Eur Respir J
1992, 5, 213–218

Bronchial responsiveness, oscillations of peak flow rate and symptoms in patients with mitral stenosis

G. Rolla*, C. Bucca*, L. Brussino*, M. Bugiani**,
S. Bergerone+, D. Malara++, M. Morea+

Bronchial responsiveness, oscillations of peak flow rate and symptoms in patients with mitral stenosis. G. Rolla, C. Bucca, L. Brussino, M. Bugiani, S. Bergerone, D. Malara, M. Morea.

ABSTRACT: To better characterize airway hyperresponsiveness reported in cardiac patients questionnaire-recorded symptoms, bronchial responsiveness to methacholine (Mch) and to ultrasonically nebulized distilled water (UNDW), diurnal oscillations of peak expiratory flow (PEF) rate were evaluated in 32 patients with moderate mitral stenosis.

Twenty patients were responsive to Mch (defined as provocative dose producing a 20% fall in forced expiratory volume in one second (PD_{20} FEV_1) <3.2 mg) (geometric mean PD_{20} FEV_1 851±154 μg SE). Only two patients showed a fall in FEV_1 >20% after UNDW challenge.

Patients responsive to Mch challenge had lower FEV_1 as percentage of vital capacity (FEV_1/VC) (80±4.8 *vs* 83±3.8%, p<0.05), higher coefficient of variation of PEF (CV-PEF) (7.1±2.8 *vs* 5±2.4, p<0.05) and higher prevalence of wheeze (70 *vs* 25%, p<0.05) in comparison with patients non-responsive to Mch challenge. CV-PEF was significantly related to FEV_1 (r=0.347, p<0.05) and maximal expiratory flow at 50% expired volume (MEF_{50}) (r=0.405, p<0.05). The probability of responding to Mch bronchial challenge increased proportionally with the increase in CV-PEF and the decrease in FEV_1, FEV_1/VC and MEF_{50}.

Airway hyperrepsonsiveness of patients with mitral stenosis seems to be more similar to that reported in bronchitic than in asthmatic patients.

Eur Respir J, 1992, 5, 213–218.

* Clinica Medica Dell'Universita' di Torino,Torino, Italy. ** Dispensario di Igiene Sociale di Torino, Italy. + Istituto di Medicina e Chirurgia Cardiotoracica, Torino, Italy. ++ Istituto di Radiologia dell'Universita' di Torino, Torino, Italy.

Correspondence: G. Rolla
Clinica Medica dell'Universita' di Torino
Via Genova 3
10126 Torino
Italy.

Keywords: Airway hyperresponsiveness; cardiac asthma; methacholine; mitral stenosis; peak expiratory flow, nebulised water.

Received: April 18, 1991; accepted after revision September 3, 1991.

Supported by a grant from the Italian Ministry for Scientific Research.

Bronchial hyperresponsiveness to methacholine or histamine has been reported in patients with lung congestion and mitral valve disease [1, 2], ischaemic heart disease [3] or left heart failure from various causes [4].

Although the pathogenesis of bronchial hyperresponsiveness in cardiac patients has not yet been clarified, possible explanations are vagal reflex from interstitial lung oedema [5], vascular reactivity of the bronchial wall [3], decrease in airway calibre [6].

From a clinical point of view, it is tempting to relate bronchial hyperresponsiveness to the common respiratory complaints of cough, wheezing and acute episodic dyspnoea, the so-called "cardiac asthma" [7], even if there are no data concerning the relationship between bronchial responsiveness and symptoms in cardiac patients. Moreover, it is not presently known whether or not bronchial hyperresponsiveness of cardiac patients is related to diurnal variation in airway calibre, as has been shown in asthmatics [8], asymptomatic adults [9] and children [10] with bronchial hyperresponsiveness, by recording variation in peak expiratory flows.

Finally, we do not know whether stimuli other than chemicals, *i.e.* hypotonic solutions, act as bronchial constricting agents in cardiac patients, as they do in many asthmatics [11].

If airway hyperresponsiveness of cardiac patients depends only on mechanical factors (airway patency), we expect to find in them a pattern of responsiveness similar to that found in bronchitic patients: lack of hypotonic solution induced bronchial obstruction, significant relationship between methacholine bronchial threshold and baseline forced expiratory volume in one second (FEV_1), absence of wide oscillations of diurnal peak expiratory flow (PEF) recordings.

Therefore, the purpose of this study was to investigate in cardiac patients: 1) the relationship between history of cardiac asthma and airway hyperresponsiveness; 2) the amplitude of diurnal variations in airway resistance, as measured by diurnal oscillations of PEF; 3) the sensitivity of ultrasound nebulized distilled water (UNDW) bronchial challenge to detect airway hyperresponsiveness in comparison with methacholine bronchial challenge.

To this end, we evaluated questionnaire-recorded symptoms, bronchial responsiveness to methacholine

and to UNDW, and diurnal oscillations of peak flow in a group of patients with mitral stenosis.

Patients and methods

Thirty two patients with moderate mitral stenosis (mean valvular area 1.35, range 1.2–1.5cm^2), mean age 51.5 yrs (SD 10.3 yrs), admitted to out-patient clinic for scheduled periodic examination, were studied after signed informed consent had been obtained. In all of the patients diagnosis was supported by physical examination (accentuated first sound, opening snap and diastolic rumbling) [12], echocardiography (characteristic square wave motion of the E to F slope of the valve during diastole) [13], and chest X-ray (left atrial enlargement, prominence of hilar arteries, normal left ventricular size, redistribution of blood flow to the apices of the lung, increased interstitial lung markings [14]. The functional area of the mitral valve was calculated by echodoppler [15].

Many patients were regularly taking digitalis and diuretics (18 were taking thiazides associated with amiloride, 5 frusemide alone and 5 frusemide associated with spironolactone). All patients were clinically stable, and had not required change in therapy in the last two months. All patients were lifetime nonsmokers. Criteria for exclusion were: atopy, as defined by personal and familial history, drug therapy that could influence bronchial reactivity (beta-blocking drugs, calcium-antagonists), recent (6 weeks) airway infection.

Study design

At the time of entry into the study, a standardized questionnaire was administered to each patient by a physician not involved in the pulmonary function laboratory. Patients were asked to attend the pulmonary function laboratory twice, on the first day for respiratory function tests and methacholine bronchial challenge and, two days later, for UNDW bronchial challenge. All patients received instructions and supervision on PEF measurements, which they started to record the day after UNDW challenge.

Questionnaire data

A standardized questionnaire was used to obtain information on respiratory symptoms and illnesses. The symptoms evaluated in the present study were defined from the American Thoracic Society (ATS) questionnaire [16] as follows: "chronic cough" - cough on most days for as long as three months of the year for two consecutive years; "wheeze" wheezing with colds and occasionally apart from colds or wheezing on most days or nights; "effort dyspnoea" shortness of breath when walking with other people of their own age on level ground. Patients were also asked about the use of more than one pillow during sleep to avoid dyspnoea ("orthopnoea").

Pulmonary function tests

Vital capacity (VC), FEV_1 and maximal expiratory flow-volume curve were obtained by a computerized water-sealed spirometer (Biomedin, Padova, Italy), according to standardized procedures [17]. Functional residual capacity was determined by helium dilution technique. For static and dynamic lung volumes reference values of European Commission of Coal and Steel were used [18]; for maximal expiratory flow at 50% of forced expiratory capacity (MEF_{50}) the values of KNUDSON *et al.* were applied [19].

Methacholine inhalation challenge was performed according to a slightly modified standard method [20]. Briefly, methacholine was inhaled from a breath-activated dosimeter (MB3 MEFAR, Brescia, Italy), powered by compressed air at 1.5–1.7 bar. The nebulization time was adjusted to about 0.7 s and the number of breaths chosen was that necessary to achieve doubling of the drug dose. The mass median aerodynamic diameter of the particles is 1.69±3.3 (GSD) μm. The output of the nebulizer was 0.01 ml·breath^{-1}. Starting from a 1% freshly prepared solution of methacholine chloride (Lofarma, Milano, Italy), doses of methacholine were progressively doubled and subsequently administered at 5-min intervals until FEV_1 had fallen by 20% from baseline or until a cumulative dose of 3,200 μg had been reached. Methacholine challenge dose-response curves were constructed by plotting the percentage fall in FEV_1 from the control value against the cumulative dose of methacholine expressed in micrograms. Measurements of airway responsiveness were determined by linear interpolation between points on the log dose-response curve and expressed as the dose of methacholine required to produce a 20% decrease in FEV_1 ($PD_{20}FEV_1$). Patients with a measured $PD_{20}FEV_1$ were defined "responsive", while patients who did not have a measurable $PD_{20}FEV_1$ were defined as "non-responsive".

UNDW bronchial challenge

Nebulized distilled water (UNDW) challenge was undertaken [21], using a 65B nebulizer (DeVilbiss, Somerset, PA) at maximal setting. This has an output of 6 ml·min^{-1} giving aerosol particles of a mass median aerodynamic diameter of 6 μm [22].

The patients inhaled water through a face-mask and oral inhalation was ensured by using noseclips. After baseline measurements were made, patients were asked to breath normally for different lengths of time to give a succession of inhaled volumes of mist, *i.e.* 3, 6, 12, 24 and 48 ml at intervals of 5 min. FEV_1 was recorded 2 min after each provocation. The inhalations were stopped when FEV_1 had fallen by 20% or more. Bronchoconstriction was analysed by constructing stimulus-response curves with FEV_1 on the ordinate as percentage of the baseline value and

with the output of the nebulizer expressed logarithmically on the abscissa. The provocative output at which inhalation of UNDW produced a 20% fall in FEV_1 (PD_{20} UNDW) was obtained by linear interpolation of the last two points on the stimulus-response curve.

Starting from the day after UNDW challenge, each patient measured his peak expiratory flow (PEF) with a mini Wright peak flow meter three times daily (0700–0800, 1300–1400, and at bedtime) for 10–14 days. On each occasion the best of three blows was recorded. Flow recordings of each patient were coded and analysed with the aid of a computer-assisted program, with no knowledge of the results of bronchial challenge.

From flow recordings diurnal variation (VAR-PEF) was estimated from the difference between the daily maximum and minimum PEF, and expressed as percentage of the maximum value. The average of the period's results (10–14 days) was used for analysis. The coefficient of variation (mean±SD) of the whole period of PEF recordings was also calculated (CV-PEF).

Ten normal subjects (mean age 45±5 yrs), with no responsiveness to methacholine challenge, served as controls for PEF oscillations.

Statistics

Mean and standard deviation (SD) were calculated for each respiratory function test. Student's t-test for the difference of the means, Pearson's correlation coefficient and simple linear regression using the least-squares method, and Chi-squared were calculated when appropriate.

The association of bronchial methacholine responsiveness with spirometric data, PEF oscillations and symptoms was analysed by semi-parametric proportional hazard regression model of Cox for censored data [23]. The response to methacholine ($PD_{20}FEV_1$) was taken as the censoring indicator. FEV_1 (as difference from 100% of predicted), FEV_1/VC (as difference from 100%), CV-PEF, VAR-PEF, dyspnoea, orthopnoea, wheezing, were taken as predictive variables. Statistical significance was defined as a p value <0.05.

Results

Twenty out of 32 patients (62.5%) had a measured bronchial threshold to methacholine (mean $PD_{20}FEV_1$ 851±154 μg). Patients responsive to methacholine, as a group, had a lower FEV_1/VC ratio in comparison with patients non-responsive to methacholine (80±4.8 *vs* 83±3.8, respectively, p<0.05) (table 1). No significant linear relationship between methacholine $PD_{20}FEV_1$ and any spirometric test was found in the 20 patients responsive to methacholine bronchial challenge.

Table 1. – Mean±SD of age, respiratory function tests and PEF oscillations in patients responsive (measured $PD_{20}FEV_1$) and non-responsive (non measurable $PD_{20}FEV_1$) to methacholine (Mch) bronchial challenge

	Mch responsive n=20	Mch non-responsive n=12
Age yrs	51±11.5	53±8.2
VC % pred	74±10.7	79±8.7
RV % pred	132±27	127±3.1
FEV_1 % pred	80±14.2	89±9.6
FEV_1/VC %	80±4.8*	83±3.8
MEF_{50} % pred	67±22.9	79±17.4
VAR-PEF % max	9±3.6	8±2.9
CV-PEF	7±2.8*	5±2.4

*: p<0.05. PEF: peak expiratory flow; VC: vital capacity; RV: residual volume; FEV_1: forced expiratory volume in one second; FEV_1/VC: FEV_1 as a percentage of vital capacity; MEF_{50}: maximal expiratory flow at 50% forced expiratory capacity; VAR-PEF: diurnal variation in PEF expressed as % maximum value; CV-PEF: coefficient of variation of the whole period of PEF recordings; $PD_{20}FEV_1$: provocation concentration producing a 20% fall in FEV_1.

Prevalence of respiratory symptoms in the total study population and by methacholine bronchial challenge are given in table 2. Patients responsive to methacholine challenge had significantly higher prevalence of wheeze as compared with patients non-responsive to methacholine challenge (70 *vs* 25% respectively, p<0.05)

Table 2. – Prevalence of respiratory symptoms in total study population and by methacholine bronchial challenge (MBC)

	MBC				Total study population n=32	
	Responsive n=12		non-responsive n=20			
symptom	n	%	n	%	n	%
Chronic cough	2	16.5	3	15	5	15.5
Wheeze	3	25	14	70*	17	53
Dyspnoea	6	50	16	80	22	69
Orthopnoea	5	41.2	10	50	15	47

*:p<0.05. Methacholine responsive or non-responsive are, respectively, patients with and without measured bronchial threshold (see Methods).

UNDW bronchial challenge caused a significant fall in FEV_1 (>20%) in only two patients, both responsive to methacholine. Mean VAR-PEF and CV-PEF were 8.75±3.3 and 6.3±2.8 in patients and 5.5 SE 1.2 and 3.1±0.7 in normals, respectively, p<0.001. In 14 and in 20 patients VAR-PEF and CV-PEF were, respectively, higher than 95th percentile of normals. The group of patients responsive to methacholine had a significantly higher value of CV-PEF in comparison with the group of patients non-responsive to methacholine challenge (7.1±2.8 *vs* 5±2.4, respectively, p<0.05) (table 1).

There was no significant linear relationship between CV-PEF or VAR-PEF and methacholine $PD_{20}FEV_1$ in the 20 patients responsive to methacholine bronchial challenge. In all of the patients there were significant relationships between CV-PEF and FEV_1 ($r=0.347$, $p<0.05$), CV-PEF and MEF_{50} ($r=0.405$, $p<0.05$) (fig. 1), VAR-PEF and MEF_{50} ($r=0.356$, $p<0.05$).

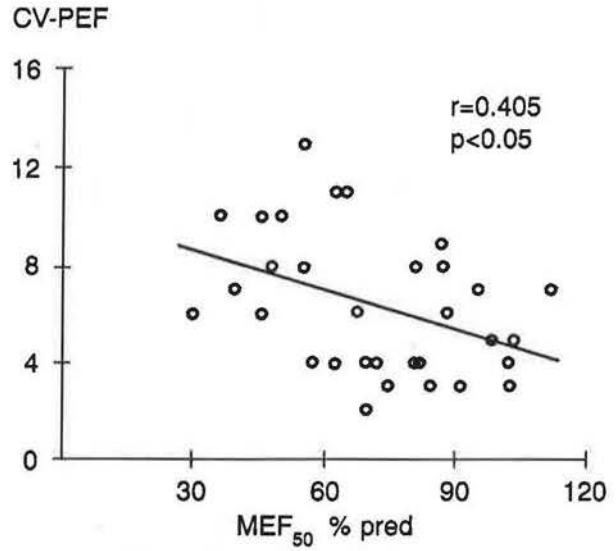

Fig. 1. – Relationship between MEF_{50} (% of predicted) and coefficient of variation of PEF (CV-PEF) in all patients. MEF_{50}: maximum expiratory flow at 50% forced expiratory flow; PEF: peak expiratory flow.

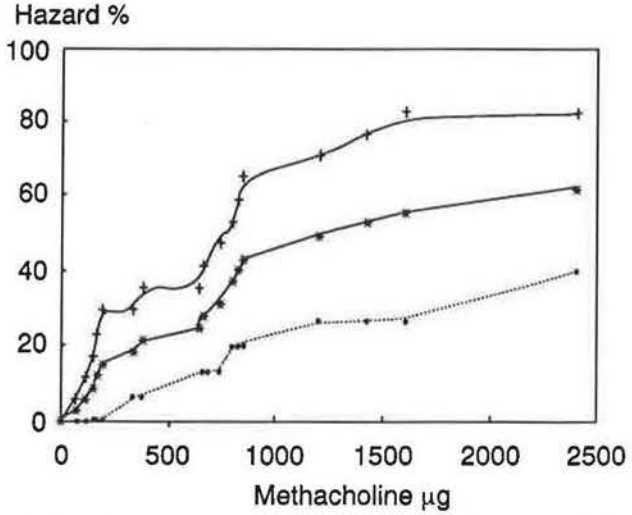

Fig. 2. – Proportional hazard cumulative risk to have a responsiveness to methacholine bronchial challenge by methacholine dose in patients with a positive or negative history of wheeze. .....•..... : no wheezing; —+—: yes wheezing; —*—: total.

The cumulative probability of methacholine bronchial responsiveness at each methacholine dose was significantly associated with history of wheezing (fig. 2), FEV_1 (as difference from 100% of predicted), FEV_1/VC (as difference from 100%), MEF_{50} (as difference from 100% of predicted), CV-PEF (table 3).

Table 3. – Factors producing a significant increase in the risk of methacholine response, as assessed by proportional hazard regression analysis

	beta	SE	HR	UL95%	LL95%	χ^2	p
Wheeze	1.338	0.506	3.81	10.49	1.39	8.0	0.020
FEV_1	0.043	0.019	1.04	1.08	1.01	4.8	0.028
FEV_1/VC	0.147	0.056	1.16	1.30	1.04	7.1	0.001
MEF_{50}	0.025	0.010	1.03	1.05	1.01	4.3	0.050
CV-PEF	0.188	0.088	1.21	1.44	1.01	5.1	0.002

beta: regression coefficients; SE: standard error, HR: hazard risks; UL95% LL95%: upper and lower confidence limits respectively. For other abbreviations see table 1 legend.

Discussion

In agreement with our previous observation [1], we found a high prevalence of bronchial responsiveness to methacholine in patients with moderate mitral stenosis. In 18 out of the 20 patients responsive to methacholine the value of $PD_{20}FEV_1$ was below the threshold reported in normals, according to an epidemiological study on normal population [24].

In the present study, patients responsive to methacholine bronchial challenge, as a group, had slightly more compromised lung function tests in comparison with patients non-responsive to methacholine bronchial challenge; the difference in mean FEV_1/VC ratio being statistically significant (table 1).

Although a linear relationship between methacholine $PD_{20}FEV_1$ and any spirometric test was not observed, the significant effects of FEV_1, FEV_1/VC, MEF_{50} on the probability of having a significant fall in FEV_1 after methacholine challenge (table 3) suggest that airway calibre plays a role in the response to bronchoconstricting agents [6] in our patients.

Until now, bronchial hyperresponsiveness of cardiac patients has been consistently shown by challenges with vasoactive stimuli, such as methacholine and histamine [1–4]. This observation led CABANES *et al.* [3] to put forward the vasoactive hypothesis, that methacholine-induced bronchoconstriction should depend on methacholine-induced vasodilation of bronchial veins, with oedema of bronchial wall and decrease in airway calibre, as supported by the protective effect of methoxamine [3]. Hypotonic solutions are thought to cause bronchoconstriction through alterations in bronchial epithelial permeability, with stimulation of subepithelial irritant receptors or release of immunological mediators [25]. In the present study UNDW caused a significant bronchoconstriction in only two patients, both hyperresponsive to methacholine. The prevalence of responsiveness to UNDW bronchial challenge observed in our patients is much lower than that reported in asthmatics [26, 27]. A similar discrepancy between airway responsiveness to methacholine and to other stimuli (*e.g.* hyperventilation) has been reported in patients with chronic bronchitis [28].

Many patients were regularly taking oral diuretics. Frusemide, only when administered by aerosol, has

been shown to inhibit bronchial responsiveness to UNDW in asthmatics [29]. Of the two observed patients responsive to UNDW, one was taking frusemide and the other hydrochlorothiazide associated with amiloride.

Other bronchial stimuli, *e.g.* metabisulphite, hypertonic solutions, cold air *etc.*, should be tried in cardiac patients before concluding that only vasoactive stimuli may elicit bronchoconstriction in them.

Nearly half of the patients had diurnal and inter-days fluctuations of PEF higher than those observed in normal subjects by us or by other authors [8–30]. In no case did the diurnal variation of PEF reach the value of 20%, as would have been expected in asthmatic patients according to the literature [31, 32].

Patients responsive to methacholine bronchial challenge had higher values of CV-PEF than non-responsive patients. We could not find a linear relationship between $PD_{20}FEV_1$ and PEF oscillations, as reported in asthmatics [8]. This was probably because the study did not cover a wide range of $PD_{20}FEV_1$, in particular high values of $PD_{20}FEV_1$, as we stopped methacholine inhalation after the cumulative dose of 3,200 μg had been reached. Nevertheless, the cumulative probability of having bronchial responsiveness to methacholine increased proportionally with the increase in CV-PEF (table 3).

In patients with mitral stenosis the oscillations of PEF could depend on variation in pulmonary congestion, occurring during the day and from day-to-day. In patients with mitral stenosis airway calibre is related to pulmonary congestion [33], hence it is not surprising that CV-PEF and VAR-PEF were significantly related to FEV_1 or MEF_{50} in our patients.

Among respiratory symptoms, only wheeze was positively and consistently associated with responsiveness to methacholine. A significant relationship between nonspecific bronchial responsiveness and wheeze has also been reported in population studies [34, 35]. As factors known to influence bronchial responsiveness were controlled in our patients, "cardiac asthma" is the most probable diagnosis for the association between bronchial responsiveness to methacholine and history of wheeze. The questionnaire used here does not allow speculation about the nature of cough reported by patients. More detailed questions about cough, focused on its relationship with non-specific stimuli, as in the International Union Against Tuberculosis and Lung Disease (IUATLD) questionnaire on asthma [36], might have been more useful to identify patients with airway hyperresponsiveness. As in the study-design there was not a random order of tests, we tried to avoid possible bias by separately administering the questionnaire and by computer analysing PEF recordings with no knowledge of the results of bronchial challenge (see Methods).

Our patients had a narrow range of mitral area (1.15–1.45 cm^2), so that we have not tested the relationship between "cardiac" variables and bronchial hyperresponsiveness in the present study. We have previously observed a significant linear inverse relationship between pulmonary capillary wedge pressure and bronchial threshold to methacholine in patients with mitral valve disease [1]. Recently, we found that bronchial responsiveness to methacholine decreased in those patients with mitral valve disease who showed a decrease in radiological score for lung oedema after mitral valve replacement [37]. At variance with our results, PISON *et al.* [38] found no change in bronchial responsiveness 15 days after intensive therapy of patients with lung congestion due to chronic heart failure. We think that 15 days is probably not a long enough time to observe a change in bronchial responsiveness. Chronic lung congestion might cause airway change, *i.e.* muscular hypertrophy [39], which could not be reversible in a short time. Unfortunately, we did not study the response to bronchodilators in our patients.

Whilst it seems that lung congestion is generally the basis for bronchial hyperresponsiveness in cardiac patients, it is not at present clear why patients with similar pulmonary haemodynamics have or have not bronchial hyperresponsiveness.

In conclusion, in patients with moderate mitral stenosis we found a high prevalence of bronchial responsiveness to methacholine, particularly if they had a history of wheeze, and a low prevalence of response to hypotonic stimuli. In these patients, PEF oscillations are higher than normals and are related to FEV_1 and associated with methacholine bronchial responsiveness. From our results, it seems that bronchial hyperresponsiveness of cardiac patients is generally more similar to that found in bronchitic rather than in asthmatic patients. The clinical value of a specific "bronchial" therapy (*e.g.* bronchodilators, antireactive drugs) in selected cardiac patients with airway hyperresponsiveness remains to be tested.

References

1. Rolla G, Bucca C, Caria E, Scappaticci E, Baldi S. – Bronchial responsiveness in patients with mitral valve disease. *Eur Respir J*, 1990; 3: 127–131.
2. Nishimura Y, Maeda H, Yokoyama M, Fukuzaki H. – Bronchial hyperreactivity in patients with mitral valve disease. *Chest*, 1990; 98: 1085–1090.
3. Cabanes LR, Weber SN, Matran R, Reynard J, Richard MO, Degeorges ME, Lockhart A. – Bronchial hyperresponsiveness to methacholine in patients with impaired left ventricular function. *N Engl J Med*, 1989; 320: 1317–1322.
4. Sasaki F, Ishizaki T, Mifune J, Fujimura M, Nishioka S, Miyabo S. – Bronchial hyperresponsiveness in patients with chronic congestive heart failure. *Chest*, 1990; 97: 534–538.
5. Kikuchi R, Sekizawa K, Sasaki H, Hirose Y, Matsumoto N, Takishima T, Hildenbrandt J. – Effects of pulmonary congestion on airway reactivity to histamine aerosol in dogs. *J Appl Physiol: Respirat Environ Exercise Physiol*, 1984; 57: 1640–1647.
6. Moreno RH, Hogg JC, Pare PD. – Mechanics of airway narrowing. *Am Rev Respir Dis*, 1986; 133: 1171–1180.

7. Plotz M. – Bronchial spasm in cardiac asthma. *Ann Intern Med*, 1947; 26: 521–525.
8. Ryan G, Latimer KM, Dolovich J, Hargreave FE. – Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway calibre. *Thorax*, 1982; 37: 423–429.
9. Ramsdale EH, Morri MM, Roberts RS, Hargreave FE. – A symptomatic bronchial hyperresponsiveness in rhinitis. *J Allergy Clin Immunol*, 1985; 75: 573–577.
10. Gibson PG, Mattoli S, Sears MR, Dolovich J, Hargreave FE. – Variable airflow obstruction in aymptomatic children with methacholine airway hyperresponsiveness. *Clin Invest Med*, 1988; 11: C105.
11. Allegra L, Bianco S. – Non-specific bronchoreactivity obtained with an ultrasonic aerosol of distilled water. *Eur J Respir Dis*, 1980; 61 (Suppl. 106): 41–49.
12. Crawley IS, Morris DC, Silverman BD. – Valvular heart disease. *In*: The Heart. JW Hurst ed., McGraw Hill, New York, 1978; pp. 994–997.
13. Tribouilloy C, Lesbre JP. – Quantification des stenoses valvulaires en echo-Doppler. *Arch Mal Coeur*, 1990; 83: 839–852.
14. Chen JTT, Behare VS, Morris JJ, McIntosh HD, Lester RG. – Correlation of roentgen findings with hemodynamic data in pure mitral stenosis. *Am J Roentgengol*, 1968; 102: 280–285.
15. Nakatani S, Masuyama T, Kodama K, Kitabatake A, Fujii K, Kamada T. – Value and limitations of Doppler echocardiography in the quantification of stenotic mitral valve area: comparison of the pressure half time and the continuity equation methods. *Circulation*, 1988; 1: 78–85.
16. Ferris BG Jr. – Epidemiology standardization project. *Am Rev Respir Dis*, 1978; 118 (part 2): 1–88.
17. American Thoracic Society Executive Committee: – Recommended standardized procedures for pulmonary function testing. *Am Rev Respir Dis*, 1978; 118 (part 2): 55–62.
18. Bolt W, Brille D, Cara M, Copper G, Houberechts A, Lavenne F, Sadoul P, Sartorelli E, Zorini O. – Aide-memoire pour la pratique de l'examen de la fonction ventilatoire pour la spirographie. *Colln Hyg Med Trav Luxembourg*, 1971; 11: 58–113.
19. Knudson RJ, Slatin RC, Lebowitz MD, Burrows B. – The maximal expiratory flow-volume curve. Normal standards, variability, and effects of age. *Am Rev Respir Dis*, 1976; 113: 587–600.
20. Chai H, Farr RS, Froehlich LA, Mathison DA, McLean JA, Rosenthal RR, Sheffer AL, Spector SL, Townley RG. – Standardization of bronchial inhalation challenge procedures. *J Allergy Clin Immunol*, 1975; 56: 323–327.
21. Higenbottam TW, Stokes T, Jamieson S, Hill L. – Bronchoreactivity in asthmatic adults with normal spirometric values. *Br Med J*, 1983; 286: 1012–1014.
22. Higenbottam TW, Jackson M, Rashdi T, Stewart S, Coutts C, Wallwork J. – Lung rejection and bronchial hyperresponsiveness to methacholine and ultrasonically nebulized distilled water in heart-lung transplantation patients. *Am Rev Respir Dis*, 1989; 140: 52–57.
23. Aitkin M, Anderson D, Francis B, Hinde J. – Statistical modelling in GLIM. Oxford Scientific Publications, 1979.
24. Cerveri I, Bruschi C, Zoia MC, Zanon P, Maccarini L, Grassi M, Rampulla C. – Distribution of bronchial nonspecific reactivity in the general population. *Chest*, 1988; 93: 26–30.
25. Hogg JC, Eggleston PA. – Is asthma an epithelial disease. *Am Rev Respir Dis*, 1984; 129: 207–208.
26. Bascom R, Bleecker ER. – Bronchoconstriction induced by distilled water. *Am Rev Respir Dis*, 1986; 134: 248–253.
27. Foresi A, Mattoli S, Corbo GM, Polidori G, Ciappi G. – Comparison of bronchial responses to ultrasonically nebulized distilled water, exercise, and methacholine in asthma. *Chest*, 1986; 90: 822–826.
28. Ramsdale EH, Robert RS, Morris MM, Hargreave FE. – Differences in responsiveness to hyperventilation and methacholine in asthma and chronic bronchitics. *Thorax*, 1985; 40: 422–426.
29. Robuschi M, Gambaro G, Spagnotto S, Vagji A, Bianco S. – Inhaled furosemide is highly effective in preventing ultrasonically nebulized water bronchoconstriction. *Pulm Pharmacol*, 1989; 1: 187–191.
30. Paggiaro PL, DiPede F, Moscato G, Dellabianca A, Giannini D, Bancalari L, Carrara M, Giuntini C. – Computer-based method to evaluate peak expiratory flow (PEF) monitoring in normal, asthmatic and non-asthmatic subjects. *Eur Respir J*, 1990; 3 (Suppl. 10): 443s.
31. Hetzel MR, Clark TJH. – Comparison of normal and asthmatic circadian rhythms in peak expiratory flow rate. *Thorax*, 1980; 35: 732–738.
32. Quackenboss JJ, Lebowitz MD, Kryzanowski M. – The normal range of diurnal changes in peak expiratory flow rates. *Am Rev Respir Dis*, 1991; 143: 323–330.
33. Cortese DA. – Pulmonary function in mitral stenosis. *Mayo Clin Proc*, 1978; 53: 321–326.
34. Rijcken B, Schouten JP, Weiss ST, Speizer FE, Van der Lende R. – The relationship of nonspecific bronchial responsiveness to respiratory symptoms in a random population sample. *Am Rev Respir Dis*, 1987; 136: 62–68.
35. Welty C, Weiss ST, Tager JB, Munoz A, Becker C, Speizer FE, Ingram RH Jr. – The relationship of airway responsiveness to cold air, cigarette smoking, and atopy to respiratory symptoms and pulmonary function in adults. *Am Rev Respir Dis*, 1984; 130: 198–203.
36. Burney PGJ, Laitinen LA, Perdrizet S, Huckauf H, Tattersfield AE, Chinn S, Poisson N, Heeren A, Britton JR, Jones T. – Validity and repeatability of the IUATLD (1984) bronchial symptoms questionnaire: an international comparison. *Eur Respir J*, 1984; 2: 940–945.
37. Rolla G, Bucca C, Brussino L, Costa P, Morea M. – Reduction of bronchial responsiveness to methacholine after mitral valve replacement. *Respiration*, 1991; 58: 81–84.
38. Pison C, Malo JL, Rouleau JL, Chalaoui J, Ghezzo H, Malo J. – Bronchial hyperresponsiveness to inhaled methacholine in subjects with chronic left heart failure at a time of exacerbation and after increasing diuretic therapy. *Chest*, 1989; 96: 230–235.
39. Spencer H. – Pathology of the lung, 3rd edn. Saunders, Oxford, 1977; p. 657.