Reference values of total respiratory resistance, determined with the "opening" interruption technique

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ABSTRACT: In a large epidemiological survey of lung function the subjects performed maximum expiratory flow volume (MEFV) manoeuvres. They were also interviewed by trained interviewers using a standardized questionnaire. In a random subset of the subjects the resistance of the respiratory system was measured with the "opening" interruption technique, in which the mouth pressure before the end of the interruption period is divided by the flow shortly after the end of it. The subset contained men and women, and smokers as well as nonsmokers, 229 of whom were considered to be healthy because they had no history of compliants and a "normal" flow-volume curve. In this group mean inspiratory and expiratory resistances did not differ significantly (0.27 and 0.29 for men and 0.39 and 0.38 kPa·l^{-1}·s for women). The averages of in- and expiratory resistance were 0.28±0.10 kPa·l^{-1}·s for men and 0.39±0.11 kPa·l^{-1}·s for women. The resistance values were slightly but significantly correlated with body height, FEV_1 and MEF_{50}, but not with smoking habits. Due to the considerable variability the method does not permit sharp discrimination between normal and abnormal subjects. However, it appears to be useful in histamine challenge testing, to detect and monitor bronchial asthma, being not subjected to the disturbing effect of forced ins- and expirations.
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The method of determining respiratory resistance by interruption of the air flow was introduced by VON NEERGAARD and WIRZ [1]. They suggested measuring respiratory flow at the mouth immediately before a short occlusion of the mouthpiece, and the driving pressure in the respiratory system shortly after the start of the occlusion. In this way the pressure represents the driving force which moves intrabronchial air, deforms lung tissue and which is also partly responsible for deformation of thoracic and abdominal tissues (MEAD and WHITTENBERGER [2]). It is influenced by the compliance of the upper airway (cheeks) [3], and by retarded equilibration of mouth- and alveolar pressure [4–6]. Reference values for this method were published by FRÉOUR et al. [7]. JAEGER [8] presented a similar method which accounted for the slow equilibration, and PETIT et al. [9] suggested recording mouth pressures measured during interruptions of different durations.

VAN DER PLAS and VOOREN [10] introduced an alternative method which consists of measuring pressure during, and flow just after the end of the interruption: it is referred to as the "opening" interruption method. This method was recently introduced in the histamine challenge test for detection of bronchial asthma because there are no disturbing effects of previous deep inspirations, because there is no need for cooperation by the patient,

and because the technique can be used simultaneously with the inhalation of aerosols [11]. Until now no reference values for this variant of the interruption method have been published. In this study resistance values, obtained in a large epidemiological study, are reported and analysed.

Patients and measurements

The data were obtained during the 1985 survey of the Vlaardingen-Vlagtwedde longitudinal lung function study [12]. All subjects were between 30 and 75 years of age. They were interviewed by trained interviewers using a slightly modified version of the Medical Research Council questionnaire. From the answers it was determined whether subjects were suffering from persistent cough or phlegm, or shortness of breath when walking with persons of the same age, wheezing of the chest, or asthmatic attacks, which are symptoms of Chronic Non Specific Lung Disease (CNSLD). People without any of these symptoms, either in the present or in the past, were assigned to the "no history" group. The questionnaire also contained questions on smoking habits. People who had stopped smoking at least one month before the study was conducted were considered to be ex-smokers.

A large group of the subjects in the study also performed maximal expiratory flow volume (MEFV) manoeuvres. Following the recommendations of the European Commission for Coal and Steel [13] we measured forced vital capacity (FVC), peak flow (PEF), maximal mid-expiratory flow (MMEF), maximum expiratory flow at 25, 50 and 75% of the forced vital capacity (MEF_{25}, MEF_{50} and MEF_{75}), and forced expiratory volume in one second (FEV_1). Reference equations for MEF_{50} and FEV_1 as reported in [13], and the corresponding residual standard deviations (SD) were used to detect abnormal subjects, as characterized by a value of MEF_{50} or FEV_1 more than 1.64 SD below the predicted value. Only persons with normal values for both MEF_{50} and FEV_1 were considered to have a normal MEFV curve.

The measurement of respiratory resistance was performed in a random subsample from the group which had already performed the flow-volume manoeuvre. This resulted in a total of 395 measurements. Of these, 16 were discarded because the resistance measurement had been technically unsatisfactory and 5 more because the resistance values showed unacceptably high differences between inspiratory and expiratory values. Of 3 persons the height value was missing and 19 flow-volume curves were discarded for technical reasons. A total of 352 records, 198 of male and 154 of female subjects remained.

Methods

Flow volume curves

Maximum expiratory flow volume curves were obtained by trained operators. After maximum inspiration the subject (in standing position) exhaled as forcibly and as long as possible through a heated, straight and smooth PVC tube with a length of 50 cm and an internal diameter of 2.5 cm, which was connected to a Lilly-type pneumotachograph equipped with differential pressure transducer (Jaeger pneumotachoscript). The flow signal was recorded by a computer which computed the usual flow volume indices. Following the ECCS recommendations at least 3 technically satisfactory MEFV curves were recorded. The FEV_1 and MEF_{50} values used in this paper are the largest values of these parameters occurring in those curves that had an FVC within 5% of the largest FVC.

Interruption method

The interruptor consisted of a tube with a diameter of 2 cm and a length of about 3 cm [14]. The distal end could be closed by a small valve which moved along the axis of the tube and was activated by a 7 cm lever, driven by an electromagnet. About 5 ms were required to open or close the valve.

The narrowed cross-section at the distal end of the tube functioned as a pneumotachograph when the valve was open. The pressure difference across the constriction, which was almost proportional to the squared flow

rate, was fed into a microcomputer which computed the corresponding flow value. Figure 1 illustrates a manoeuvre for the determination of inspiratory resistance. During inspiration the valve was closed when a predetermined flow rate of 0.2 $l \cdot s^{-1}$ was reached. Next the pressure at the proximal side of the valve - equal to mouth pressure - was measured, and the valve was opened when the pressure reached a value of 0.4 kPa. The pressure data obtained during interruption were used to estimate by extrapolation the pressure at about 16 ms after opening. Respiratory resistance, R_{rs}, was calculated as the ratio of this extrapolated pressure and the corresponding flow. In this way all resistance values were determined not at one and the same arbitrary flow, as in bodyplethysmographic and other resistance measurement methods, but at one and the same arbitrary pressure.
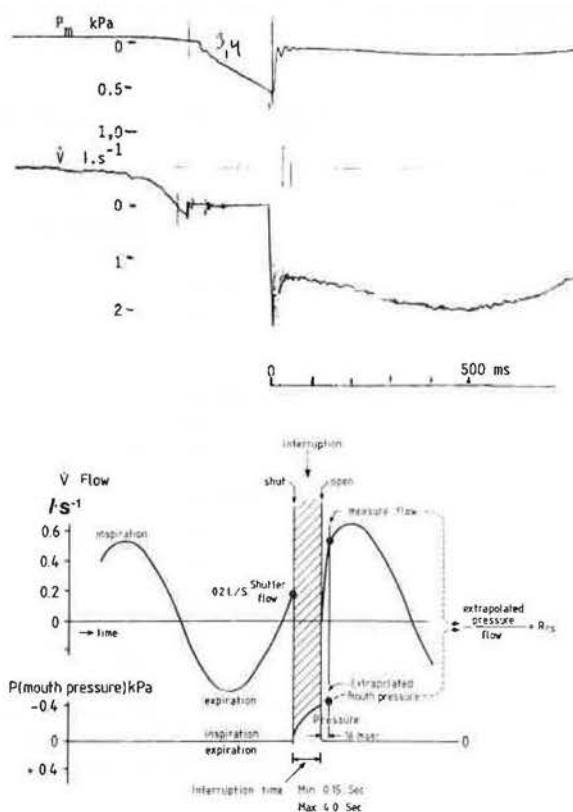

Fig. 1. – Course of measurements in the opening interruption technique. Real tracings of mouth pressure and flow against time in the upper panel, schematic explanation in lower panel. The shutter is closed as soon as an inspiratory flow of 0.2 $l \cdot s^{-1}$ is reached and opened when the pressure in the mouth becomes 0.4 kPa. Extrapolated mouth pressure at 16 ms after opening (after correction for resistance of the equipment) is divided by the flow measured at 16 ms after opening.

It is essential for the accuracy of the method, that mouth pressure and corresponding flow rate are measured within a very short time. It is assumed that respiratory effort behaves smoothly, and that big shifts in expiratory effort do not occur within a period of 45 ms.

The subjects breathed spontaneously in the sitting position with their elbows on a table. They wore a noseclip

and supported their cheeks with their fingertips. Resistance was first measured during expiration, for at least 5 consecutive breathing cycles, immediately after which followed at least 5 successive inspiratory measurements. The standard deviation of the resistance values was computed online and displayed to the operator. The objective was to obtain 5 consecutive resistance values with a coefficient of variation of at most 15%. Additional measurements were made if necessary. This could not be achieved in 16 cases. However, the material discussed here does not contain measurements with a standard deviation higher than 0.06 kPa·l^{-1}·s. The data to be presented are the mean values of the inspiratory (R_{in}) and expiratory (R_{ex}) resistances.

During the survey, three different resistance measurement instruments were used and subjects as well as instructors were assigned at random to these instruments. To check whether there was an instrument bias, a oneway analysis of variance (ANOVA) was performed for men and women separately. Differences between the instruments were not significant and therefore the results of the three instruments were pooled.

between smokers and nonsmokers were nowhere significant.

To be on the safe side in both women and men we decided that the reference group, i.e. the group with healthy subjects who were normal with respect to respiratory resistance, should consist of asymptomatic subjects with a normal MEFV curve. We disregarded smoking behaviour. This resulted in normal groups of 121 men and 108 women. In normal men the mean R_{in} and mean R_{ex} were 0.27±0.11 and 0.29±0.10 kPa·l^{-1}·s. For normal women these figures were 0.39±0.14 and 0.38±0.10 kPa·l^{-1}·s respectively. In both groups the differences between R_{in} and R_{ex} were not significant at the 10% level. Taking the average of inspiratory and expiratory resistance we found a mean R_{rs} of 0.28±0.10 kPa·l^{-1}·s in normal men and of 0.39±0.11 kPa·l^{-1}·s in normal women.

In these groups the influence of age, height, weight and overweight - as expressed in the Quetelet index - on R_{ex} and R_{in} were investigated by performing stepwise regression analysis for males and females separately. The upper part of table 2 shows which variables were entered

Table 1. – Mean values for R_{rs}

			Normal MEFV		Abnormal MEFV	
			nonsmokers	smokers	nonsmokers	smokers
Male	NH	R_{in}	0.258	0.290	0.448	0.323
		R_{ex}	0.282	0.309	0.416	0.379
		n	81	40	4	8
Female	NH	R_{in}	0.389	0.394	0.408	-
		R_{ex}	0.377	0.392	0.698	-
		n	76	32	1	0
Male	PH	R_{in}	0.307	0.304	0.433	0.433
		R_{ex}	0.301	0.327	0.412	0.401
		n	16	32	4	13
Female	PH	R_{in}	0.458	0.444	0.457	0.480
		R_{ex}	0.436	0.470	0.467	0.487
		n	26	11	4	4

Mean values for R_{rs} in kPa·l^{-1}·s for the different subgroups. $R_{in}=R_{rs}$ during inspiration, $R_{ex}=R_{rs}$ during expiration. NH: negative history for CNSLD, PH: positive history for CNSLD.

Results

On the basis of sex, flow volume curve (normal or abnormal), history (CNSLD or no CNSLD) and smoking behaviour (smoker or not-smoker), the subjects were divided into 16 groups. The mean results are given in table 1. Both resistance values differed significantly (p<0.001) between men with normal and those with abnormal MEFV curves. In women the difference was significant (p<0.025) only for R_{ex}. Regarding the anamnestic data, the differences between the groups with and without CNSLD were significant at the 2.5% level, except for R_{ex} in men. In general, subjects with positive history had somewhat higher resistance. Finally the differences

into the equations by the stepwise procedure using a 5% significance level for entry. Although the coefficients had values which agree with common sense, i.e. slightly negative for height, and slightly positive for age and weight, the multiple correlation coefficients which are also shown in table 2 were very low. The regression of R_{in} on age, height and weight in women produced the highest multiple correlation coefficient, 0.25. The influence of the various MEFV indices on R_{in} and R_{ex} was investigated in the same way. The lower part of table 2 shows the results of a stepwise regression of R_{in} and R_{ex} on the MEFV indices FVC, FEV_1, PEF, MEF_{25}, MEF_{50}, MEF_{75} and MMEF.

Table 2. – Regression coefficients for anthropometric and spirometric data

		Intercept	Height	Age	Weight	R^2
Male	R_{in}	1.25	-0.68		0.003	0.13
	R_{ex}''	0.94	-0.37			0.07
Female	R_{in}	1.27	-0.74	0.003	0.003	0.25
	R_{ex}''	0.98	-0.37			0.05

		Intercept	FVC	FEV_1	PEF	
Male	R_{in}	0.55	-0.058			0.22
	R_{ex}''	0.44	-0.033			0.09
Female	R_{in}	0.86		-0.083	-0.034	0.29
	R_{ex}''	0.55		-0.060		0.09

Multiple regression coefficients for height, age and weight, and for FVC, FEV_1 and PEF, obtained with stepwise regression analysis. R^2 is the squared multiple correlation coefficient.

Discussion

Reference values for respiratory resistance measured by the interruption technique have been published rather infrequently. FRÉOUR et al. [7] found values between 0.12 and 0.32 kPa·l^{-1}·s, which were influenced by smoking, sex and clinical state of obstruction, but not by age. They did not report differences between inspiratory and expiratory resistance.

Reference values for resistance measured by means of the forced oscillation technique have been published far more frequently [15–18]. Almost all of these authors found mean values between 0.22 to 0.25 kPa·l^{-1}·s for normal men and women. Many of them found little or no influence of smoking, and one ([15]) not even influence of sex. Table 3 shows some mean values from the literature.

Intra-individual variability in chronic obstructive subjects is relatively large in the classical interruption technique, in which flow rate and mouth pressure are measured before and after closure of the shutter respectively [10, 14, 19].

In the "opening" interruption technique (OI) however, mouth pressure and flow are measured respectively before and after opening of the shutter. Just after opening the distribution of gas flow is essentially determined by local resistances, and little influenced by local time constants. Although an interruption of 0.15–0.30 s may be too short for complete equilibration between local alveolar pressures in patients, what is measured is probably closer to a "pure resistance" than the values obtained by bodyplethysmography [20] or by the forced oscillation method [10]. This decreased influence of mechanical non-homogeneity may be responsible for the lower intra-individual variability of resistance with this method [6, 14].

The mean R_{rs} in our study was 0.33 kPa·l^{-1}·s, which is substantially higher than was reported in other studies. Alinear pressure-flow relationships are unlikely to be the only cause because pressure was triggered at about 0.4 kPa, so $\dot{V}$ should have been on average 1.2 l·s^{-1}. From Rohrer's equation it follows that at that flow the average contribution of alinear resistance to R_{rs} amounts to 0.036 kPa·l^{-1}·s, which should make resistances measured by the OI method about 0.03 kPa·l^{-1}·s higher than in the other studies, where alinear resistance is much smaller.

Pressure-flow relationships at the start of a respiratory movement however can be influenced by force-velocity relationships originating in the muscles [21], which means that with constant effort, the pressure exerted by the muscles falls as velocity increases, which has virtually the effect of an additional resistance.

We used the Quetelet index as an index of obesity. It did not show any relationship with R_{rs} in our study (table 2). This could mean that a large mass of tissue offers the same resistance as a small mass, or that the contribution of the resistance of thoracoabdominal tissues (R_w) to R_{rs} measured by the interruption technique is negligible. AMREIN et al. [15], who found a correlation between resistance and weight, did not measure resistance including R_w, but only airway resistance. LÀNDSÉR et al. [17] found a positive correlation between relative weight and total resistance including R_w. This, however, is the only indication of a positive influence of obesity on R_w in the literature.

Table 3. – Reference values in literature

Author	Year	Method	Ř	SD	A	S	H	Sm	W	n
FRÉOUR [2]	71	I	0.23	0.056	-	-	ND	+	ND	43
SOBOL [8]	68	F	0.22	0.056	-	-	-	-	ND	34
JIEMSRIPONG [9]	76	F	0.25	0.062	ND	+	ND	±	ND	76
PESLIN [18]	81	F	0.27	0.078	+	+	-	+	ND	118
LÀNDSÉR [16]	82	F	0.25	0.061	+	ND	+	-	+	407
AMREIN [15]	69	BP	0.185	0.060	-	+	-	ND	+	1260
This study	89	OI	0.330	0.117	-	++	+	-	-	229

Some data on reference values of respiratory or airway resistance found in the literature. I: classical interruption technique (R_{rs}); F: forced oscillation technique (R_{rs}); BP: body plethysmography (R_{aw}); OI: opening interruptor (R_{rs}); Ř: mean resistance (average of in- and expiration) in men and women together; SD: standard deviation. In further columns presence (+) or absence (-) are indicated of a significant relation with age (A), sex (S), body height (H), smoking habits (Sm) or overweight (W). ND=not done. n: number of subjects in the study.

In only one of the previous studies [17] the presence of some correlation between resistance and body height was also found. The existence of such a correlation is logical because anthropometric dimensions are widely accepted as good predictors of all static lung volumes [13] and could in the same way relate to the diameters of the bronchi.

We did not find significant differences between R_{in} and R_{ex} in the reference groups, neither did most other authors mention such a difference. The relatively great difference between the mean R_{rs} of men and women could be based on the most obvious difference between male and female airways: the dimensions of the glottis [23].

Further, we did not see any significant influence of smoking on resistance. This is in agreement with the conclusion of other authors [16, 17] that the influence of smoking is smallest among all influences. The lung function index which is most influenced by smoking, is the slope of phase III of the nitrogen washout curve [24]. This index, however, is to a large extent connected to peripheral airway disturbance. On the other hand, pure frictional resistance is mainly determined by the dimensions of the central airways [25]. This could suggest that R_{rs}, as measured by OI, concerns almost exclusively (i.e. for 80%, c. f. [25]) the central airways, while smoking affects the resistance of the peripheral airways.

In the group of "normal" subjects, i.e. subjects with negative history and a normal MEFV curve, variability in resistance was very large. This was also reported by some of the authors shown in table 3. Apparently in this adult population respiratory- and airway-resistance, in contrast to spirometric parameters, have no direct relation with anthropometric dimensions.

Among the "abnormal" subjects scatter is also large, and there is considerable overlap between both groups. For sharp discrimination between subjects with normal and abnormal ventilatory function the OI technique does not seem to be the right choice. The method however turned out to be useful in histamine challenge testing, to detect and monitor bronchial asthma [11]. In this field it is thought to be equivalent to methods using FEV_1, but the results are much less dependent on the cooperation of the patient, and the technique itself is much less laborious than methods based on R_{aw} or FEV_1.

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Valeurs de référence de la résistance respiratoire totale, déterminées avec la technique d'interruption "ouverte". P. Vooren, B. van Zomeren.

RÉSUMÉ: Au cours d'une enquête épidémiologique importante de la fonction pulmonaire, des sujets ont exécuté des manoeuvres de débit volume expiratoire maximum. Ils ont également été interviewés par des interrogateurs entraînés utilisant un questionnaire standardisé. Chez une fraction de sujets déterminée au hasard, la résistance du système respiratoire a été mesurée par la technique d'interruption "ouverte" dans laquelle la pression à la bouche avant la fin de la période d'interruption est divisée par le débit peu après la fin de celle-ci. L'échantillon contenait hommes et femmes, fumeurs aussi bien que non fumeurs; il comportait 229 sujets considérés comme bien portants sur la base de l'absence de plaintes à l'anamnèse et sur la base d'une courbe débit volume normale. Dans ce groupe, les résistances moyennes inspiratoires et expiratoires ne sont pas significativement différentes (0.27 et 0.29 pour les hommes, et 0.39 et 0.38 kPa·l^{-1}·s pour les femmes). Les moyennes des résistances inspiratoires et expiratoires furent de 0.28±0.10 kPa·l^{-1}·s pour les hommes et de 0.39±0.11 kPa·l^{-1}·s pour les femmes. Les valeurs de résistance s'avèrent légèrement mais significativement en corrélation avec le poids corporel, le VEMS et le débit expiratoire maximum 50, mais non avec les habitudes tabagiques. En raison d'une variabilité considérable, la méthode ne permet pas de discrimination étroite entre les sujets normaux et anormaux. Toutefois, elle apparaît utile pour les tests de provocation à l'histamine et pour déceler et suivre l'asthme bronchique, car elle n'est pas sujette aux effets perturbateurs des inspirations et des expirations forcées.
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