Bronchial responsiveness in patients with mitral valve disease

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ABSTRACT: Bronchial responsiveness has been evaluated in patients with chronic lung congestion secondary to mitral valve disease. Methacholine bronchial challenge was performed by intermittent aerosol generation in 31 patients with mitral valve disease, 18 in New York Heart Association (NYHA) Class II and 13 in NYHA Class III, non-atopic and with baseline forced expiratory volume in one second/vital capacity (FEV1/VC) >85% of predicted and in 30 normal controls. Haemodynamic data were available in 17 patients. The methacholine bronchial provocation dose causing a 35% fall of airway conductance (PD35Gaw) was significantly lower in patients (507±125 μg) than in normals (2779±315 μg), (p<0.001). In patients log PD35Gaw was significantly correlated with mean pulmonary artery pressure (r=0.53, p<0.05), mean pulmonary capillary wedge pressure (r=0.67, p<0.01), but not with any spirometric parameters. Bronchial hyperresponsiveness seems to be common in patients with mitral valve disease and evidence of lung congestion.


Dyspnoea, cough and wheezing, the characteristic symptoms of bronchial asthma, are often reported in cardiac patients with lung congestion ("cardiac asthma").

The common denominator underlying the asthmatic diathesis is a nonspecific hyperirritability of the tracheobronchial tree [1]. The phenomenon consists of bronchoconstriction elicited by a wide range of nonspecific stimuli (histamine, methacholine etc.), not effective in non-asthmatic people, unless high doses are administered [2].

It is not known whether increased bronchial responsiveness is also present in cardiac patients with chronic lung congestion. We previously observed that interstitial lung oedema, experimentally induced in healthy subjects by rapid saline infusion, increased the bronchial responsiveness to methacholine [3].

Recently, CABANES et al. [4] demonstrated bronchial hyperresponsiveness in patients with coronary heart disease and left ventricular failure, whilst EICHACKER et al. [5], in a group of older and more incapacitated patients with left ventricular failure, disproved the presence of bronchial hyperresponsiveness. In the present study we investigated the influence of chronic interstitial lung oedema on bronchial responsiveness, studying methacholine bronchial challenge in patients with mitral valve disease (MVD) and evidence of chronic lung congestion.

Patients and methods

Thirty one consecutive patients with MVD, mean age: 57±2 yrs, admitted to hospital for scheduled periodic examination, were studied after signed informed consent had been obtained. The diagnosis was supported by physical, echocardiographic and chest X-ray examinations in all patients and by cardiac catheterization in a subgroup of 17 patients, in whom there was clinical evidence of combined valve disease. Three of these patients (nos 4, 5 and 10) had previously had valvulotomy and presented clinical evidence of mitral regurgitation (two) and restenosis (one).

Patients were classified according to criteria suggested by the New York Heart Association [6]: 11 patients were in functional Class II (breathlessness on exertion) and 20 were in functional Class III (symptomatic with ordinary activity, such as personal care). Many patients were regularly taking digitalis and diuretics. All patients were clinically stable, and had not required change in therapy in the last two months. All patients were nonsmokers. Criteria for exclusion were: atopy, a forced expiratory volume in one second/vital capacity (FEV1/VC) <85% of predicted, drug therapy that could influence bronchial reactivity (beta-blocking drugs, calcium antagonists), NYHA Class IV, heavy smoking history, recent (6 weeks) airway infection.

Spirometry

Vital capacity (VC), forced expiratory volume in one second (FEV1), and maximal expiratory flow-volume curve were obtained by a computerized rolling seal spirometer, according to recommended standardized procedures [7]. Airway resistance and thoracic gas volume were
Fig. 1. - Individual and mean values of methacholine provocation log-dose (log PD₃₅sGaw in µg) in normals and in patients with mitral valve disease. In six normal subjects (not included) PD₃₅sGaw was not measurable. PD₃₅sGaw: provocation dose producing 35% fall in specific conductance of the airways; MVD: mitral valve disease.

Fig. 2. - Frequency distribution of PD₃₅sGaw in normals and in patients with mitral valve disease. Cases in whom a threshold could not be detectable are included in >2000 µg (6 normals). For abbreviations see legend to figure 1.

Fig. 3. - Correlation between methacholine provocation dose (log PD₃₅sGaw) and pulmonary capillary wedge pressure (Ppw) in patients with mitral valve disease. r=0.67; p<0.01.

Briefly, methacholine was inhaled from a breath-activated dosimeter (MB3 Mefer, Brescia, Italy), powered by compressed air at 1.5–1.8 bar. The preset time of aerosol delivery was 0.6 s, with an output of 0.009 ml per breath. The median mass aerodynamic diameter of the particles is 1.69±0.03 3.3 micron. Methacholine chloride (Sigma Chemicals, St. Louis) was inhaled in increasing concentrations (1, 2, 5, 10, 25 and 50 mg·ml⁻¹) starting from 1 mg·ml⁻¹, five breaths of each concentration. sGaw was measured 2 min after each challenge until it was reduced by at least 35% from its control values or until the maximal methacholine concentration was reached. Methacholine challenge dose-response curves were constructed by plotting the percentage fall of sGaw from the control value against the cumulative dose of methacholine expressed in µg.

Measurements of airway responsiveness were determined by linear interpolation between points on the log dose-response curve and expressed as the dose or log-dose of methacholine required to produce a 35% decrease in sGaw (PD₃₅sGaw or log PD₃₅sGaw).

The same procedure, with the same criteria for exclusion, was performed in a group of 30 normal subjects, randomly recruited from hospital staff, 15 female, with a mean age 52±2 yrs not significantly different from the patient group, 10 nonsmokers and 20 light smokers (less than 10 cigarettes a day). With the same procedure for methacholine inhalation challenge, PD₃₅sGaw ranged from 27–920 µg in our laboratory in a group of 18 subjects with asthma.

Cardiac catheterization

Right and left catheterization was performed in 17 patients with MVD, using standard procedures. Pressures
were measured with the patient supine and were referenced to the mid-axillary line. Mean pressures were obtained by electronic integration. Pressures were measured using Statham p23 transducers and displayed on the oscilloscope and recorded on heat-sensitive paper. Cardiac outputs (CO) were measured in triplicate with the thermodilution technique using 10 mL of iced 5% dextrose as indicator [12]. Output was calculated from the indicator-dilution curve by an Edwards strip-chart recorder, model 9811.

Haemodynamic measurements included: cardiac index (CI), calculated from cardiac output (CO), measured in triplicate with the thermodilution technique and normalized for body surface area; mean pulmonary pressure (MPP), obtained by electronic integration; pulmonary wedge pressure Ppw; and pulmonary vascular resistance (PVR) calculated from the formula (MPP/Ppw)/
\[ \text{CO} \times 80, \text{where 80 converts mmHg to dynes}\cdot\text{s}^{-1}\cdot\text{cm}^{-2}. \]

Experimental procedure

All patients were studied in the morning. After baseline respiratory function tests had been performed, the patients were challenged with methacholine. Pulse and pressure were recorded after each inhalation. In a group of 17 patients cardiac catheterization was performed the day after respiratory function evaluation.

Statistics

Means and standard error (se) were calculated for each respiratory function test, PD₃₅sGaw and haemodynamic data. Student’s t-test for unpaired data, 95% C.I. (confidence limits) for the difference of the means and Chi-squared were calculated when appropriate. PEARSON’S correlation coefficient and simple linear
regression using the least-squares method were also employed. Statistical significance was defined as a p value <0.05.

Results

Bronchial challenge was well tolerated by all patients, without significant change in blood pressure or pulse rate. Clinical data, individual and mean values of lung function and haemodynamic variables of MVD patients are reported in Table 1. In six of the normal subjects (20%), PD₃sGaw could not be calculated with the doses of methacholine used; mean PD₃sGaw in the remaining subjects was 2779±385 μg (Cl±72).

Methacholine PD₃sGaw was significantly lower in patients with MVD (507±101 μg, Cl±205) in comparison with normals, p<0.001.

Individual PD₃sGaw values of MVD patients overlapped those of normals in only five cases. Moreover, whilst methacholine bronchial threshold could be calculated in all MVD patients, no significant fall of sGaw was found even with the highest methacholine dose in six controls (20%).

Figure 1 shows the individual values and the means of methacholine PD₃sGaw in MVD patients and controls. Figure 2 shows the frequency distribution of PD₃sGaw at various cumulative methacholine concentrations in the two groups. Between the two subgroups of patients, with/without cardiac catheterization, the only significant difference was a higher prevalence of mitral regurgitation in the former (14/17 vs 6/14, p<0.05), in which there were also more patients in Class III (13/17 vs 7/14, ns) and with tricuspidal regurgitation (9/17 vs 3/14, ns). No significant difference was found in the two subgroups with regard to age, PD₃sGaw or any respiratory function test.

In MVD patients no significant relationship was observed between PD₃sGaw and any spirometric test, age or NYHA class. In MVD patients log PD₃sGaw was significantly related to MPP (r=0.53, p<0.05), Ppw (r=0.67, p<0.01) (fig. 3) but not to PVR (r=0.41, ns).

Discussion

Our findings show that bronchial responsiveness to methacholine is increased in patients with MVD in NYHA Class II and III, with evidence of lung congestion. In fact, most MVD patients had methacholine PD₃sGaw as low as those commonly observed in asthmatics (see Method).

sGaw is a more sensitive index of change in airway calibre than FEV₁ [13], leaving the possibility that bronchial hyperresponsiveness was overestimated in our patients. However, we found a marked difference in the means of PD₃sGaw observed in patients and in normals, with very little overlap.

As all factors known or presumed to influence bronchial reactivity were carefully controlled (smoke, atopy, recent respiratory infections, drugs etc.) [14], chronic interstitial lung oedema is the most probable explanation for the increased bronchial responsiveness observed in our patients with MVD. It is interesting to observe that the patient with the highest PD₃sGaw value (no. 3), quite in the normal range, had a very low cardiac output and tricuspidal regurgitation, which might both serve to prevent a rise in the pulmonary venous pressure and give protection from pulmonary oedema [15].

Abnormalities in pulmonary function in patients with MVD have been reported for many years [16] and are consistent with those observed in our patients: a reduction in vital capacity and total lung capacity, a decrease of FEV₁ and maximal expiratory flow at 50% of vital capacity. The physiological changes seen in MVD patients may be mainly due to accumulation of interstitial fluid around bronchioles and/or organization of longstanding interstitial pulmonary oedema which may result in fibrosis [17]. Old pathologic observations of bronchi in patients with MVD indicated thickened walls, with prominent bronchial veins.

From the above physiologic and pathologic considerations it can be argued that our observed increased bronchial responsiveness might depend merely on reduction in airway calibre. In our patients, however, no correlations were found between methacholine bronchial threshold and any respiratory function parameter. Recently MORENO et al. [18] have emphasized that a small increase in bronchi wall thickness could cause a marked increase in airway responsiveness to bronchoconstricting agents, with a negligible increase in resting airway resistance. As bronchial veins drain into pulmonary capillaries and veins, it is not surprising that bronchial mucosal oedema has been reported in patients with radiologic evidence of lung congestion [19].

Marked oedema of the bronchi has been observed on bronchoscopic examination in unselected patients with left ventricular failure [20]. CARANES et al. [4] emphasized this anatomical aspect of bronchial circulation to explain the bronchial hyperresponsiveness to methacholine that they found in coronary heart disease patients with left ventricular failure.

The correlations between MPP, Ppw and PD₃sGaw observed in our patients with MVD point to an association between interstitial lung oedema and bronchial reactivity, as we observed previously in acute interstitial lung oedema experimentally induced in healthy subjects by rapid saline infusion [3].

In asthmatic subjects bronchial hyperresponsiveness has been related to airway inflammation [21]. We are not aware of any pathologic reports of inflammatory cellular infiltration in bronchial walls of patients with MVD.

A possible link between increased bronchial responsiveness and interstitial lung oedema, apart from the reduction of airway calibre, remains speculative. In dogs, acute pulmonary vascular congestion renders the bronchi hyperresponsive to histamine through vagal reflexes [22]. CHUNG et al. [23] found that cooling of the vagnally suppressed bronchial hyperresponsiveness caused by injection of large amounts of fluid in dogs.

It has been suggested that increased hydrostatic pressure in bronchial microvasculature may heighten
sensitivity of irritant lung receptors [24] and that J receptors may be stimulated by excess pericapillary interstitial fluid eliciting an airway constrictive reflex [25]. Pulmonary congestion may thus cause an increase in bronchomotor tone through vagal reflexes and an increase of vagal tone has been found to be one of the mechanisms underlying bronchial hyperresponsiveness in asthma [26].

In the present study we found no relationship between symptoms and bronchial responsiveness, but we did not study asymptomatic or mildly symptomatic patients and we excluded NYHA Class IV patients.

In conclusion, our results show that bronchial hyperresponsiveness is present in patients with MVD and chronic lung congestion. We suggest that in these patients this finding may contribute to the common respiratory complaints of cough, wheezing and acute episodic dyspnoea.

References


Réactivité bronchique chez les patients atteints de maladie de la valve mitrale. G. Rolla, C. Bucca, E. Caria, E. Scappaticci, S. Baldi.

RÉSUMÉ: La réactivité bronchique a été évaluée chez des patients atteints d’une congestion pulmonaire chronique secondaire à une maladie de la valve mitrale. La provocation bronchique à la methacholine a été réalisée par production intermittente d’aérosol chez 31 patients avec maladie valvulaire mitrale, 18 appartenant à la classe II de la “New York Heart Association” (NYHA), et 13 de la classe III, tous non atopiques, dont le rapport de Tiffeneau était supérieur à 85% des valeurs prédites, ainsi que chez 30 contrôles normaux.

Les données hémodynamiques sont disponibles chez 17 patients. La dose de methacholine au cours de la provocation bronchique, provoquant une chute de 35% de la conductance des voies aériennes (PD_{50Gaw}), est significativement plus faible chez les patients (507±442 µg) que chez les normaux (2.79±1.358 µg), (p<0.001). Chez les patients, log PD_{50Gaw} est en corrélation significative avec la pression artérielle pulmonaire moyenne (r=0.53, p<0.05), avec la pression capillaire pulmonaire moyenne bloquée (r=0.67, p<0.01), mais avec aucun des paramètres spirométriques. L’hyperréactivité bronchique semble fréquente chez les patients atteints de maladie valvulaire mitrale avec congestion pulmonaire évidente.