation dose was given in 4 inhalations of 5 microlitres. Doses of histamine biphosphate and methacholine bromide in physiologic saline given with 5 minutes intervals, were 0.25, 0.5,1,2,4,8,16, 32,64 and 128 x 10^{-5} g. Physiologic saline solution was inhaled before histamine or methacholine to detect non-specific responses. Lung function was measured by FOT (13,21). With FOT resistance (R_{rs}) and reactance (X_{rs}) of the respiratory system are recorded simultaneously over a frequency spectrum of 2 to 26 Hz. R_{rs}

is mainly determined by the patency of the central airways, X_{rs} is influenced by elastic properties of lung tissue and chest wall and by mass-intertial properties of air within the central airways (21).

Frequency dependence of R_{rs} (dR_{rs}/df) can be calculated because a range of frequencies is applied within a few seconds. dR_{rs}/df is a sensitive index of uneveness of ventilation. It is mainly determined by the patency of the peripheral airways (23). $\overline{R_{rs}}$, R_{rs6}, $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$ (see list of abbreviations) were simultaneously obtained by on-line analysis of the oscillatory signals as described elsewhere (11,13). These measures were chosen because they can be considered to be the most characteristic of FOT (13). Each challenge was preceded by 5 consecutive FOT measurements from which the mean baseline values and their standard deviations (SD) were calculated. The mean of 3 technically satisfactory FOT measurements was taken to construct a dose-response curve. Threshold dose (TD) and provocative dose (PD) were calculated from the dose-response curves by linear interpolation. TD is defined as the dose of histamine or methacholine which causes a 2 SD change, while PD is defined as the dose which causes a predetermined percentage change from mean baseline lung function (22). This percentage change is usually based on the coefficient of variation of the lung function parameter used. There are two reasons why the coefficient of variation is not a good measure of variability for $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$. Firstly, the coefficient of variation can only be used if the variability is proportional to the measured value. For $\overline{R_{rs}}$ and R_{rs6} this is valid, but for $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$ it is not (13). Secondly, $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$ approximate zero as either a negative or a positive value. Hence, the coefficients of variation are high (14). Therefore PD $\overline{dR_{rs}/df}$ and PD $\overline{X_{rs}}$ can hardly be defined. FOT indices could not be calculated in every child because technical statisfactory dose response curves were not always obtained. TD or PD to histamine and methacholine were only calculated if baseline lung function values and the reproducibility of the 5 consecutive baseline measurements (i.e. a coefficient of variation of R_{rs6} less than 12 percent) (14) were comparable on both days. Bronchial challenge was ended after inhalation of 128×10^{-5} g histamine or methacholine or after PD had been obtained. Induced bronchoconstriction was reversed by 2×10^{-4} g fenoterol and 0.2×10^{-4} g ipratropium bromide by metered dose inhaler.

The study was approved by the local medical ethics committee.

Statistical analysis

Wilcoxon's paired signed rank test (31) was used to compare mean individual baseline lung function values on the two test days as well as the effect of bronchodilatation. The within-subject 24 hours interval variability of BR to histamine and methacholine and the reproducibility of BR to histamine were evaluated using the two-way analysis of variance. The contributions to the total variability of the measurements are quantified through analysis of variance according to the model shown below (32).

Source of variation	DF (= degrees of freedom)
Between subjects	n−1
Between days	1
Residual variability	n−1
Total	2n−1

The factor subjects is considered to be random, whereas the factor days is considered as fixed (possible systematic drift). The reproducibility of the measurements is expressed as a standard deviation of the log value (SD repr.). This is obtained from residual variability to which the between-days variability may be added, unless the latter turns out to be consistently statistically significant (32). For a single individual the variability between independently repeated measurements can be characterized as to be on average within ± 2 SD repr. of the overall mean value for that individual in about 95% of measurements.

Results

Baseline functions

Individual baseline values of $\overline{R_{rs}}$, R_{rs6}, $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$ on the two occasions, expressed as standard scores (ss) (i.e. mean measured value minus mean expected values divided by the standard deviation of the mean expected value) for both groups of asthmatic children are shown in table 1. Baseline values were not different between both days ($p > 0.05$). All indices improved significantly after bronchodilatation ($p < 0.05$).

Variability of BR to histamine and methacholine

Individual data of TD and PD to histamine and methacholine are shown in figure 1. The between-days variability did not differ significantly ($p > 0.05$) from the residual variability. Hence they were taken together. The within-subject variability expressed as a standard deviation, which represents the reproducibility between days and within days, is displayed in table 2. Although TD and PD values were often lower for methacholine than for histamine this was only significant for TD $\overline{R_{rs}}$ ($p > 0.05$). TD and PD values were not significantly related to baseline values of lung function or to bronchial smooth muscle tone (difference between baseline lung function before and after bronchodilatation). In figure 2 this is shown for BR to histamine measured by PD_{40} R_{rs6}.

24 hours interval within-subject reproducibility of BR to histamine

Individual data of TD and PD to histamine are shown in figure 3. The between-days variability did not significantly ($p > 0.05$) differ from the residual

variability. Hence they were taken together. The within-subject reproducibility expressed as a standard deviation is displayed in table 2.
TD and PD were not related to baseline values of lung function or to bronchial smooth muscle tone.

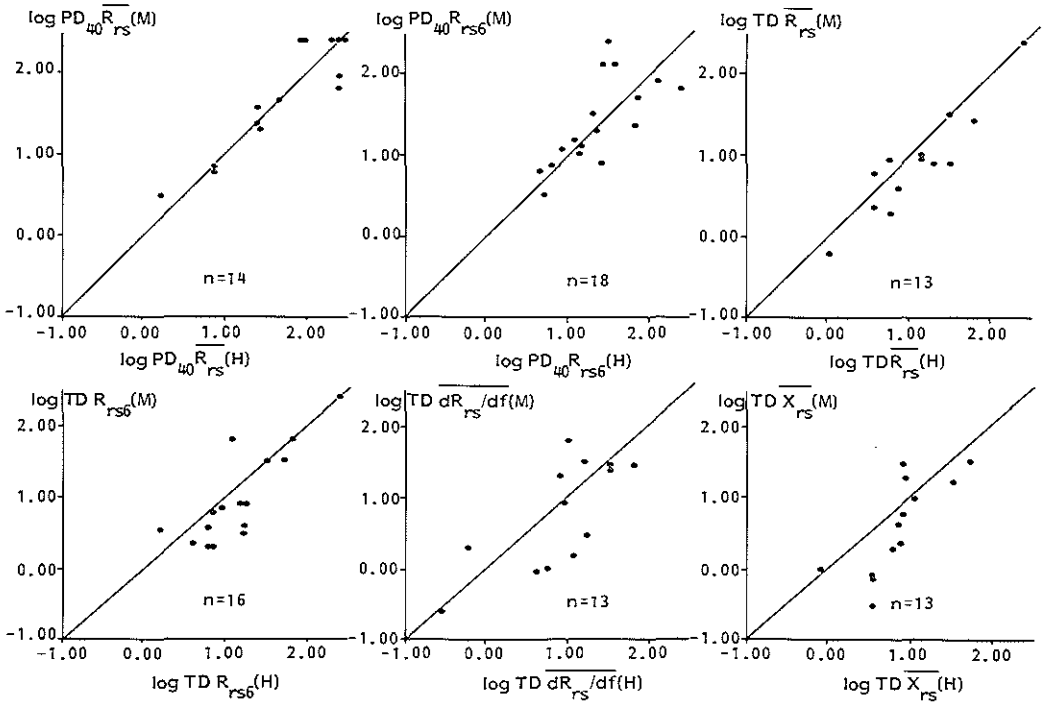

Figure 1. BR to histamine and methacholine on two consecutive days in preschool asthmatics measured by FOT. TD $\overline{X_{rs}}$, TD $\overline{dR_{rs}/df}$, TD R_{rs6}, TD $\overline{R_{rs}}$, PD_{40} R_{rs6} and PD_{40} $\overline{R_{rs}}$ ($x10^{-5}$ g) see list of abbreviations. TD and PD values could not be calculated in all cases because of technical reasons. TD and PD are shown on a log scale (—— = line of identity).

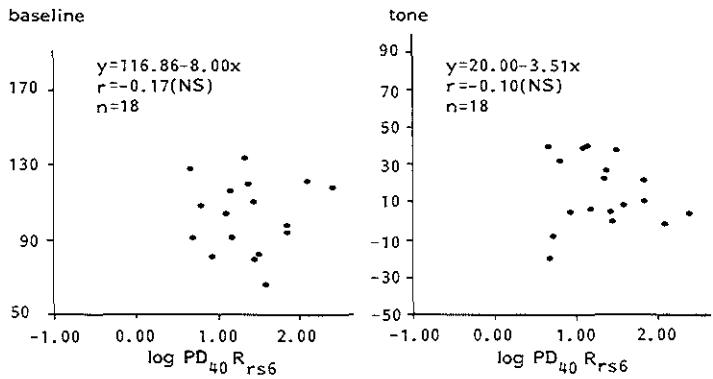

Figure 2. Influence of baseline airway calibre and bronchial smooth muscle tone measured by R_{rs6} (see list of abbreviations) on BR calculated by PD_{40} R_{rs6} ($x10^{-5}$ g). These data are representative for other FOT indices as well.

Table 1. Baseline lung function values on both occasions, measured by FOT and expressed as standard scores (ss) from predicted (13).

Group 1

	$\overline{R_{rs}}$(ss)		R_{rs6}(ss)		$\overline{dR_{rs}/df}$(ss)		$\overline{X_{rs}}$(ss)	
	H	M	H	M	H	M	H	M
1	3.35	2.93	2.05	1.40	–1.65	–0.83	–2.36	–1.82
2	–0.18	–0.14	–0.25	–0.28	–0.50	–0.33	1.44	1.14
3	–0.61	–0.51	0.13	0.41	–2.48	–2.81	–1.03	–1.17
4	0.36	0.02	0.74	0.60	–1.65	–1.49	0.66	0.91
5	0.81	0.77	1.22	0.84	–2.31	–1.98	0.53	0.04
6	0.10	0.18	0.84	0.70	–2.48	–2.48	–1.36	–1.62
7	–0.05	–0.22	0.23	0.02	–1.49	–1.32	–0.29	–0.35
8	0.02	0.05	–0.20	–0.10	–0.50	–0.50	1.91	1.73
9	–2.42	–2.42	–2.15	–2.18	–0.33	–0.33	2.05	2.00
10	0.58	0.65	0.78	0.69	–1.98	–1.49	0.12	–0.32
11	–0.99	–0.99	–0.75	–0.69	–0.83	–0.82	0.49	0
12	–0.19	–0.32	0.42	–0.68	–1.32	–2.31	0.21	–0.13
13	1.11	1.18	1.67	1.39	–0.83	–1.49	1.78	1.40
14	–1.10	–0.98	–0.83	–0.90	–0.83	–0.83	0.40	0.08
15	0.40	0.58	1.31	1.26	–3.47	–3.30	–2.49	–1.84
16	–0.58	–0.60	–0.16	–0.36	–1.98	–1.82	0.99	0.55
17	1.17	1.49	1.64	2.04	–2.64	–3.30	–0.75	–1.57
18	–0.31	–0.13	0.27	0.23	–2.15	–1.98	–0.05	–0.29
19	–1.74	–1.55	–1.33	–1.08	–1.82	–2.15	1.71	0.56

Group 2	$\overline{R_{rs}}$(ss)		R_{rs6}(ss)		$\overline{dR_{rs}/df}$(ss)		$\overline{X_{rs}}$(ss)	
	day 1	day 2	day 1	day 2	day 1	day 2	day 1	day 2
1	–0.84	0.09	–0.92	–0.02	–0.33	0	–0.47	–0.21
2	1.03	1.23	1.11	1.54	–1.32	–2.15	–1.40	–2.36
3	–0.34	0.24	–0.87	0.15	0.33	–0.33	–0.51	–0.71
4	0.84	0.89	1.01	2.40	–1.65	–4.13	–0.16	–2.68
5	0.08	0.10	2.07	1.04	–1.82	–1.98	–3.85	–3.77
6	2.48	2.09	4.38	3.41	–5.12	–2.97	–5.89	–3.78
7	2.19	1.03	2.94	1.95	–2.48	–2.64	–3.21	–1.28
8	0.77	0.18	0.34	0.57	0.99	–0.66	1.27	1.54
9	2.09	1.81	2.73	2.17	–2.81	–2.48	–1.42	–1.57
10	–0.92	–0.82	–0.44	–0.40	–0.83	–0.99	0.49	0.81
11	0.18	2.62	1.31	3.03	–2.48	–1.49	–1.03	–0.88
12	1.05	1.03	1.31	1.23	–1.16	–1.16	0.35	0.52
13	0.36	0.65	0.14	0.74	0.33	–0.66	1.39	0.78
14	1.62	2.01	1.66	2.14	0.17	–0.50	0.01	1.13
15	0.75	0.32	1.25	1.39	–2.15	–3.30	–0.99	–1.36
16	–0.77	–0.81	–0.66	–0.62	–0.33	–0.50	–0.23	–0.05
17	2.21	1.56	2.83	3.20	–1.82	–3.96	–4.68	–6.60
18	0.70	0.48	0.58	0.81	0.17	–0.33	0.30	–0.58
19	–1.27	–1.31	–1.06	–1.26	0.17	–0.33	0.48	0.74
20	0.97	0.28	0.75	0.11	–0.17	–0.33	–0.23	0.70
21	2.99	0.84	4.13	0.98	–3.80	–0.17	–2.51	–1.75

Table 2. Within-subject 24 hour interval variability of BR to histamine and methacholine and reproducibility of BR to histamine expressed as a standard deviation. (SD repr.) of individual average measurement values (log scale), meaning that for one individual the variability between independently repeated measurements can be characterized as to be on average within ± 2 SD repr. of the overall mean value for that individual in about 95% of measurements.
Statistical analysis by two way analysis of variance (DF = degrees of freedom).

	SD reproducibility	
	group 1 histamine-methacholine	group 2 histamine-histamine
$\log PD_{40}$ $\overline{R_{rs}}$	0.19 ; DF = 14	0.30 ; DF = 17
$\log PD_{40}$ R_{rs6}	0.28 ; DF = 18	0.35 ; DF = 21
logTD $\overline{R_{rs}}$	0.22 ; DF = 13	0.22 ; DF = 17
logTD R_{rs6}	0.28 ; DF = 16	0.28 ; DF = 18
logTD $\overline{dR_{rs}/df}$	0.38 ; DF = 13	0.26 ; DF = 21
logTD $\overline{X_{rs}}$	0.35 ; DF = 13	0.27 ; DF = 19

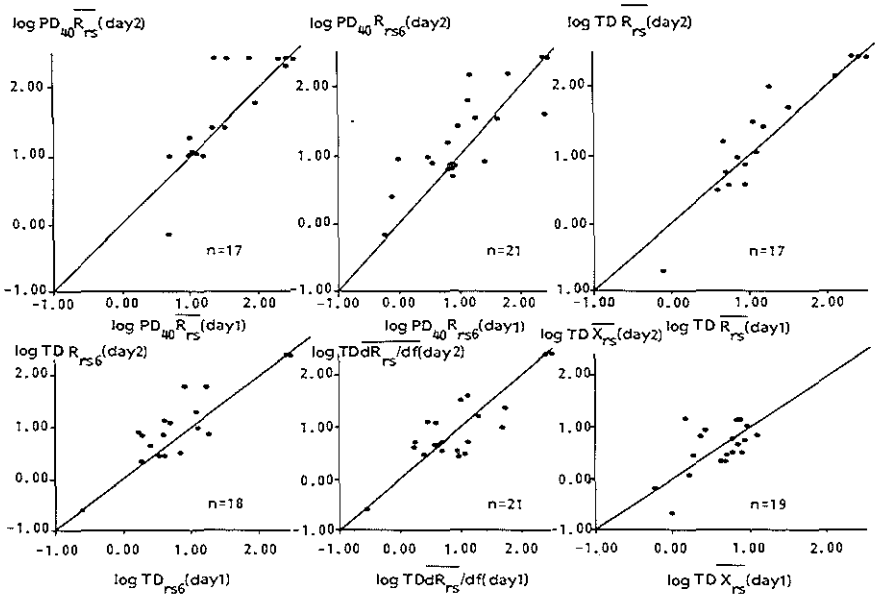

Figure 3. 24 hours interval within-subject reproducibility of BR to histamine measured by FOT. TD and PD values as in figure 1. (—— = line of identity).

Discussion

We compared BR to histamine and methacholine in a group of young asthmatics. Lung function was measured by FOT (13,21). As this demands only passive cooperation of the child the method is suitable in children from the age of about 2. With FOT, resistance of the respiratory system (R_{rs}), frequency dependence of R_{rs} vs. frequency ($\overline{dR_{rs}/df}$) and reactance of the respiratory system (X_{rs}) are measured simultaneously. R_{rs} values are mainly determined by the patency of the central airways, while X_{rs} values are influenced by mass-inertial and elastic properties of lung tissue, chest wall and peripheral airways (21). $\overline{dR_{rs}/df}$ is considered as a sensitive index of unevenness of ventilation (23).

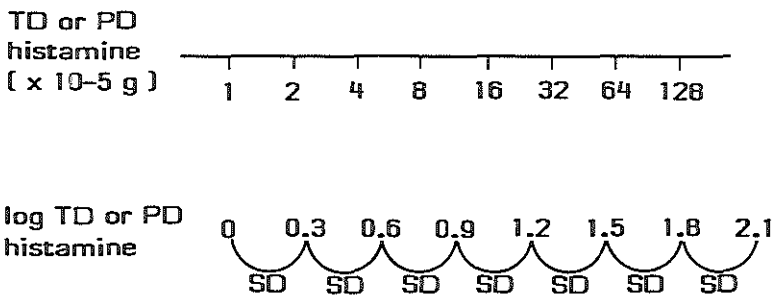

Figure 4. Consecutive doses of inhaled histamine expressed as absolute values and as log values. As the calculated SD of reproducibility of log TD or log PD is about 0.3 this implies that the relative deviations are a factor 2 above or below the observed TD or PD values.

FOT was shown to be as reliable and sensitive as flow-volume curves in detecting induced bronchoconstriction (14). The results of inhalation provocation tests are influenced by a variety of technical factors (15,26,28,34). Both the inspired dose (15) and the distribution area of the aerosol (26,28,34) are important determinants of the response. In adults various techniques of aerosol generation and inhalation give comparable results (28). In young children aerosol delivery by a dosimeter (4,7) is preferable over tidal breathing to obtain the best possible standardization, since the dose inhaled by tidal breathing (26) is rather unpredictable. We assume that mouth deposition of histamine and methacholine was equal on both days, although this does not imply equal deposition in the lungs. The dosimeter was operated during the first part of inspiration by using a timing adjustment which was about half the inspiration time. To enhance lung deposition we asked the children to hold their breath for a few seconds after aerosol delivery.

The definitions of TD and PD imply that TD values are lower than PD values (4). In a previous study (14) we found that PD_{40} R_{rs6} and PD_{40} $\overline{R_{rs}}$ were closely correlated with, and equally sensitive as PD_{20} FEV_1, PD_{40} $MEFV_{25}$ and PD_{40} $PEFV_{25}$ to show induced bronchoconstriction. König et al. (20) have shown that R_{rs6} values were highly correlated with spirometric values in 4-19 years old asthmatics. We found no relationship between baseline lung function or the change in lung function after bronchodilatation and BR. This is in agreement with data Chung and co-workers found in adult asthmatics (9) and healthy individuals (9,10).

We found a close correlation between the effect of histamine and methacholine in most of our asthmatic children 3 to 7 years of age. The standard deviation of the reproducibility of log TD and log PD_{40} values to either histamine or methacholine with a 24 hours interval is about 0.3. This implies that in an individual 95% of the results of repeated measurements will lie between minus or plus 2 times the value of an observed TD or PD value (figure 4). This is in agreement with findings in adult asthmatics (18,29) and healthy persons (2,8) as well as in adults with chronic bronchitis (3). However, some individuals may react differently to histamine and methacholine (5,33). In most patients TD methacholine values were slightly lower than TD histamine values, although differences were only significant for TD $\overline{R_{rs}}$.

Histamine and methacholine challenges were performed in a randomized sequence. Individual and mean baseline lung function as well as the bronchodilating effect of inhaled fenoterol and ipratropium bromide were similar on both days. Hence, the lower TD methacholine values cannot be explained by differences in baseline airway diameter or bronchial smooth muscle tone. The most plausible explanation is that, although both histamine and methacholine may have cumulative effects when inhaled at short intervals (6,35) the effect of a low dose of methacholine is more pronounced in this respect than the effect of a low dose of histamine due to a more protracted duration of the action of methacholine (6). Hence a cumulative effect might become apparent at lower methacholine than histamine dosages. PD methacholine values were not significantly different from PD histamine values. This indicates that after inhalation of higher dosages of methacholine and histamine possible cumulative effects of both agents are equal.

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CHAPTER 7. LUNG FUNCTION AND BRONCHIAL RESPONSIVENESS IN CHILDREN WHO HAD INFANT BRONCHIOLITIS

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Abstract

A number of studies has shown that children who had infant bronchiolitis have an increased risk for recurrent episodes of wheezing. A genetic predisposition to atopy mentioned in some studies is contested by others. Lung function abnormalities and increased bronchial responsiveness (BR) are described after infant bronchiolitis. We investigated children who had had the clinical syndrome of infant bronchiolitis and compared these with asthmatic children and healthy children of the same age as regards baseline lung function, increase of lung function after bronchodilatation and responsiveness to histamine. We found that most children with current symptoms had either abnormal baseline lung function, increased bronchial smooth muscle tone or increased BR. These subjects are comparable to mild asthmatics. The children without current symptoms are comparable to healthy children in these respects. Recurrent respiratory symptoms after bronchiolitis should be regarded as mild asthma and treated as such.

List of abbreviations

BR	bronchial responsiveness
FOT	forced pseudo-random noise oscillometry
PD	provocative dose; dose which causes an arbritrary percentage change from mean baseline lung function value
R_{rs6}	resistance of the respiratory system measured by FOT at 6 Hz oscillation frequency ($cm.H_2O.l^{-1}.s$)
$\overline{dR_{rs}/df}$	frequency dependence of R_{rs} calculated over the complete frequency spectrum ($cm.H_2O.l^{-1}.s^2$)
ss	standard score

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2. Paper submitted for publication.

Introduction

The relationship between the occurrence of infant bronchiolitis and recurrent wheezing in childhood has been examined in a number of studies (1,2,3,4,5). Most of these have shown that children who had infant bronchiolitis have an increased risk for recurrent episodes of wheezing. Although some have contested this thesis (6,7) it appears that infants with a genetic predispostion to atopy are more likely to wheeze with respiratory viral infections (i.e. Respiratory Syncytial virus)(8). Much controversy exists about the nature of bronchiolitis (4,5). Bronchiolitis, per se, might contribute to the development of subsequent wheezing, or illness diagnosed as bronchiolitis may be an early marker of asthma.

Total respiratory resistance by forced oscillations in infants during the acute phase of bronchiolitis was found to be increased (9). Although recovery from bronchiolitis almost invariably occurs over days or weeks (3), a substantial proportion of the children involved appear to have subsequent episodes of wheeze and cough which may last after the age of about four (3,5,10). Lung function abnormalities may be present in the years after infant bronchiolitis (4,10,11). Even after 10 years Pullan and Hey found signs of residual peripheral airways disease (4). Also increased bronchial responsiveness has been described in children who had infant bronchiolitis (12,13).

We investigated children who had the clinical syndrome of infant bronchiolitis (14) and compared these with asthmatic children of the same age as regards baseline lung function, bronchial smooth muscle tone and bronchial responsiveness to histamine. The aim of the study was to investigate the relationship between infant bronchiolitis and asthma in later life.

Methods

Subjects

16 children, aged 2.6 to 12.8 years who had bronchiolitis in infancy, were investigated after 2.5 to 12.5 years. As infants, aged 1 to 18 months, they were admitted to hospital because of clinical symptoms and signs of bronchiolitis; i.e. tachypnoea, hyperinflation, widespread crepitations, hypercapnia ($pCO_2 > 47$ mm Hg) and hypoxaemia ($pO_2 < 80$ mm Hg). Viral studies were performed in 11 subjects. Positive serology of RS virus was found in 6 and of adenovirus in 1.

42 asthmatic children, aged 3.6 to 8.5 years were studied when in a stable clinical condition. Medication, if any, was stopped at least one day before. They were separated into 2 groups with regard to the severity of the disease. The 27 subjects with periodic symptoms who only needed bronchodilators when symptomatic were classified as mild asthmatics. The 15 who were treated daily with inhaled beta agonists and who often inhaled steroids were classified as severe asthmatics.

Nineteen normal controls aged 5.5 to 8.5 years were recruited from the reference population we investigated before (15). All had a negative current or past history of asthma or other recurrent respiratory disease.

None of the children had an upper respiratory tract infection in the 2 weeks prior to the study.

Written informed consent was obtained from the parents of all children.

History

Medical history of present and past respiratory symptoms as well as a family history concerning asthma or hay-fever in 1st and 2nd degree relatives were obtained from a questionnaire administered by ED (16).

Lung function

Lung function was measured by FOT (15,17,18). During measurements the child is seated behind the apparatus with a mouth piece in the mouth. The nose is clipped and mouth floor and cheeks are fixed to eliminate shunting of airflow to the upper airways. With the forced oscillation technique which we applied the resistance (R_{rs}) and reactance (X_{rs}) of the total respiratory system can be measured simultaneously over a frequency spectrum of 2-26 Hz. R_{rs} is mainly determined by the frictional pressure losses due to airflow within the central airways. Hence, it is largely dependent on the diameter of the central airways and only to a limited degree on the resistance of the lungs and chest wall (17). X_{rs} is mainly determined by the compliant properties of the chest-lung system and by the inertance of lung tissue, chest wall and air within the central airways. Because R_{rs} and X_{rs} are measured over a frequency spectrum the frequency dependence of R_{rs} ($\overline{dR_{rs}/df}$) can be calculated as well (16,17). $\overline{dR_{rs}/df}$ is considered to be a measure of unevenness of ventilation (19). It is mainly determined by the diameter of the peripheral airways (17,19,20). From FOT we selected the resistance of the respiratory system at 6 Hz oscillation frequency (R_{rs6}) as a measure of the patency of the central airways and $\overline{dR_{rs}/df}$ as a measure of the patency of the peripheral airways. R_{rs6} was chosen because 6 Hz oscillation frequency proved to be the lowest frequency with a favourable signal to noise ratio (17) and because this frequency is used in other oscillation techniques as well (10,11).

All children had a physical examination prior to lung function measurements.

Bronchial responsiveness

BR was determined by the inhalation of histamine. Histamine was delivered to the mouth by a Rosenthal-French dosimeter (21) which was connected to a

DeVilbiss nebulizer type 646. The dosimeter was triggered by slow inhalation from FRC to TLC. The nebulizer was operated by compressed air at 20 p.s.i. The timing adjustment of the dosimeter was 0.6 seconds. Each provocation dose was given in 4 inhalations of five microlitres with an interval between doses of at least 5 minutes. Doses of histamine biphosphate in physiologic saline were 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128 x 10^{-5} g. Physiologic saline was inhaled before histamine to exclude non-specific responses. Each challenge was preceded by 5 consecutive FOT measurements from which the mean baseline value was calculated. The mean of the 3 FOT measurements with greatest similarity was taken to construct a dose-response curve.

The provocative dose (PD) was calculated from the dose-response curve by linear interpolation. PD_{40} R_{rs6} is defined as the dose of histamine which causes a 40 per cent increase from mean R_{rs6} baseline value. In a previous study (18) we showed that PD_{40} R_{rs6} is closely correlated with PD_{20} FEV_1 (i.e. the dose of histamine which causes a 20 per cent decrease from mean FEV_1 baseline value) (18). Bronchial challenge was ended after inhalation of 128 x 10^{-5} g histamine or after PD_{40} R_{rs6} had been obtained.

Bronchial smooth muscle tone

About 15 minutes after the completion of the histamine provocation, after baseline had been reached, 2 x 10^{-4} g fenoterol and 0.2 x 10^{-4} g ipratropium bromide were given by metered dose inhaler to obtain bronchodilatation. The difference between baseline lung function and values after bronchodilatation was considered as the degree of reversible bronchial smooth muscle tone.

Mean expected baseline values of R_{rs6} and $\overline{dR_{rs}/df}$ were taken from the reference population we investigated before (15). Reference BR values were obtained from 19 randomly selected healthy children, aged 5.5 to 8.5 years, who were recruited from the population mentioned above (15). Lung function and BR indices were expressed as standard scores (ss); i.e. measured value minus mean expected value divided by the standard deviation of the mean expected value.

Baseline R_{rs6} was called increased if its value was higher than 1.65 ss and $\overline{dR_{rs}/df}$ was called decreased if its value was lower than -1.65 ss (95% unilateral confidence limits) from expected mean (15).

BR was called increased if log PD_{40} R_{rs6} was lower than -1.65 ss from reference BR, i.e. PD_{40} R_{rs6} lower than 30 x 10^{-5} g histamine.

The bronchodilating effect of inhaled fenoterol and ipratropium bromide was called significant with a greater than 1.65 ss change from individual mean baseline.

The study was approved by the local medical ethics committee.

Statistical analysis

The Wilcoxon two sample test was used to analyse differences of mean baseline values, differences in bronchodilatation as well as differences in PD_{40} R_{rs6} to histamine between the groups. Differences were considered significant with p values less than 5 percent.

Results

Symptoms (table 1)

10 of the children who had had bronchiolitis suffered from recurrent respiratory symptoms (i.e. regular episodes of cough and wheeze during respiratory tract infection) at the time of investigation (62.5%) (table 1). 4 had previous symptoms until about 5-6 years of age. 2 children had no recurrent symptoms after the episode of bronchiolitis .

Table 1: Baseline lung function, bronchial smooth muscle tone and bronchial responsiveness according to symptoms and family history of asthma or hay-fever in children who previously had bronchiolitis.

	respiratory symptoms	age at investigation in yrs.	1st or 2nd degree relative with asthma	baseline function (ss)		bronchial smooth muscle tone (change in ss after bronchodilatation)		bronchial responsiveness	
				R_{rs6}	dR_{rs}/df	R_{rs6}	dR_{rs}/df	$PD_{40}R_{rs6}$ (x 10^{-5} g)	$PD_{40}R_{rs6}$ (ss)
1		4.8	+	-0.67	0	-0.85	-0.83	48	-0.88
2		3.4		0.86	-1.83	-1.88	1.17	19	-2.49
3		5.2	+	0.72	-2.00	0.37	1.17	26	-1.95
4		6.2	+	1.71	-2.67	-0.75	1.02	14	-3.02
5	CURRENT	11.8	+	0.48	-0.50	-0.88	-0.16	62	-0.44
6		6.7		1.00	-2.00	-	-	52	-0.75
7		5.1	+	-0.34	-0.50	-0.26	2.85	27	-1.88
8		4.6		1.26	-2.33	-0.77	2.83	42	-1.12
9		12.5	+	0.10	-1.83	-	1.50	57	-0.59
10		2.6	+	1.94	-0.17	-	-	>128	0.82
11		9.0	+	-0.22	0.17	0.01	0.16	>128	0.82
12	PAST	11.9		0.60	0.33	-0.60	-0.83	54	-0.68
13	NO CURRENT	12.8	+	0.11	-0.33	0	0	94	0.29
14		6.3		0.48	-1.50	-0.54	0.51	36	-1.39
15	NO PAST	5.5	+	0.12	-0.67	-0.14	-0.32	64	-0.39
16	NO CURRENT	8.3		1.08	0	-1.38	1.16	56	-0.62

Family history of asthma or hay-fever (table 1)

10 children who had had bronchiolitis (62,5%) had a 1st or 2nd degree relative with asthma or hay-fever (table 1). 20 mild asthmatics (74%) and all severe asthmatics had a positive family history. 6 per cent of the reference population we studied before (15) had a 1st or 2nd degree relative with asthma or hay-fever.

Lung function

Baseline values (table 1, figure 1)

Only children who had bronchiolitis with current respiratory symptoms showed increased R_{rs6} and/or decreased $\overline{dR_{rs}/df}$ baseline values.
Baseline R_{rs6} was increased in 2 and baseline $\overline{dR_{rs}/df}$ was decreased in 6.

Baseline R_{rs6} was not statistically different between the groups of children but baseline $\overline{dR_{rs}/df}$ was significantly lower in subjects with current symptoms who had bronchiolitis than in those without. It did not differ between bronchiolitis subjects with current symptoms and mild asthmatics, but was significantly lower in the severe asthmatic patients.

BR to histamine (table 1, figure 2)

PD_{40} R_{rs6} in the children who had bronchiolitis was intermediate between PD_{40} in asthmatic and healthy subjects. PD_{40} in children with current symptoms was significantly different from PD_{40} in healthy subjects but not from PD_{40} in mild asthmatics.

Decreased PD_{40} was found in 4 children who had bronchiolitis and had current respiratory symptoms. None of the children without current symptoms showed a decreased PD_{40}. In the asthmatic individuals PD_{40} proved to be related to the severity of the symptoms. PD_{40} in the severe asthmatics was signficantly lower than in the mild asthmatics ($p < 0.01$).

Bronchial smooth muscle tone (table 1, figure 3)

R_{rs6} was measured in 7 and $\overline{dR_{rs}/df}$ in 8 children who had bronchiolitis with current symptoms; R_{rs6} and $\overline{dR_{rs}/df}$ were measured in 6 children without current symptoms. R_{rs6} improved significantly in 1 and $\overline{dR_{rs}/df}$ in 2 symptomatic and in none of the asymptomatic subjects. A moderate but not significant improvement in R_{rs6} or $\overline{dR_{rs}/df}$ (between 1 and 1.65 ss) was present in 4 children with and in 1 subject without current symptoms. R_{rs6} improved significantly in 5 of the mild and in 6 of the severe asthmatic patients. $\overline{dR_{rs}/df}$ improved significantly in 7 of the mild as well as in 7 of the severe asthmatic subjects. In none of the healthy children was a significant improvement in R_{rs6} and $\overline{dR_{rs}/df}$ found. 1 healthy child showed a change between 1 and 1.65 ss in both R_{rs6} and $\overline{dR_{rs}/df}$. The improvement of both R_{rs6} and $\overline{dR_{rs}/df}$ was significantly more pronounced in the symptomatic children who had bronchiolitis than in the healthy subjects ($p < 0.05$). A more than 1 ss improvement of $\overline{dR_{rs}/df}$ was found in 6 out of 8 symptomatic children who had bronchiolitis and in only 1 out of 19 healthy subjects. This difference between the groups is significant ($p < 0.05$). No significant differences existed between symtomatic children who had bronchiolitis and mild and severe asthmatics. On the other hand no signficant differences existed between asymptomatic children who had bronchiolitis and healthy subjects.

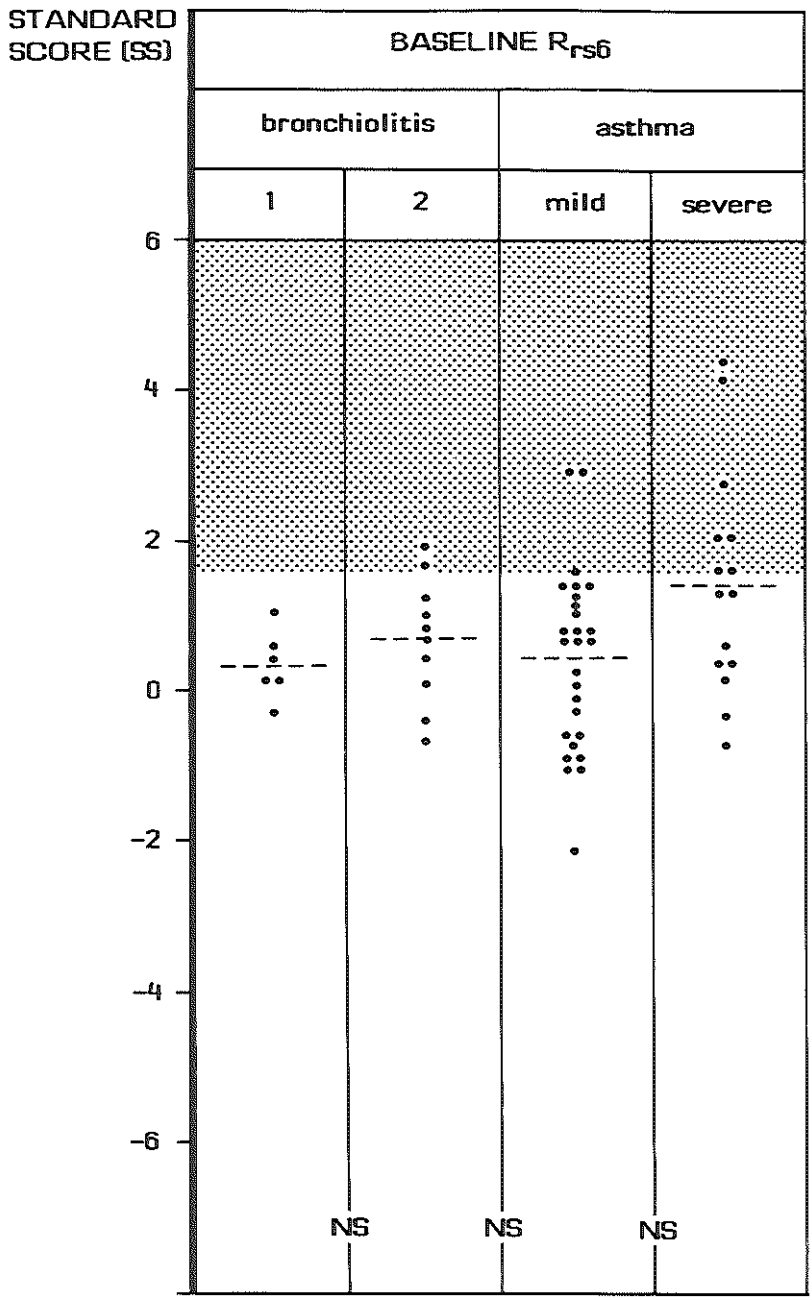

Figure 1a: Children who have had infant bronchiolitis compared to asthmatic children; baseline lungfunction measured by R_{rs6} expressed as standard scores (ss) from baseline values in healthy subjects. (The shaded area indicates the abnormal range beyond + or -1.65 ss; --- = mean value; 1) = no current respiratory symptoms, 2) = current respiratory symptoms)

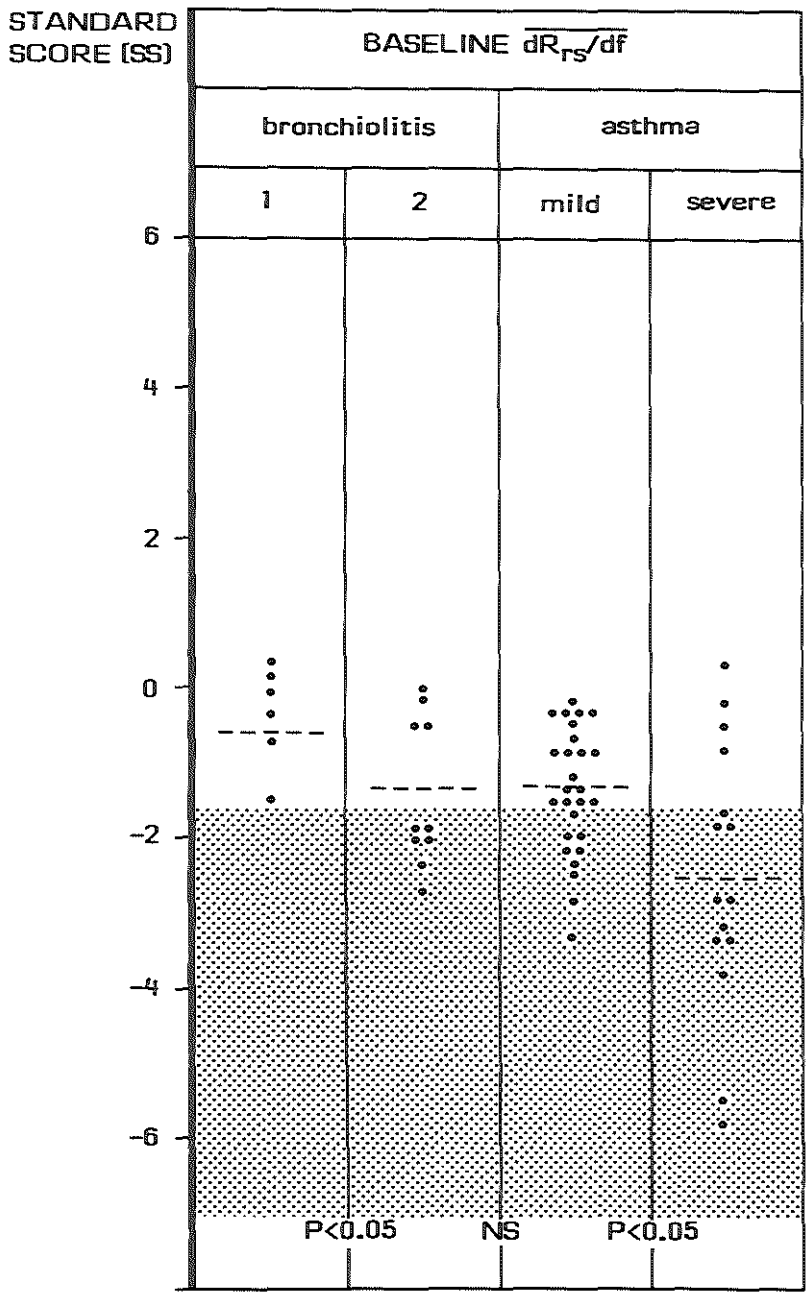

Figure 1b: Children who have had infant bronchiolitis compared to asthmatic children; baseline lungfunction measured by $\overline{dR_{rs}/df}$ expressed as standard scores (ss) from baseline values in healthy subjects. (The shaded area indicates the abnormal range beyond + or -1.65 ss; --- = mean value; 1) = no current respiratory symptoms, 2) = current respiratory symptoms)

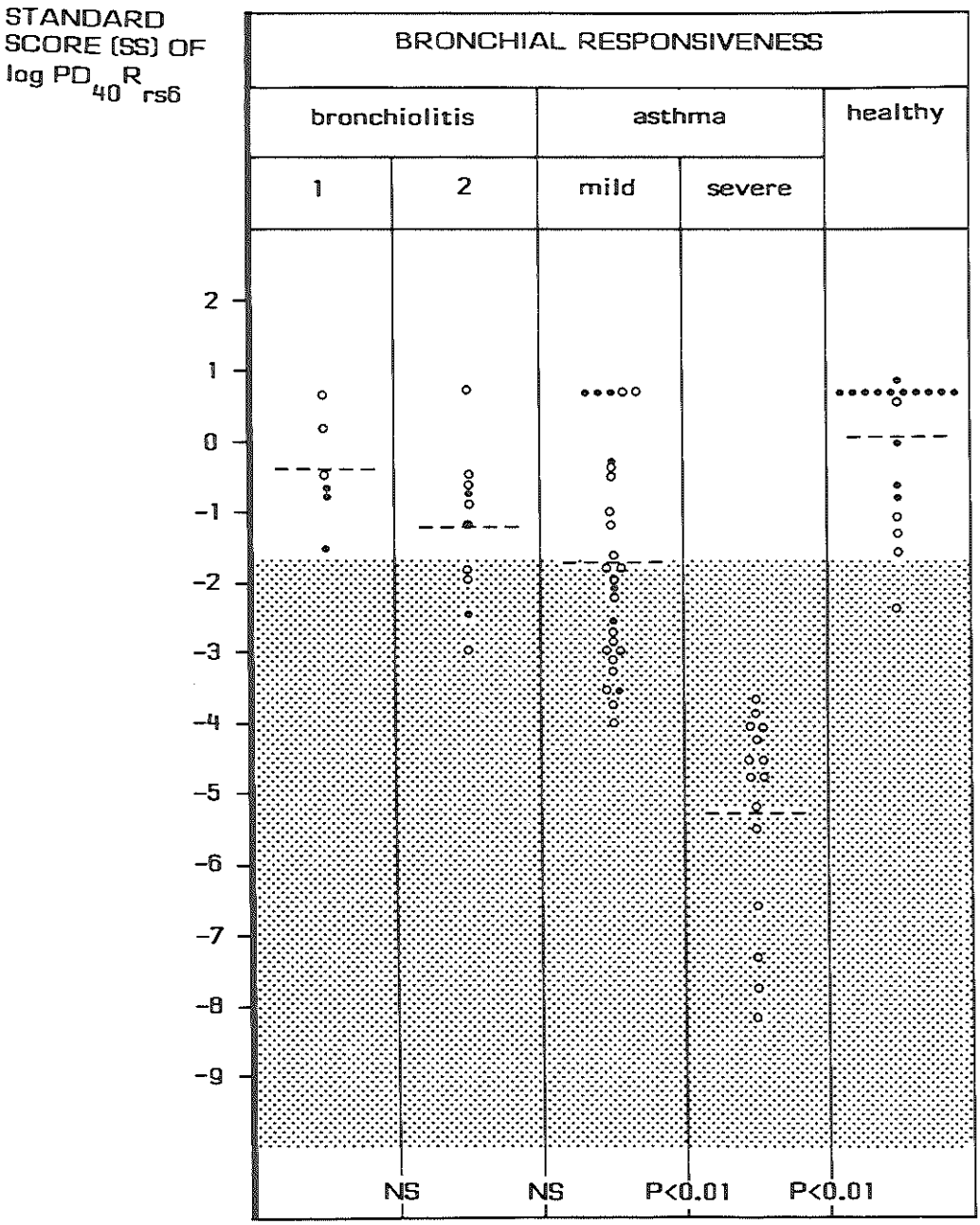

Figure 2: BR to histamine measured by PD_{40} R_{rs6} expressed as standard scores (ss) from PD_{40} R_{rs6} in healthy subjects. (The shaded area indicates the abnormal range beyond -1.65 ss; --- = mean value; 1) = no current respiratory symptoms, 2) = current respiratory symptoms;° positive, • negative family history of asthma; BR not significantly different in bronchiolitis 1) and healthy subjects. PD_{40} values > 128 x 10^{-5} g histamine were considered as being 128 x 10^{-5} g to calculate mean PD_{40} and standard deviation in healthy children.

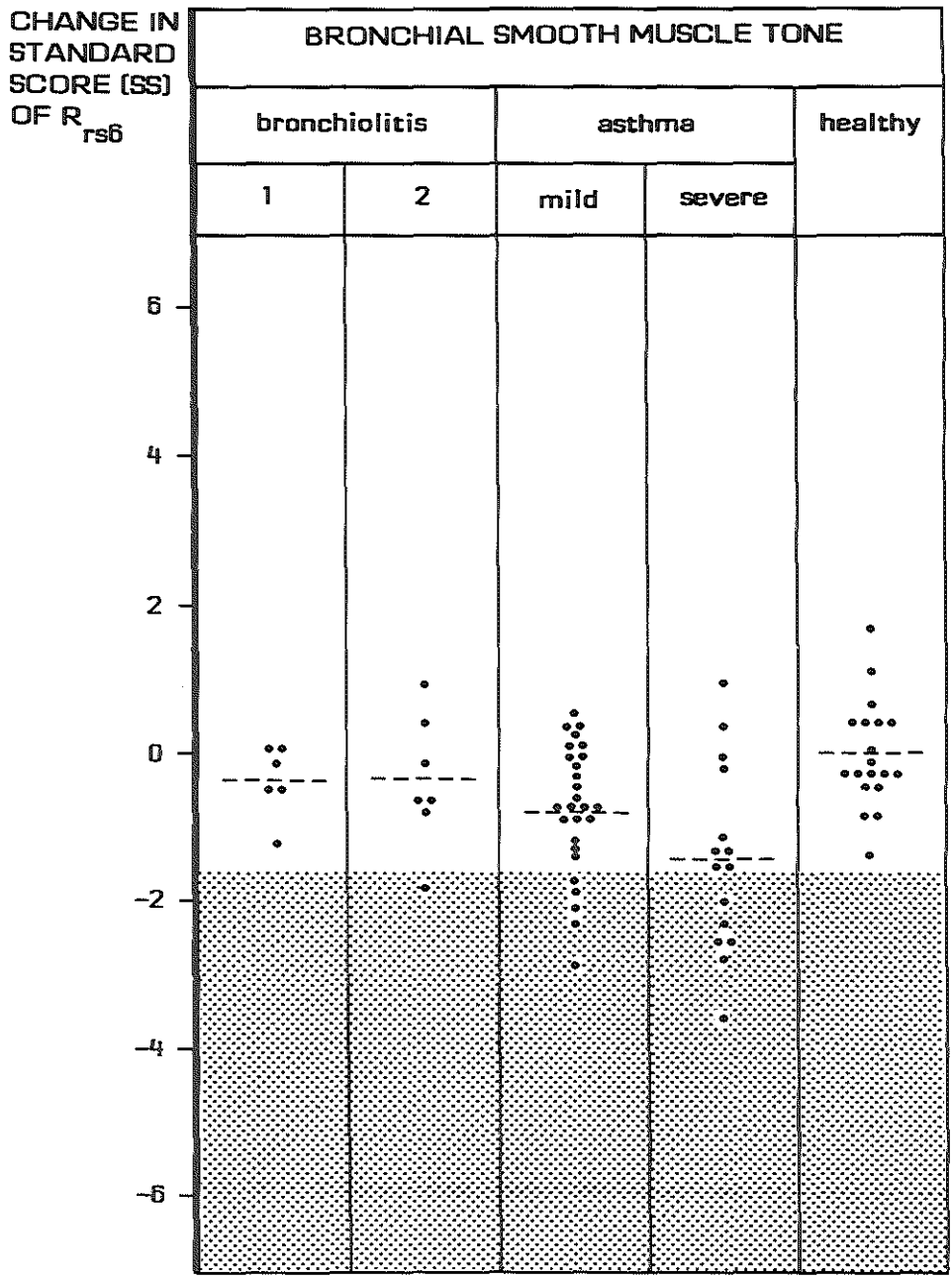

Figure 3a: Change in standard scores (ss) of R_{rs6} after bronchodilatation in children who have had bronchiolitis and in asthmatic and healthy subjects (17). (The shaded area indicates the abnormal range beyond - or +1.65 ss change; --- = mean value; 1) = no current respiratory symptoms, 2) = current respiratory symptoms)

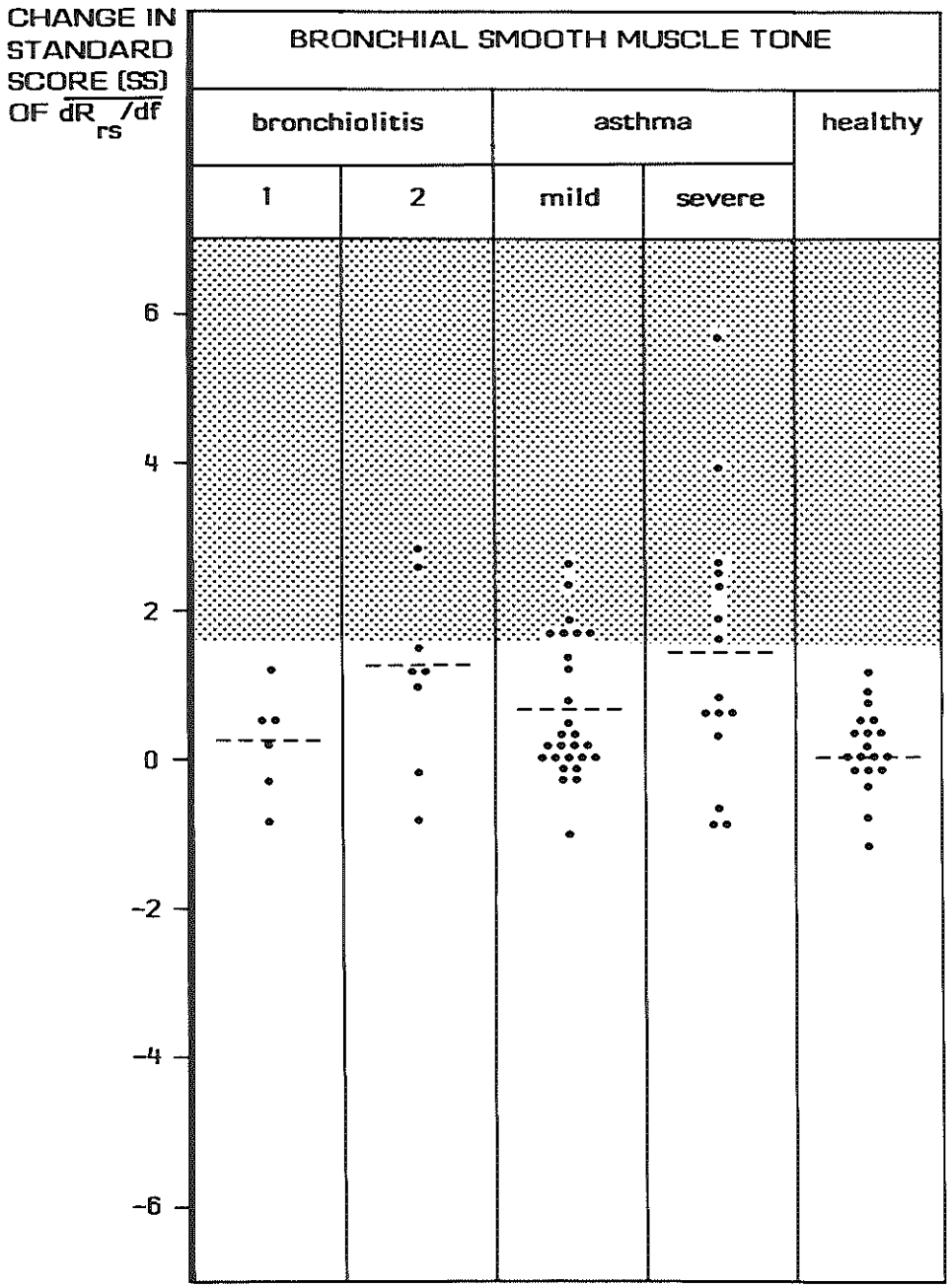

Figure 3b: Change in standard scores (ss) of and $\overline{dR_{rs}/df}$ after bronchodilatation in children who have had bronchiolitis and in asthmatic and healthy subjects (17). (The shaded area indicates the abnormal range beyond - or +1.65 ss change; — = mean value; 1) = no current respiratory symptoms, 2) = current respiratory symptoms)

Combined data

Individual data of children who had bronchiolitis are shown in table 1. Baseline lung function of all children without symptoms was within the normal range. The same is true for bronchial smooth muscle tone and BR.

The majority of the children (7 out of 10) with current respiratory symptoms showed either abnormal baseline lung function values, increased bronchial smooth muscle tone or decreased PD_{40} R_{rs6} to histamine. This was not the case in the asymptomatic subjects. The combination of three indices was present in 1 (number 2) and of 2 indices in 4 (numbers 3,4,7,8).

7 out of the 10 children with current symptoms had a positive family history of asthma or hay-fever. This was the case in 3 out of the 6 children without symptoms. In the asthmatic children and in the healthy subjects PD_{40} was lower in case of a positive family history to asthma or hay-fever in 1st and 2nd degree relatives. This difference was not found in the children who had bronchiolitis.

Discussion

Infant bronchiolitis is characterized by an acute onset of wheezing, cough, dyspnoea and rhinorrhoea with hyperinflation (3). Bronchiolitis is a clinical syndrome which is recognizable although not entirely distinct from certain other lower respiratory tract disorders. This leads to much controversy about the nature of bronchiolitis (14).

Children hospitalized because of bronchiolitis represent only a small proportion of all children with this syndrome who are presented to the general practitioner (22,23). We studied whether subjects who were hospitalized because of infant bronchiolitis had characteristics of asthma during later life. Several investigators found that after infant bronchiolitis there was a high incidence of recurrent respiratory symptoms (4,5,10), abnormal lung function (i.e. decreased forced expiratory flows; increased TGV, R_{aw} and R_{rs}) (4,10,11,13), increased bronchial smooth muscle tone (10) and increased BR (4,12,13).

This is the first study in which the presence of respiratory symptoms in relation to main characteristics of asthma (i.e. bronchial patency, bronchial smooth muscle tone and BR) is investigated in subjects who had infant bronchiolitis. They were compared in these respects to asthmatic subjects and to the results of measurements performed in healthy individuals (15).

Lung function was measured by FOT as this method can easily be performed in young children, because only passive cooperation is needed. Because many children investigated were under six years of age, and hence too young to perform expiratory manoeuvres in a reproducible way, FOT was preferred over spirometry. FOT is described in detail elsewhere (17). From FOT R_{rs6} and $\overline{dR_{rs}/df}$ were calculated. The within-subject reproducibility of 5 consecutive FOT measurements and forced expiratory flow-volume curves is about the same (18). PD_{40} R_{rs6} has been shown to be as sensitive to detect induced bronchoconstriction as PD_{20} FEV_1 (18).

62% of children who had bronchiolitis had recurrent respiratory symptoms at the time of the study. Henry et al. (11) found a prevalence of 82% at 2 years of age and others between 40 and 50% (1,4,5) 6-10 years after the initial illness. Recurrent respiratory disease after infant bronchiolitis tends to improve with time in a number of children, but in others symptoms continue to be present.

Central airway patency as measured by R_{rs6} in the children who had had bronchiolitis and still had respiratory symptoms did not differ from that in the symptom-free subjects or in children with mild asthma. However, in the individuals who previously had bronchiolitis with current symptoms $\overline{dR_{rs}/df}$ was significantly lower than in the ones without, and about the same as in mild asthmatics. Hence peripheral airway patency in symptomatic children with previous bronchiolitis seems to be comparable to that in individuals with mild asthma. The asymptomatic subjects with previous bronchiolitis were comparable in this respect to healthy children. When > 1.65 ss (i.e. 95% unilateral confidence limit) was applied as criterion of significant improvement in indices of airway patency after bronchodilatation, no statistical calculations on the differences between the various groups with respect to the bronchial smooth muscle tone could be performed because of insufficient data. When > 1 ss was taken it appeared that significantly more symptomatic children who had had bronchiolitis improved than healthy individuals, which indicates that the bronchial smooth muscle tone in the symptomatic bronchiolitis group might be higher than in the healthy subjects. No significant differences existed in this respect between the symptomatic children who had had bronchiolitis and the mild or severe asthmatics respectively . Bronchial smooth muscle tone in the asymptomatic children who had had bronchiolitis was not signficantly different from that in healthy subjects.

BR in symptomatic children who had infant bronchiolitis was significantly increased compared to BR in healthy individuals and of the same level as BR in mild asthmatic patients. $PD_{40}\ R_{rs6}$ values $> 128 \times 10^{-5}$ g histamine were considered as being 128×10^{-5} g to calculate mean PD_{40} and standard deviation in healthy children. As most of them did not react after inhalation of 128×10^{-5} g this implies that the calculated mean PD_{40} in healthy subjects is lower than the real mean. Hence differences in BR between healthy subjects and asthmatics or children who had bronchiolitis will be greater than calculated and visualized in figure 2. BR in individuals who had bronchiolitis but were symptomfree, was not significantly different from BR in healthy individuals. It was moderately increased in only 1 subject.

Most subjects who have had bronchiolitis and have current respiratory symptoms showed either abnormal baseline lung function, increased bronchial smooth muscle tone or increased BR to histamine. Combinations were present in 5. There was no relationship with a family history of asthma and hay-fever. As we were not allowed to study atopy we have no information about the atopic state in these subjects. An increased prevalence of atopic disorders in children who had infant bronchiolitis has been reported (1), but could not be confirmed by others (4,7). As atopy is prevalent in about 30 per cent of the healthy population (16) it is not a sensitive or specific marker of asthma and therefore of minor

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CHAPTER 8. INFLUENCE OF LUNG INJURY DURING EARLY LIFE (BRONCHOPULMONARY DYSPLASIA, NEAR-DROWNING) ON THE DEVELOPMENT OF LUNG FUNCTION AND BRONCHIAL RESPONSIVENESS

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Abstract

Severe lung injury during early life may affect the growth and development of the respiratory system. In particular injury of immature lung structures may cause subsequent damage of peripheral airways, leading to recurrent respiratory symptoms and lung function abnormalities. By means of pseudo-random noise oscillometry we investigated whether lung injury in early life due to bronchopulmonary dysplasia or near-drowning caused a decrease in bronchial patency, increased bronchial smooth muscle tone or increased bronchial responsiveness to histamine. We found that lung injury in early life may cause a mild increase in frequency dependence, but not increased bronchial smooth muscle tone or increased bronchial responsiveness. We conclude that lung injury in early life may lead to residual abnormalities of peripheral airways. Whether these are of future clinical significance remains to be seen.

List of abbreviations

BR	bronchial responsiveness
FOT	forced pseudo-random noise oscillometry
PD	provocative dose; dose which causes an arbritrary percentage change from mean baseline lung function value.
TD	threshold dose; dose which causes a 2 SD change from mean baseline lung function value.
R_{rs6}	resistance of the respiratory system measured by FOT at 6 Hz oscillation frequency ($cm.H_2O.l^{-1}.s$).
$\overline{dR_{rs}/df}$	frequency dependence of R_{rs} calculated over the complete frequency spectrum ($cm.H_2O.l^{-1}.s^2$).
ss	standard score.
BPD	bronchopulmonary dysplasia
ND	near-drowning

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2. Paper submitted for publication.

Introduction

Increased BR can be considered as a genetically determined characteristic of asthma (1), whose expression can be brought about by various environmental factors (2,3,4). The question is whether lung injury in early life can cause a permanent increase in BR. Moderately increased BR has been described in children after bronchopulmonary dysplasia (BPD) (5) as well as in survivors of a near-drowning accident (ND) (6). Lung injury in early life may affect the growth and development of the respiratory system (7). We measured baseline respiratory resistance, the effect of maximal bronchodilatation and BR to histamine in children who had severe lung injury in early life (i.e. BPD due to artificial ventilation for hyaline membrane disease) and in children who experienced ND and compared the results with data from healthy children of the same age without a history of present or past respiratory disease.

Methods

Subjects

– BPD: 16 children aged 3.3. to 10.6 years (mean 6.3 years) were studied. All were born prematurely after a gestational age of 26 to 34 weeks (mean 28.1 weeks). They were admitted to hospital because of hyaline membrane disease. All had severe BPD diagnosed on roentgenological (8) and clinical (9) grounds (table 1).

– ND: 25 children, aged 3.4 to 8.2 years (mean 5.5 years), were studied 0.6 to 5.7 years (mean 3.1 years) after admission to hospital because of a ND accident. 7 had symptoms of ARDS and needed artificial positive end-expiratory pressure ventilation. None had BPD after the ND accident. Ages at ND varied from 1.1 to 5.4 years (mean 2.6 years) (table 2).

19 healthy previously studied children aged 5 to 8 years (10) were used as reference population.

None of the children had upper respiratory tract symptoms in the 2 weeks prior to the study.

Written informed consent was obtained from the parents of all subjects.

History

A medical history of current and past respiratory symptoms (i.e. recurrent episodes of cough and wheezing) as well as a family history of asthma or hay-fever in 1st and 2nd degree relatives was obtained by a questionnaire administered by ED (11).

Lung function

Lung function was measured by the forced pseudo-random noise oscillation technique (FOT) (10,12). FOT is a convenient method for children from about 2 years of age because only passive cooperation is needed. From FOT we selected R_{rs6} and $\overline{dR_{rs}/df}$. R_{rs6} is mainly determined by the diameter of the central airways (13). $\overline{dR_{rs}/df}$ is considered to be a measure of unevenness of ventilation (14). It is mainly determined by the diameter of the peripheral airways (10,14)

All children had a physical examination prior to lung function measurements.

Bronchial smooth muscle tone

15 minutes after completion of the histamine provocation 2×10^{-4} g fenoterol and 0.2×10^{-4} g ipratropium bromide were given by metered dose inhaler to obtain bronchodilatation. The difference between baseline and values after bronchodilatation was considered as the degree of bronchial smooth muscle tone.

Bronchial responsiveness (BR)

BR was determined by the inhalation of histamine. Histamine was delivered to the mouth by a Rosenthal-French dosimeter (15) which was connected to a DeVilbiss nebulizer type 646. The dosimeter was triggered by slow inhalation from FRC to TLC. The nebulizer was operated by compressed air at 20 p.s.i. The timing adjustment of the dosimeter was 0.6 seconds. Each provocation dose was given in 4 inhalations of 5 microlitres. Doses of histamine biphosphate in physiologic saline inhaled with 5 minutes intervals were 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128 x 10^{-5} g. Physiologic saline was inhaled before histamine to exclude non-specific responses.

Each challenge was preceded by 5 consecutive FOT measurements from which the mean baseline value and the standard deviation were calculated. The mean of the 3 FOT measurements with the greatest similarity was taken to construct a dose-response curve.

PD and TD were calculated from the dose-response curve by linear interpolation. PD_{40} R_{rs6} was defined as the dose of histamine which caused a 40 per cent increase from mean $\underline{R_{rs6}}$ baseline value. PD_{40} R_{rs6} is closely correlated with PD_{20} FEV_1 (16). TD $\overline{dR_{rs}/df}$ was defined as the dose of histamine which caused a 2 SD decrease from mean baseline $\overline{dR_{rs}/df}$.
It is a sensitive index of induced bronchoconstriction (16). Bronchial challenge was ended after inhalation of 128 x 10^{-5} g histamine or after PD_{40} R_{rs6} had been obtained.

We were not allowed to perform skin prick tests or blood gas sampling in the children who had BPD, the subjects who survived ND or the healthy individuals.

Mean expected baseline values of R_{rs6} and $\overline{dR_{rs}/df}$ were taken from a reference population which we had previously studied (10) and who had a negative current or past history of pulmonary injury, asthma or other recurrent respiratory disease. All lung function and BR indices were expressed as standard scores (ss); i.e. mean measured value minus mean expected value divided by the standard deviation of the mean expected value. Baseline R_{rs6} was called increased if its value was higher than +1.65 ss and $\overline{dR_{rs}/df}$ was called decreased if its value was lower than -1.65 ss (95% unilateral confidence limits) from the expected mean (19). BR was considered to be increased if PD or TD were lower than -1.65 ss from reference BR. (i.e. PD_{40} $R_{rs6} < 30 \times 10^{-5}$ g and $TD < 11 \times 10^{-5}$ g histamine). The bronchodilating effect of inhaled fenoterol and ipratropium bromide was called significant with a greater than 1.65 ss change from individual mean baseline. The change in ss was calculated from the mean value after bronchodilatation minus the individual mean baseline value divided by the standard deviation of the baseline value.

Statistical analysis

The Wilcoxon two sample test was used to analyse differences of baseline values, as well as differences in PD_{40} R_{rs6} and TD $\overline{dR_{rs}/df}$ to histamine between the groups. Bronchodilatation was analysed with the signed rank test. Differences were considered significant with p values less than 5 percent.

Results

Symptoms

– **BPD**: 6 children had recurrent respiratory symptoms (i.e. cough, wheezing) with respiratory tract infections at the time of investigation (table 1). 1 subject (number 6) had exercise induced symptoms. 2 had symptoms which disappeared after the age of 4. 7 subjects had never had recurrent symptoms after discharge from hospital. 1 child (number 16) had post intubation tracheal stenosis. He suffered from several episodes of acute laryngotracheobronchitis, but had no symptoms of lower respiratory tract disease.

– **ND**: 4 children had recurrent respiratory symptoms. However in all of them these were present before the accident. The frequency and severity did not increase thereafter (table 2).

Family history

3 children who had BPD (19%) and 9 children who had a ND accident (36%) had a 1st or 2nd degree relative with asthma or hay-fever. 6% of the healthy children of the reference population (10) had a positive family history.

	respiratory symptoms	age at investigation in yrs.	1st or 2nd degree relative with asthma	gestational age in wks.	Northway (8)	Toce (9) day 21	baseline function (ss) R_{rs6}	baseline function (ss) dR_{rs}/df	bronchial smooth muscle tone (change in ss after bronchodilatation) R_{rs6}	bronchial smooth muscle tone (change in ss after bronchodilatation) dR_{rs}/df	bronchial responsiveness $PD_{40}R_{rs6}$ x 10^{-3} g	bronchial responsiveness $PD_{40}R_{rs6}$ ss	bronchial responsiveness TD dR_{rs}/df ss
1		4.7		32	3	23	2.13	-2.67	0.13	-0.33	117	0.56	-1.03
2		5.1		29	4	20	-0.64	-1.17	0.46	-0.50	18	-3.61	-1.99
3	CURRENT	5.0		20	4	20	0.98	-0.50	0.67	-1.17	72	-0.19	-0.16
4		6.8		20	4	20	0.87	-3.50	-4.25	4.80	84	-0.38	-0.16
5		4.4		27	3	20	1.84	-4.00	-0.02	0.02	80	0	-0.12
6		7.0	+	32	3	10	1.74	-3.00	-1.98	2.17	>128	0.02	0.20
7	PAST	6.0		28	3	22	0.75	-1.50	-0.31	-1.67	48	-0.86	-1.30
8	NO CURRENT	9.2	+	29	4	25	0.28	-1.50	0.83	-0.67	20	-1.76	-1.25
9		6.2		34	3	12	1.18	-2.17	1.12	1.50	38	-2.58	-1.89
10		5.5		32	3	19	0.31	-1.50	-	-	84	-0.38	-2.79
11		10.5	+	32	3	3	-0.26	0.67	-	-	>128	0.02	-0.84
12	NO PAST	3.3		28	3	15	1.11	-0.33	0.05	-0.50	24	-2.09	-2.48
13	NO CURRENT	7.2		28	2	20	-0.19	-0.67	0.27	1.00	93	0.26	-1.00
14		5.8		28	3	5	1.88	-1.33	0.47	1.00	>128	0.82	-
15		4.4		28	1	10	0.16	-1.69	-0.54	1.33	>128	0.82	-1.16
16		7.3		31	3	23	5.30	-6.67	-0.31	-0.33	>128	0.82	0.79

Table 1: Children who had bronchopulmonary dysplasia (BPD); clinical data; individual baseline R_{rs6} and dR_{rs}/df values, change of lung function after bronchodilatation and BR to histamine expressed as standard score (i.e. mean measured value minus mean expected value divided by the standard deviation of the mean expected value; ss) differences from data in healthy children. (# abnormal range; Northway (8): roentgenological scoring system of BPD; Toce (9): clinical scoring system of BPD, presented values at day 21)

	secondary drowning	1st or 2nd degree relative with asthma	age at near-drowning in yrs.	age at investigation in yrs.	baseline function (ss) R_{rs6}	baseline function (ss) dR_{rs}/df	bronchial smooth muscle tone (change in ss after bronchodilatation) R_{rs6}	bronchial smooth muscle tone (change in ss after bronchodilatation) dR_{rs}/df	bronchial responsiveness $PD_{40}R_{rs6}$ x 10^{-3} g	bronchial responsiveness $PD_{40}R_{rs6}$ ss	bronchial responsiveness TD dR_{rs}/df ss
1		+	2.2	4.3	-1.75	-1.16	0.01	0	32	-1.58	-0.79
2		+	3.1	6.0	0.38	-1.82	1.73	-0.33	30	-1.28	-2.54
3			2.4	8.1	1.20	-0.50	-0.35	-0.17	80	-0.50	-0.80
4			2.3	7.2	-0.20	-0.98	-0.21	-0.50	100	0.38	-0.03
5			1.8	5.3	-1.10	-0.66	-0.57	0.33	>128	0.82	-0.96
6			0.8	5.1	0.04	-1.65	-0.10	-0.33	90	0.20	-2.07
7			1.8	4.4	-0.33	-1.65	-0.05	-0.17	>128	0.82	0.05
8			3.0	8.0	1.77	-1.16	-1.61	0	03	0	-0.05
9		+	1.7	5.5	1.70	-1.49	0.48	-1.65	>128	0.82	-1.57
10			3.0	7.5	-0.15	-1.16	-0.17	0	50	-0.82	-0.78
11			2.3	5.3	0.02	-0.66	-0.57	0	42	-1.12	-0.05
12			1.3	4.6	-1.31	0.83	0.15	-1.16	38	-1.28	-1.03
13		+	3.7	4.6	0.77	0	0.05	-2.31	20	-2.41	-1.89
14			2.6	5.1	-1.45	0	-0.13	-0.50	05	0.11	-2.00
15			2.1	5.6	-1.07	-0.50	1.03	0	26	-1.95	-1.54
16			2.7	3.4	-0.08	-1.65	-	-	>128	0.82	0.75
17		+	2.4	6.2	0.03	-0.99	-1.00	0.66	24	-2.09	-1.83
18			2.2	3.8	0.55	-2.48	-	-	40	-0.99	-
19	+		1.9	4.6	0.45	-2.97	0.05	2.31	>128	0.82	0.21
20	+	+	1.9	3.7	0.18	1.90	0.35	+4.29	17	-2.88	-2.31
21	+		4.5	6.9	-1.13	0	0.34	-0.33	>128	0.82	0.33
22	+	+	1.9	4.7	2.83	-1.98	-3.61	1.98	>128	0.82	-0.51
23	+		0.2	0.2	-0.71	-0.50	-0.38	0	83	-0.41	-0.75
24	+		5.4	6.0	-0.94	0.17	0.45	0	26	-1.82	-1.83
25	+	+	1.4	4.7	-0.22	-0.83	-0.04	-0.50	58	-0.53	0.75

Table 2: Children who survived a near-drowning accident; symbols and explanation as in table 1

Lung function by forced pseudo-random noise oscillometry

Baseline values

– BPD (table 1): R_{rs6} was increased in 3 of the 6 children with current symptoms at the time of the study. Decreased $\overline{dR_{rs}/df}$ values were found in 4. Of the 10 children without current symptoms R_{rs6} was increased in 2 and $\overline{dR_{rs}/df}$ was decreased in 3.

– ND (table 2): R_{rs6} was increased in 2 children and $\overline{dR_{rs}/df}$ was decreased in 4. Secondary drowning did not affect lung function measured by FOT.

R_{rs6} was not significantly different in the children who had BPD, the subjects who experienced ND and the healthy individuals. $\overline{dR_{rs}/df}$ was significantly lower in the children who had BPD with current respiratory symptoms than in the healthy children. Although $\overline{dR_{rs}/df}$ was lower in these symptomatic BPD children than in the asymptomatic ones or the subjects who survived ND, differences were not significant. There was a large overlap.

Bronchial smooth muscle tone

– BPD (table 1): Increased smooth muscle tone assessed by R_{rs6} as well as $\overline{dR_{rs}/df}$ was found in 2 out of the 6 children with current symptoms. None of the subjects without current or past respiratory symptoms had increased bronchial smooth muscle tone.

– ND (table 2): A significant decrease of R_{rs6} was found in 2 subjects. $\overline{dR_{rs}/df}$ increased in two. In one of them the decrease in R_{rs6} was associated with the increase in $\overline{dR_{rs}/df}$.

BR to histamine

– BPD (table 1): Increased BR was found in 1 out of the 6 children with current respiratory symptoms according to PD_{40} R_{rs6} as well as TD $\overline{dR_{rs}/df}$. According to both criteria BR was also found to be increased in 2 subjects who never had recurrent respiratory symptoms. According to PD but not to TD, BR was increased in a child who only had symptoms in the past and according to TD but not to PD in a child who never had symptoms.

– ND (table 2): Increased BR was found in 5 subjects according to PD_{40} R_{rs6} and in 7 according to TD $\overline{dR_{rs}/df}$. BR was not significantly different between children who had secondary drowning and those who had not. 4 children with increased BR had a positive family history of asthma or hay-fever.

PD_{40} R_{rs6} was not significantly different between the children who had BPD and the subjects who survived ND. They did also not differ significantly from PD_{40} R_{rs6} in healthy individuals (24). However, according to TD $\overline{dR_{rs}/df}$ BR was

higher in the children who had BPD and who survived ND than in the healthy subjects ($p < 0.05$).

Discussion

Early pulmonary injury in the period of rapid lung growth, i.e. the first years of life (17,18), can induce bronchiolar lesions which may disturb alveolar and vascular growth (7). After BPD the incidence of recurrent lower respiratory tract illness in many children is high (19). In the majority symptoms improve during the first 3 years of life and after the age of 4 most subjects who had BPD as a neonate seem to have lost their increased susceptibility to pulmonary infections (20) and have a normal cardiopulmonary function (21).

Complete recovery of pulmonary dysfunction after ND in a few weeks period has been described in adults (22) as well as in children (6).

For the measurement of lung function we applied the forced pseudo-random noise oscillation technique (FOT) (12). The intra-subject reproducibility of 5 consecutive FOT measurements is about the same as that of forced expiratory flow-volume curves (16). $PD_{40}\ R_{rs6}$ appears to be as sensitive as $PD_{20}\ FEV_1$ while TD $\overline{dR_{rs}/df}$ is more sensitive (20).

In the aetiology of BPD many factors such as hyperoxia (23), prolonged positive pressure ventilation (24), vitamine E deficiency (25) and complications such as sepsis and pneumothorax (20) seem to be involved (26).

In BPD widespread alveolar, bronchiolar and bronchial injury with subsequent epithelial metaplasia and hyperplasia is seen. Capillary basement membranes show thickening, with early development of intra-septal collagen (20). The microscopic characteristics of lung injury with adult respiratory distress syndrome (ARDS) are interstitial edema, fibrin thrombi in small vessels, platelet and leucocyte aggregates, hyaline membranes around the alveolar ducts and often alveolar oedema and extravasation of red blood cells into either the interstition or alveolar space (27).

There is resemblance between findings in neonatal and adult respiratory distress syndrome (28). In both there is injury of alveolar and bronchiolar structures. Increased collagen synthesis with disturbance of the normal architecture was described in animal studies (29) as well as in studies in children who survived BPD (20). These changes are very similar to those seen in ARDS (30).

Several investigators showed residual lung function abnormalities even years after BPD, such as increased airway resistance, decreased compliance, decreased static and dynamic lung volumes and expiratory flows, and slightly abnormal arterial oxygen and carbondioxide values (21,23,24,31,32,33). They speculate that these might be caused by growth impairment after lung injury at an early age (7).

Recovery from alveolar and bronchiolar damage in survivors of ARDS is

usually complete with little or no residual defects in lung function and no increased prevalence of recurrent respiratory symptoms (34). However, subtle abnormalities of gas exchange were described in patients who survived ARDS (35) which may indicate incomplete repair of lung injury. Little is known about residual abnormalities after ND without ARDS, but significant lesions seem unlikely.

About 40 per cent of children who had BPD still had recurrent respiratory symptoms at the time of the study when they were between four and seven years of age. No respiratory symptoms that could be attributed to the accident were present in the children who survived ND. Residual abnormalities of the central airways as assessed by R_{rs6} and the peripheral airways as assessed by $\overline{dR_{rs}/df}$ were more prevalent in the children who had BPD than in the subjects after ND. Abnormal baseline $\overline{dR_{rs}/df}$ values were present especially in the children with current symptoms who had BPD. These findings indicate that lung injury in early life may induce residual damage of the peripheral airways.
Our findings can probably explain the abnormalities of gas exchange described by others (35). Because we could not perform blood gas analysis we have no information about it in our children after BPD or ND.

The duration of hyperoxic damage and positive pressure ventilation in infants with IRDS who develop BPD is longer than in most patients with ARDS due to ND. None of our subjects who survived ND developed BPD. It seems therefore likely that alveolar and bronchiolar damage was far more severe in the infants with IRDS and BPD than in the children with a ND accident. Hence the repair process of BPD will probably have taken more time and may have been less complete than after ND. BPD occurred at an earlier stage of lung development than ND. Immaturity of lung structures may also have influenced the repair process and lung development (36). These factors are the most likely explanation for the differences found in children who had BPD and children who survived ND.

Neither in the children who had BPD nor in the individuals who survived ND was there a significant change in respiratory resistance after bronchodilatation. There is no evidence that pulmonary injury during early life influences the regulation of bronchial smooth muscle tone. As far as we know this has not been looked into before.

Although the degree of BR in the children who had BPD or ND seemed to be more pronounced than in the healthy children the differences were not significant when measured by PD_{40} R_{rs6}. When measured by TD $\overline{dR_{rs}/df}$ BR was higher in the children who had BPD and in the individuals who survived ND than in the healthy subjects. A relatively high number of these children showed a 1 to 1.65 ss difference from TD $\overline{dR_{rs}/df}$ in healthy subjects. An explanation for this may be that TD $\overline{dR_{rs}/df}$ is about twice as sensitive as PD_{40} R_{rs6} to indicate induced bronchoconstriction (16). The degree of increased BR was moderate and far less than is usually seen in asthma (37). Comparable data have been described before in children who had BPD (5) or survived a ND accident (6).

The reason of the moderately increased BR in children who had lung damage in early life is not clear. It seems unlikely that it is due to differences in bronchial patency or bronchial smooth muscle tone between children who had BPD or ND and healthy individuals. Damage to the airway epithelium and subsequent disordered repair with metaplasia and hyperplasia may be one of the explanations but remains speculative.

Conclusion

The high proportion of children who had BPD with current respiratory symptoms who shows increased baseline R_{rs6} and decreased $\overline{dR_{rs}/df}$ values indicates that after lung injury during early life obstruction of central and more importantly of peripheral airways may occur. Lung injury during early life does not seem to influence mechanisms that regulate bronchial smooth muscle tone. Only some children show moderately increased BR.

Whether the underlying lesions, which are not defined, are a risk factor for adult lung disease is unknown.

Hence we are left with 2 questions:

1. what is the best therapeutic approach when a child presents with recurrent respiratory symptoms after bronchopulmonary dysplasia or near-drowning;
2. will intervention modify the disease process and reduce the risk of chronic obstructive lung disease?

These questions can neither be answered nor can a reasonable speculation be made. It seems however logical to treat respiratory symptoms in subjects who experienced severe lung damage with great care.

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Requests for reprints

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CHAPTER 9. GENERAL DISCUSSION AND SUMMARY

Increased bronchial smooth muscle tone and increased bronchial responsiveness (BR) are generally considered to be characteristics of asthma (de Vries et al., 1964; Boushey et al., 1980). They can only be quantified by means of lung function measurements. Although symptoms of asthma often originate during preschool age, lung function cannot routinely be determined at such a young age. If the hypothesis is valid that early intervention is important for the future outcome of asthma, assessment of abnormal lung function and increased BR as early as possible may be important.

Increased BR is usually considered to be a genetically determined characteristic of asthma (Sibbald et al., 1980a; Hopp et al., 1984). It can be brought to expression by various environmental factors such as viral respiratory tract infections (Walsh et al., 1961; Empey et al., 1976; de Jongste et al., 1984) or inhaled pollutants (Orehek et al., 1976; Golden et al., 1978; Holtzman et al., 1979; Sheppard et al., 1980). Natural exposure to allergens, especially with delayed type reactions (Cartier et al., 1980) and exposure to cigarette smoke (Gerrard et al., 1980) can temporarily enhance BR.

The degree of BR is related to the severity of respiratory symptoms in asthma (Cockcroft et al., 1977; Duiverman et al., 1985d). Subjects without a recent history of asthma or hay-fever may develop symptoms which are associated with increased BR after exposure to agents which produce bronchial inflammation. This was experimentally shown in dogs after exposure to ozone by Fabbri et al. (1984) and O'Byrne et al. (1984). They concluded that increased BR induced by ozone is closely linked to an inflammatory response involving neutrophil infiltration of bronchial epithelium.

If lung function and BR in young children needs to be measured suitable methods must be available. In this thesis lung function measurements by forced pseudo-random noise oscillometry (FOT) are used. FOT can easily be used from about 2½ years of age because only passive cooperation is needed (Lándsér et al., 1976a). König et al. (1984) adapted FOT for use in still younger children by adding a flexible tube and face-mask to the system. However since quiet spontaneous breathing is essential to obtain successful results in infants measurements can only be performed after sedation to prevent crying.

An electrical lung model is useful to explain the theoretical background of forced oscillometry (Duncan, 1975; Nelkon and Parker, 1975). The analogy between physiological and electrical variables is described in chapter 2 (pp 17-33).

With FOT total respiratory resistance (R_{rs}) and reactance (X_{rs}) of the respiratory system are recorded simultaneously over a frequency spectrum of 2 to 26 Hz. R_{rs} is mainly determined by the patency of the central airways, X_{rs} is influenced by elastic properties of lung tissue and chest wall and by mass-inertial proper-

ties of air within the central airways. X_{rs} can alternatively be expressed as "a dynamic compliance" (Cdyn) by the transformation Cdyn = 1/2 πf X_{rs} (Lándsér et al., 1979). Frequency dependence of R_{rs} ($\overline{dR_{rs}/df}$) can be calculated because a range of frequencies is applied simultaneously. It is a sensitive index of unevenness of ventilation. It is mainly determined by the patency of the peripheral airways (Mead, 1969; Woolcock et al., 1969; Kjeldgaard et al., 1976; Cutillo and Renzetti; 1983).

One FOT measurement takes 16 seconds. The child is seated upright behind the apparatus while its nose is clipped and the cheeks and mouth floor are fixed. Inappropriate fixation leads to shunting of oscillation signals in the upper airways (Michaelson et al., 1975; Solymár 1982). As a consequence measured R_{rs} values will be too low. Because we applied FOT in young children cheeks and mouth-floor fixation was performed by the investigator. This has the advantage that, besides proper fixation it can be felt whether the child is relaxed and whether tongue movements and swallowing take place. These movements should be prevented because they may influence the signal to noise ratio in an adverse way. If they occur the recording should be ommitted. It is advisable that the subject is seated upright. Results of studies on different positions of the neck showed that with proper fixation of cheeks and mouth-floor, flexion of the neck caused a small but significant change of R_{rs} and X_{rs} values from values obtained in baseline position. Extension of the neck had the opposite effect (figure 3.1, page 36-37).

Both R_{rs} and X_{rs} are determined by the patency of the upper and large intrapulmonary airways. When changes in R_{rs} and X_{rs} were expressed as standard scores (ss) in relation to values obtained in the baseline position (e.g. mean value in abnormal position minus mean value in baseline position divided by the standard deviation of the baseline value), they appeared in most subjects to be less than 1.65 ss i.e. within the 95% unilateral confidence limits of R_{rs6} and mean X_{rs} ($\overline{X_{rs}}$). $\overline{dR_{rs}/df}$ was not systematically affected by flexion or extension of the neck. This can be explained by the fact that this index is mainly determined by the patency of the peripheral airways.

If the conditions of fixation and head position are fulfilled FOT is a reliable lung function method for children from about 2 years of age. R_{rs} values and R_{aw} obtained by whole body plethysmography are highly correlated (i.e. $\overline{R_{rs}}$ vs. R_{aw}: r = 0.65; R_{rs6} vs. R_{aw}: r = 0.78) (figure 2.17, page 32) (Duiverman et al., 1983). The within-subject variability of 5 consecutive FOT R_{rs} measurements is about the same as that of forced expiratory flow-volume indices (i.e. about 10%) (table 1, page 62). The coefficients of variation of $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$ are high (table 1, page 62). This is due to the fact that dR_{rs}/df and X_{rs} fluctuate around zero, as either a negative or a positive value and their mean values approximate zero. FOT proved to be as sensitive as forced expiratory flow-volume curves to detect methacholine-induced bronchoconstriction (figure 3, pp 63-64). (Duiverman et al., 1985b).

R_{rs} and X_{rs} appeared to be influenced by the child's sex (S), age (A), height (H) and weight (W) (Duiverman et al., 1985a). For the precise computation of the complete R_{rs} and X_{rs} vs. frequency (f) curves a large number of coefficients is needed in order to construct the R_{rs} and X_{rs} vs. f curves as a function of these variables.

The reasons are:
1. R_{rs} and X_{rs} vs. f curves are non-linear and are described by 4 successive derivatives with respect to f (pp 50-51).
2. the prediction of each derivative requires height, weight together with a non-linear function of age.
3. this prediction varies with sex.

The complete prediction equations are given in the Appendix added to chapter 4. For diagnostic purposes simplified prediction functions can be used because the complete R_{rs} and X_{rs} vs. f curves are mainly characterized by the mean values of R_{rs} ($\overline{R_{rs}}$), X_{rs}, ($\overline{X_{rs}}$) and dR_{rs}/df ($\overline{dR_{rs}/df}$). Hence, it suffices to supply reference values for $\overline{R_{rs}}$, $\overline{X_{rs}}$ and $\overline{dR_{rs}/df}$ as a function of A, S, H and W (table 1, page 46).

Although there is an overlap between boys and girls when taking the complete R_{rs} - or X_{rs} - f curves into account, we found three marked differences between the sexes:
1) R_{rs} values were significantly higher in boys than in girls at ages 4 and 12, but were not different at about 8 years of age (table 2, page 46);
2) Frequency dependence of resistance was present in healthy boys up to about 5 years of age but not in girls of the same age or in older children (figure 3 and 5, pp 44-45);
3) X_{rs} values were significantly more negative in boys than in girls (table 2, pag 46).

In young children lung volume and airway diameter are smaller than in older subjects. This results in higher R_{rs} and lower X_{rs} values. The differences in R_{rs} and X_{rs} found between boys and girls below the age of about 8 are compatible with the fact that the airway diameter is greater in girls than in boys (Hogg et al., 1970). The higher R_{rs} values in boys aged 12 years than in girls of the same age may be explained by the fact that many girls but not boys have already reached puberty, in which the growth spurt is accompanied by an increase in airway diameter. Both frequency dependence and more negative X_{rs} values support the hypothesis that the diameter of the peripheral airways is smaller in young boys than in young girls. These findings are compatible with studies which suggest a dysanaptic growth pattern of airways, parenchyma and thoracic cage in the sense that until the age of about 5 length and diameter of peripheral airways lag behind growth of the central airways and the lungs (Cudmore et al., 1962; Hogg et al., 1970; Simon et al; 1972; Pagtakan et al., 1984; Hibbert et al., 1984).

Various indices from dose-response curves to inhaled methacholine determined by FOT and forced expiratory flow-volume curves were compared in 9 to 16 year old asthmatics. The following indices were derived from the dose-response curves:

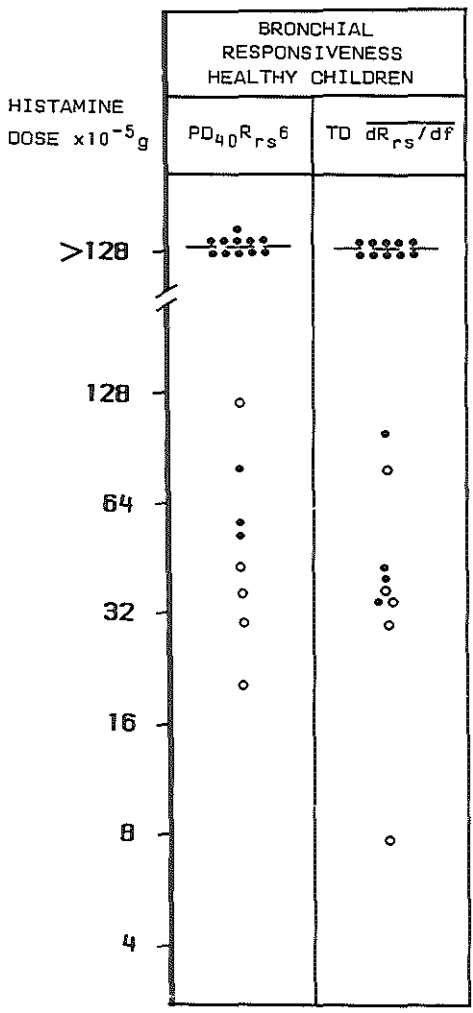

Figure 9.1. Bronchial responsiveness to histamine measured by forced pseudo-random noise oscillometry in healthy children 5 to 8 years of age. (-- median value; o 1st or 2nd degree relative with asthma or hay fever).

1. threshold dose (TD); i.e. the lowest dose which caused a significant change (2 SD) from the mean of at least 5 consecutive baseline values;
2. provocative dose (PD); i.e. the dose which caused an arbritrary predetermined (%) change from mean baseline lung function.

TD indices obtained by FOT detected induced bronchoconstriction after inhalation of a lower dose of methacholine than TD indices from flow-volume curves. However there was a large overlap. TD $\overline{X_{rs}}$ proved to be significantly lower than TD R_{rs6}, TD $\overline{R_{rs}}$, TD $MEFV_{25}$, TD $PEFV_{25}$ and TD FEV_1. Although also lower than TD $\overline{dR_{rs}/df}$ this difference was not significant (for explanation of symbols see table of symbols, abbreviations and units on pages 9 and 10). For

clinical purposes TD indices can be used in asthmatics in whom severe induced bronchoconstriction should be prevented. $\overline{TD\ dR_{rs}/df}$ values measured in 19 healthy previously studied children (Duiverman et al., 1985a) are shown in figure 9.1. Median value was > 128 x 10^{-5} g histamine. Most children did not react even after inhalation of 128 x 10^{-5} g histamine. Inhalation of higher dosages of histamine would have caused side effects. To calculate mean TD $\overline{dR_{rs}/df}$ these children were regarded as if they reacted after inhalation of 128 x 10^{-5} g. Hence the calculated mean value of TD $\overline{dR_{rs}/df}$ (i.e. 72 x 10^{-5} g histamine) is too low. As this is higher than 64 x 10^{-5} g (i.e. the highest dose generally used in clinical practice) this supposition is justified. It is obvious that TD values were found to be significantly lower than PD values. PD obtained from FOT was lower than PD derived from flow-volume curves. However the differences were not significant. For routine purposes $PD_{40}\ R_{rs6}$ appeared to be a sensitive and feasible FOT index to define BR. It was highly correlated with the commonly used $PD_{20}\ FEV_1$ (r = 0.84) (figure 9.2).

The median $PD_{40}\ R_{rs6}$ was > 128 x 10^{-5} g (figure 9.1). When calculated in the same way as TD $\overline{dR_{rs}/df}$ the mean $PD_{40}\ R_{rs6}$ in healthy children was 83 x 10^{-5} g histamine. BR to histamine measured by $PD_{40}\ R_{rs6}$ as well as by TD $\overline{dR_{rs}/df}$ is significantly higher in asthmatic patients and healthy subjects with a positive family history of asthma or hay-fever then in the ones without (figure 9.1; figure 2, page 91).

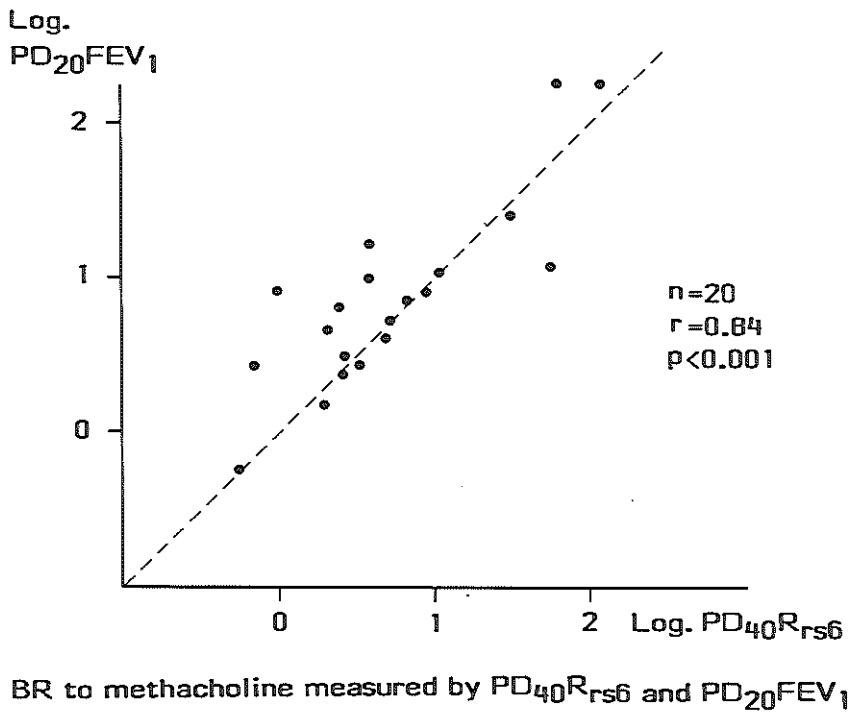

Figure 9.2. Bronchial responsiveness to histamine measured by $PD_{40}\ R_{rs6}$ and $PD_{20}\ FEV_1$.

The within-subject reproducibility of BR to methacholine and histamine was measured in asthmatic patients aged 3 to 8 (Duiverman et al., 1985c). Standard deviations of log TD and PD_{40} were used to calculate the reproducibility by a two way analysis of variance. The reproducibility of the response was measured by the standard deviation of log TD and log PD to histamine vs. methacholine and to histamine vs. histamine.
Within a 24 hour interval, it was about 0.3 (table 2, page 77), which implies that the relative deviations were about a factor 2 above or be low the observed TD or PD values (figure 4, page 78). Hence the 24 hour reproducibility of BR measured by FOT in young asthmatic children proved to be good.

Both methacholine and histamine have cumulative effects when inhaled at short intervals (Cartier et al., 1983; Tremblay et al., 1984). If we compare the data of Cartier et al. (1983) with the data of Neijens et al. (1982) and Tremblay et al. (1984), it seems that cumulation occurs after inhalation of lower doses of methacholine than of histamine. This is also supported by the finding that values of TD methacholine were lower than values of TD histamine while values of PD were the same. (figure 1, page 75).

We did not find a significant correlation between baseline $\overline{R_{rs}}$, R_{rs6}, $\overline{dR_{rs}/df}$ and $\overline{X_{rs}}$ and TD or PD to methacholine or histamine. This is in agreement with findings in asthmatic (Chung et al., 1982) and healthy subjects (Chung et al., 1982; Chung and Snashall, 1984). However, they found that whereas the slope of the dose-response curve was correlated to the starting airway calibre in asthmatics but not in normal subjects, PD_{35} sG_{aw} (i.e. 35 per cent decrease from baseline sG_{aw}) was not correlated to baseline airway calibre.

To attempt to answer the question whether severe lung injury at an early age might induce permanent changes in the respiratory system we carried out a follow-up study of children who had bronchiolitis in infancy (Duiverman et al., 1985d), or who had neonatal bronchopulmonary dysplasia (BPD) Duiverman et al., 1985e). We also studied children who experienced a near-drowning accident (ND) (Duiverman et al., 1985e).

Infant bronchiolitis is a clinical syndrome which is characterized by the acute onset of wheezing, cough, dyspnoea, rhinorrhoea and hyperinflation (Wohl and Chernick, 1978). A viral infection (RS virus, adenovirus) is often found in conjunction with infant bronchiolitis. It may be difficult to make a distinction between bronchiolitis and asthma. This results in controversial opinions about the nature of bronchiolitis (McConnochie, 1983). Although recovery from bronchiolitis almost invariably occurs over days or weeks, a substantial proportion of the children involved have subsequent episodes of wheeze and cough in the following years (Stokes et al., 1981; Pullan and Hey, 1982; Henry et al., 1983). The question arises whether these respiratory symptoms are the result of airway damage by the viral infection or whether infant bronchiolitis was an early marker of asthma. From our data and from data in the literature (Wohl and Chernick; 1978) it appears that the children who were admitted to hospital because of infant bronchiolitis and in whom recurrent respiratory symptoms continue to be present after preschool age often have characteristics of asthma (i.e. decreased airway

patency, increased bronchial smooth muscle tone or increased BR) (figures 1,2 and 3, pp 89-93) (Duiverman et al., 1985d).
Airway patency, bronchial smooth muscle tone and BR were normal in the other children in whom respiratory symptoms disappeared during preschool years. In these subjects symptoms which were present after the bronchiolitis episode may have been related to airway damage and disappeared during the recovery period. It therefore seems that children with previous bronchiolitis who continue to have respiratory symptoms after the age of about 4 should be regarded as asthmatics and be treated as such.

Severe lung injury during early life may affect the growth and development of the respiratory system (Thurlbeck, 1982). Injury of immature lung structures may especially cause subsequent damage of peripheral airways (Fagan, 1982). Many children have a high incidence of lower respiratory tract illness in the first years after BPD (Shankaran et al., 1984). However symptoms improve in the majority during the first 3 to 4 years of life. Several investigators showed residual lung function abnormalities after neonatal respiratory distress syndrome and BPD (i.e. increased airways resistance, decreased compliance, decreased static and dynamic lung volumes and expiratory flows and slightly abnormal arterial oxygen and carbon dioxide values) (Lamarre et al., 1973; Stocks and Godfrey, 1976; Borkenstein et al., 1980; Smyth et al., 1983). Lung damage in survivors of adult respiratory distress syndrome is usually repaired with little or no residual defects in lung function (Rinaldo and Rodgers, 1982). Subtle abnormalities of gas exchange (Fanconi et al., 1985) indicating residual peripheral airway damage have been described. Moderately increased BR has been described after BPD (Mallory and Motoyama, 1984; Wheeler et al., 1984) and ND (Laughlin en Eigen, 1981).

We investigated the presence of recurrent respiratory symptoms, decreased airway patency, increased bronchial smooth muscle tone and increased BR in 3 to 10 year old children who had lung injury during early life (i.e. BPD due to artificial ventilation beause of neonatal respiratory distress syndrome) or in the first years of life (i.e. ND with or without adult respiratory distress syndrome) (Duiverman et al., 1985e). Results were compared with data from healthy children of about the same age without past or current respiratory symptoms or severe lung injury. Only mild abnormalities were found during later childhood in those children who suffered from pulmonary injury in early life. The most common finding was abnormal peripheral airway patency as assessed by $\overline{dR_{rs}/df}$ in symptomatic children who had BPD (table 1, page 103). Neither bronchial smooth muscle tone nor BR assessed by PD_{40} R_{rs6} was increased in these subjects. Some showed moderately increased BR when TD $\overline{dR_{rs}/df}$ was used. An explanation for this may be that TD $\overline{dR_{rs}/df}$ is about twice as sensitive as PD_{40} R_{rs6} in indicating induced bronchoconstriction (Duiverman et al., 1985b). No residual abnormalities were found after ND.

Future studies

We recommend to measure lung function and BR in children with respira-

tory symptoms at as young as possible age since early detection of abnormalities and treatment of symptoms may be important for the prognosis of childhood obstructive lung disease. Although several studies indicate a relationship between obstructive lung disease in adults and childhood asthma (Barter and Campbell, 1976; Burrows et al., 1977; Blair, 1977) the question of whether childhood asthma is a risk factor for reversible or irreversible airways obstruction in adults remains unsolved. The same is true for the underlying lesions after lung injury in early life. The question can only be resolved by longterm prospective studies starting at a young age. The feasibility of these studies is however limited. FOT is a suitable method to determine bronchial patency and BR in children who are too young to perform spirometry or flow-volume measurements. It is not known whether pharmacological intervention in children with characteristics of asthma (i.e. bronchoconstriction and increased BR) will modify the future outcome. Neither can a reasonable speculation be made. Well designed prospective studies should be carried out to answer this question.

FOT should be adapted to permit measurements in children younger than 2 years of age (König et al., 1984). Apart from clinical applications, for instance trials on the efficacy of drugs, it might then be possible to differentiate better between genetic and environmental influences on the development with age of bronchial patency, bronchial smooth muscle tone and BR.

HOOFDSTUK 10. SAMENVATTING

Toegenomen bronchiale prikkelbaarheid (BR) wordt algemeen beschouwd als een erfelijk bepaald kenmerk van astma (Sibbald et al., 1980b), dat in belangrijke mate bijdraagt tot het manifest worden van symptomen. Deze treden vaak voor het eerst op tijdens de kleuterleeftijd (Burrows et al., 1977; Samet et al., 1983). Als de hypothese juist is, dat vroegtijdige herkenning en behandeling van astma het verloop hiervan in gunstige zin beïnvloeden, dan is het vaststellen van longfunktie afwijkingen en verhoogde BR op zo jong mogelijke leeftijd geïndiceerd (Kerrebijn, 1982). Hiervoor is longfunktie onderzoek noodzakelijk. Echter, betrouwbaar longfunktie onderzoek is over het algemeen slechts mogelijk indien het kind aktief kan en wil meewerken. Dit maakt de meeste methoden ongeschikt voor toepassing bij kinderen jonger dan 6 jaar (Weng and Levison, 1969; Dickman et al., 1971; Polgar and Weng, 1979; Dockery et al., 1983). De geforceerde oscillatie techniek (Lándsér et al., 1976a) is een longfunktie methode die bij jonge kinderen kan worden toegepast, omdat slechts passieve medewerking (stil zitten en spontaan rustig ademen gedurende 16 seconden) nodig is.

In dit onderzoek is de toepasbaarheid van de geforceerde oscillatie techniek volgens Lándsér (FOT) (1976a) op de kleuterleeftijd nagegaan. Met behulp van FOT werd het vóórkomen van bronchusobstructie, alsmede de aanwezigheid van een toegenomen tonus van het bronchiaal gladspierweefsel en toegenomen BR onderzocht bij 3- tot 7-jarige kinderen met astma, bij kinderen die op zuigelingenleeftijd bronchiolitis doormaakten, bij kinderen zonder symptomen van astma maar met een ernstige beschadiging van de longen op zeer jonge leeftijd (bronchopulmonale dysplasie (BPD), bijna verdrinking), en bij gezonden.

Hoofdstuk 1 beschrijft de motieven en de vraagstellingen van het onderzoek. Een korte bespreking met betrekking tot pathofysiologie van astma en toegenomen BR alsmede de klinische betekenis zijn weergegeven.

Hoofdstuk 2 beschrijft de theoretische achtergronden van de geforceerde oscillatie techniek aan de hand van een elektrisch long model. Hoewel niet alle facetten van de oscillatie techniek met behulp van een elektrisch model kunnen worden verklaard biedt dit inzicht in de fysische achtergronden. Geforceerde oscillometrie werd voor het eerst gepresenteerd door DuBois et al. (1956). Een kort historisch overzicht van de ontwikkelingen tot de methode volgens Lándsér et al. (1976a) wordt beschreven.

Met behulp van een lage tonen luidspreker worden geluidsgolven van 2-26 Hz gesuperponeerd op de rustige spontane ademhaling. Drukverandering en stroomsnelheid worden aan de mond gemeten. Hieruit en uit de fase verschuivingen tussen druk en stroomsnelheid kunnen de weerstand (R_{rs}) en de reactantie (X_{rs}) van het respiratoire systeem door digitale filtering simultaan worden berekend. R_{rs} wordt voornamelijk bepaald door de diameter van de bovenste en de centrale luchtwegen, terwijl X_{rs} bepaald wordt door de elasticiteit en de traagheid

van het long-luchtweg systeem inclusief de thoraxwand. Omdat R_{rs} en X_{rs} gemeten worden over een frequentiespectrum (2-26 Hz) in plaats van bij één enkele frequentie, is het mogelijk de frequentie-afhankelijkheid van R_{rs} (dR_{rs}/df) en X_{rs} te onderzoeken. Op basis van de longmodellen volgens Otis et al. (1956) en volgens Mead (1969), in de praktijk getest door Kjeldgaard et al. (1976), kan worden verklaard dat het optreden van frequentie-afhankelijkheid een indicatie is voor bronchusobstructie in de perifere luchtwegen.

In hoofdstuk 3 is de invloed van niet gestandaardiseerde meetomstandigheden met betrekking tot gemeten R_{rs6}, $\overline{dR_{rs}/df}$ en $\overline{X_{rs}}$ waarden besproken. Kleine afwijkingen in posities van het hoofd van het kind ten opzichte van de oscillator alsmede een afwijkende positie van de tong en een toegenomen tonus van mondbodem en farynx musculatuur blijken slechts geringe betekenis te hebben. Een goede fixatie van de wangen en de mondbodem is van meer belang. Wij adviseren derhalve jonge kinderen niet toe te staan de fixatie zelf te verrichten, maar de wangen en mondbodem te steunen met de handen van de onderzoeker.

Omdat de beschreven methode nog niet eerder toegepast is bij kinderen is allereerst een referentiewaarden onderzoek verricht. De resultaten zijn besproken in hoofdstuk 4.

Referentiewaarden voor R_{rs} en X_{rs} versus frequentie (f) zijn gemeten bij 255 gezonde kinderen van 2.3 tot 12.5 jaar (Duiverman et al., 1985a). Deze werden geselecteerd op basis van een negatieve anamnese t.a.v. astma (tenminste 5 maal per seizoen hoesten en/of opgeven van sputum gedurende minstens 10 dagen indien niet behandeld; recidiverende aanvallen van benauwdheid of piepen; benauwdheid of piepen in rust of na inspanning) en het ontbreken van pulmonale afwijkingen bij algemeen lichamelijk onderzoek. De referentiewaarden zijn afhankelijk van het geslacht, de leeftijd, de lengte en het gewicht (tabel 1, blz. 46). Bij een lengte groter dan gemiddeld voor de leeftijd is R_{rs} lager en X_{rs} hoger. Het omgekeerde is het geval indien de lengte geringer is dan gemiddeld. Hoewel de invloed van het gewicht minder sterk is dan die van de lengte, blijkt overgewicht hogere R_{rs} en lagere X_{rs} waarden te veroorzaken. Het omgekeerde is het geval bij een gewicht dat lager is dan gemiddeld voor de leeftijd en de lengte.

Tussen jongens en meisjes bestaan 3 opvallende verschillen (figuren 3,4,5 en 6, blz 44, 45 en 47).

1. Op jonge leeftijd is $\overline{R_{rs}}$ hoger bij jongens dan bij meisjes. Op 8-jarige leeftijd is geen verschil aanwezig, terwijl op 12-jarige leeftijd $\overline{R_{rs}}$ bij jongens opnieuw hoger is dan bij meisjes.
2. Jongens beneden ongeveer 5 jaar vertonen frequentie-afhankelijkheid van R_{rs}. Dit is niet geval bij oudere jongens of bij meisjes.
3. $\overline{X_{rs}}$ is op alle leeftijden lager bij jongens dan bij meisjes.

De hogere $\overline{R_{rs}}$ waarden wijzen op een kleinere luchtwegdiameter bij jongens dan bij meisjes jonger dan 5-6 jaar en ouder dan 10-11 jaar. Op basis van het longmodel van Mead (1969) kunnen de frequentie-afhankelijkheid en de lagere $\overline{X_{rs}}$ waarden bij jongens beneden de 5 jaar worden verklaard uit ten opzichte van meisjes minder wijde perifere luchtwegen.

In hoofdstuk 5 is een vergelijking van verschillende FOT en flow-vlume indices voor het aantonen van methacholine-geïnduceerde bronchoconstrictie besproken.

BR is gemeten door middel van provocatie met histamine en methacholine. Een constante hoeveelheid agens werd toegediend in de mond door middel van een aan een DeVilbiss vernevelaar type 646 gekoppelde Rosenthal-French dosimeter. De geïnhaleerde monddoses bedroegen 0.25, 0.5, 1,2,4,8,16,32,64 en 128 x 10^{-5} gram histamine of methacholine.

Drempel dosis (TD) en provocatie dosis (PD) zijn berekend uit een dosis-effect curve door lineaire interpolatie (figuur 2, blz. 60). TD is gedefineerd als de dosis die een verandering veroorzaakt die even groot is als 2 x de standaard afwijking van de gemiddelde basiswaarde van de toegepaste longfunktieindex (Dehaut et al., 1983); het gemiddelde en de standaardafwijking zijn bepaald uit 5 achtereenvolgende metingen direct vóór de provocatie. PD is gedefinieerd als de dosis welke een tevoren vastgestelde percentuele verandering van de toegepaste longfunktie index ten opzichte van de gemiddelde basiswaarde tengevolge heeft (Dehaut et al., 1983). De provocatie werd beëindigd nadat 128 x 10^{-5} gram histamine of methacholine werd geïnhaleerd of eerder indien de PD bereikt werd. Bronchoconstrictie werd opgeheven door toediening per dosis aerosol van 2 x 10^{-4} gram fenoterol en 0.2 x 10^{-4} gram ipratropium bromide.

Methacholine inhalatie is verricht bij 20 astma patiënten, 9 tot 16 jaar oud. Het effect is gemeten met behulp van FOT ($\overline{R_{rs}}$, R_{rs6}, $\overline{dR_{rs}/df}$ en $\overline{X_{rs}}$) (zie lijst van afkortingen) en maximale en partiële expiratoire flow-volume curves (FEV_1, $MEFV_{25}$, $PEFV_{25}$). TD en PD zijn weergegeven in figuur 3, blz. 63-64). TD $\overline{X_{rs}}$ is de meest gevoelige index. De verschillen tussen TD $\overline{X_{rs}}$ en de andere indices zijn significant (signed rank test; $p < 0.05$) met uitzondering van het verschil tussen TD $\overline{X_{rs}}$ en TD $\overline{dR_{rs}/df}$. De TD waarden gemeten met de overige indices verschillen niet significant van elkaar. Hieruit volgt dat deze even gevoelig voor het aantonen van methacholine-geïnduceerde bronchoconstrictie zijn als de TD waarden die zijn verkregen met indices van een volledige of partiële flow-volume curve. TD waarden zijn significant lager dan PD waarden (signed rank test; $p < 0.01$). PD_{40} R_{rs6} (de dosis die een 40% toename van R_{rs} bij 6 Hz ten opzichte van de basismeting veroorzaakt) komt goed overeen met PD_{20} FEV_1 (de dosis die een 20% daling van het FEV_1 geeft) ($r = 0.84$; $p < 0.001$) (figuur 9.2, blz. 115).

De intra-individuele reproduceerbaarheid van 5 opéénvolgende FOT metingen komt overeen met die van flow-volume curves (tabel 1, blz 62). FOT blijkt dus een gevoelige en reproduceerbare longfunktiemethode voor het aantonen van methacholine geïnduceerde bronchusobstructie te zijn.

BR voor histamine en methacholine werd vergeleken bij astmatische kinderen 3.6 tot 7.8 jaar oud en is besproken in hoofdstuk 6. De metingen vonden gerandomiseerd plaats op 2 opéénvolgende dagen om 9.00 uur in de ochtend. Van de FOT metingen zijn de $\overline{R_{rs}}$, R_{rs6}, $\overline{dR_{rs}/df}$ en $\overline{X_{rs}}$ berekend. Basis long funktiewaarden verschilden niet significant op beide dagen (tabel 1, blz 76). Alle indices verbeterden significant (> 2 SD) na bronchusverwijding. Dit betekent dat bij deze jonge astmatische kinderen een toegenomen tonus van het bronchiaal

glad spierweefsel bestond. De TD en PD voor histamine en methacholine zijn weergegeven in figuur 1 (blz 75). BR voor histamine en methacholine komt goed overeen. De reproduceerbaarheid uitgedrukt als de standaard deviatie van log TD en PD waarden bedraagt ongeveer 0.30. Dit betekent dat de relatieve variatie een factor 2 hoger en lager dan de gemeten TD of PD waarden bedraagt. Dat wil zeggen dat de berekende dosis met 95% zekerheid, indien het onderzoek wordt herhaald met of histamine dan wel methacholine, zal liggen tussen de helft en het dubbele van deze dosis (figuur 4, blz 78).

De intra-individuele 24-uur reproduceerbaarheid van BR voor histamine werd gemeten met behulp van FOT bij 21 kinderen met astma 3.9 tot 8.5 jaar oud. De metingen vonden plaats om 9 uur in de ochtend. Basis longfunktiewaarden verschilden niet significant op beide dagen (tabel 1, blz 76). Alle indices verbeterden significant na bronchusverwijding, hetgeen impliceert dat ook bij deze kinderen een toegenomen tonus van het bronchiaal glad spierweefsel bestond. TD en PD waarden zijn weergegeven in figuur 3, (blz. 78). De intra-individuele 24 uur reproduceerbaarheid van BR voor histamine, uitgedrukt als de standaard deviatie van log TD en PD is ongeveer 0.30. Dit betekent dat de relatieve variatie een factor 2 hoger of lager dan de gemeten TD en PD waarden bedraagt (figuur 4, blz 78).

De variabiliteit komt overeen met die welke is gevonden bij oudere astma kinderen onderzocht met behulp van andere longfunktie methoden (Hariparsad et al., 1983).

In hoofdstuk 7 is een follow-up studie beschreven bij kinderen die op zuigelingenleeftijd bronchiolitis doormaakten. Verscheidene studies hebben aangetoond dat na bronchiolitis een verhoogd risico voor het optreden van recidiverende luchtwegobstructie bestaat. Een aantal kinderen blijkt op ongeveer 4-jarige leeftijd geen klachten meer te hebben, terwijl deze bij anderen persisteren. De kinderen die bronchiolitis doormaakten zijn vergeleken met astma patienten en gezonden van dezelfde leeftijd wat betreft hun ademweerstand, het effect van bronchusverwijdende medicatie en BR voor histamine. De meeste kinderen die na bronchiolitis nog recidiverende respiratoire klachten vertoonden bleken hetzij een toegenomen ademweerstand te vertonen (figuur 1, blz 89-90), dan wel een toegenomen tonus van het bronchiaal glad spierweefsel (figuur 3, blz 92-93) of een matig toegenomen BR (figuur 2, blz 91) of een combinatie hiervan (tabel 1, blz 87). Zij kunnen worden vergeleken met kinderen met milde astmatische verschijnselen. Daarentegen bleken kinderen zonder klachten vergelijkbaar te zijn met gezonde leeftijdgenoten. Respiratoire klachten na bronchiolitis op zuigelingenleeftijd die na de peuterleeftijd blijven bestaan dienen te worden beschouwd als astma en dienen als zodanig te worden behandeld.

De invloed van ernstige longbeschadiging op jonge leeftijd op de ontwikkeling van de ademweerstand, de bronchiale spiertonus en de BR is beschreven in hoofdstuk 9. Metingen werden verricht bij kinderen die bronchopulmonale dysplasie (BPD) tijdens de neonatale periode doormaakten en bij kinderen die op peuterleeftijd een bijna-verdrinkingsongeval overleefden. Gevonden parameters

werden vergeleken met die gevonden bij gezonden van dezelfde leeftijd.

Vroege beschadiging van de longen blijkt bij de meeste kinderen geen afwijkingen in de ademweerstand gemeten met de R_{rs6}, de bronchiale spiertonus of de BR ten gevolge te hebben gehad (tabel 1 en 2, blz 103). De ademweerstand gemeten met de $\overline{dR_{rs}/df}$ blijkt daarentegen bij 4 van de 6 kinderen met luchtwegklachten die BPD hadden gestoord te zijn. Dit was niet het geval bij degenen met een bijna-verdrinkings ongeval. $\overline{dR_{rs}/df}$ is een maat voor de doorgankelijkheid van de perifere luchtwegen. Beschadiging van immatuur longweefsel, zoals bij BPD, kan leiden tot een gestoorde groei en ontwikkeling van de longen (Thurlbeck, 1982). Met name afwijkingen ter plaatse van de perifere luchtwegen kunnen het gevolg zijn. Het zijn namelijk deze luchtwegen die niet alleen nog incompleet aangelegd zijn, maar waar ook de grootste beschadiging opgetreden is (Fagan, 1982). Wat de betekenis van deze afwijkingen is voor de ontwikkeling van de longen op de lange termijn is nog onbekend.

Als vroegtijdige herkenning en behandeling van bronchusobstructie en toegenomen BR belangrijk zijn voor het verloop van bronchusobstructieve aandoeningen op lange termijn, kan het objectiveren hiervan op jonge leeftijd gewenst zijn. De geforceerde oscillatie techniek is daarvoor een methode die gemakkelijk kan worden toegepast omdat slechts passieve medewerking van het kind verlangd wordt.

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POST SCRIPTUM

De afronding van een promotie onderzoek is slechts mogelijk door de hulp van velen.

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Curriculum vitae

De schrijver van dit proefschrift werd op 3 september 1951 te Moordrecht geboren. In 1969 behaalde hij het diploma HBS-B aan de Rijks-HBS te Gouda. Na 1 jaar militaire dienst in Breda en 's-Hertogenbosch werd de studie in de geneeskunde aan de Medische Faculteit Rotterdam aangevangen. Van 1-2-73 tot 1-9-74 was hij als student-assistent werkzaam op de afdeling Kindergeneeskunde van het Sophia Kinderziekenhuis Rotterdam. Het arts-diploma werd op 16-12-76 behaald aan de Erasmus Universiteit te Rotterdam. Van 1977 tot 1981 specialiseerde hij zich in de Kindergeneeskunde in het Sophia Kinderziekenhuis (hoofd: Prof.Dr. H. K. A. Visser). Op 1 januari 1981 werd hij als kinderarts in het specialisten-register ingeschreven. Van 1981 tot 1984 volgde hij een opleiding tot kinderarts-pumonoloog op de afdeling longziekten van het Sophia Kinderziekenhuis (hoofd van de afdeling longziekten: Prof.Dr. K. F. Kerrebijn). Sindsdien is hij als wetenschappelijk hoofdmedewerker op de afdeling longziekten werkzaam. Hij is getrouwd met Marian Oudijk en heeft twee kinderen: Sytse en Marieke.

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