
**Bronchoalveolar lavage in allergic asthma**

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Bronchoalveolar lavage (BAL) has improved knowledge of the defence mechanisms of the human lung and the inflammatory and immune mediated changes involved in the pathogenesis of diseases of the pulmonary parenchyma [1]. In addition, it has been used in disorders of the airways such as allergic occupational and intrinsic asthma and chronic bronchitis, in which the bronchial components of lavage may produce more useful information than the alveolar components. Fluid containing mainly components from the airways compartment can be obtained by bronchial lavage (BL).

In bronchial asthma, inflammation is thought to play an important role in perpetuating bronchial hyperreactivity and obstruction. Clinical and morphological observations on biopsy or autopsy specimens support this hypothesis, but the relative importance of the various immunological and mediators released by them is not established.

In patients with allergic asthma, BL and BAL have made it possible to study: 1) the cell populations, antibodies and mediators present in the bronchial tree which may contribute to airway hyperreactivity and inflammation; 2) the mechanisms of allergic asthmatic response after bronchial exposure to the sensitizing allergen; 3) the action and efficacy of drugs.

Inflammatory cells present in the asthmatic lung vary with stage, severity and type of disease. In mild asthmatics studied during disease quiescence BAL showed a mild increase in % eosinophils and neutrophils [2, 3]. In BL from asymptomatic patients, Crimi et al. [4] found increased albumin and specific IgE's, correlating well with the results of bronchial challenge. These data suggest that airways inflammation with increased airway capillary permeability is present in asthmatics even at time of quiescence. Mast cells, which are believed to play a major role in response to allergen, were found in BAL of mild asthmatics during clinically asymptomatic periods [5–8]. Also, the level of histamine in BAL of asthmatics was higher than in BAL of controls [7] and correlated with bronchial hyperresponsiveness [6, 7]. However, Rankin et al. [9] found that levels of histamine in BAL of asthmatics did not differ from controls or correlate with mast cell or basophil count. Weiss et al. [10] showed that pulmonary activation of mast cells occurs after allergen challenge in subjects with sleep and asthma and, to a lesser degree, in those with only one alone.

Mast cells do not, therefore, seem to be constantly involved in patients with day-to-day asthma but are probably recruited in response to allergen inhalation or other stimuli. Conflicting results may depend on the stage and severity of disease. When bronchial hyperresponsiveness was systematically determined a significant negative correlation was found between methacholine PC20 and % mast cells, eosinophils and epithelial cells recovered from BAL.

The combination of bronchial provocation test (BPT) with BL and/or BAL provides new insights into events following allergen inhalation. Exposure to specific antigen causes increased permeability of bronchial mucosa resulting in visual evidence of oedema and migration of more proteins into the bronchial lumen [11]. Mignolo et al. [12] showed an increased % neutrophils and eosinophils in BAL within 4 h of BPT, whilst eosinophils alone were still increased 24 h later; all but one patient developed a dual response to bronchial challenge. De Monchy et al. [13] showed an increased % eosinophils...
It is 6-7 h of BPT only in patients who developed a dual asthmatic response, whilst no differences were found between patients with isolated early asthmatic reaction and patients with late asthmatic reaction. Higher levels of specific IgE's 72 h after allergen challenge in BL of patients who developed a dual asthmatic response than in BL of patients with an isolated early asthmatic response. However, the percentage of neutrophils and eosinophils in these two groups was not different and in the control group was similar.

These findings indicate that airway inflammation occurs after experimental allergen exposure, resulting in epithelial damage both in patients with dual reaction and in patients with isolated early reaction. A more pronounced, persistent cellular influx into the lung is probably responsible for the development of the late asthmatic reaction. It also seems that epithelial cells are a target of the inflammatory reaction which follows allergen inhalation.

Macrophages appeared suddenly after local bronchial challenge with a further increase 48 h later [14]. Electron microscopy showed highly activated cells, evidenced by folded membranes, vesicles, cytoplasmatic projections and phagocytosed mast cell granules [14]. After specific IgE-antigen-antibody complex stimulation alveolar macrophages from asthmatics release PAF-acether, which has recently been proposed as an important mediator of inflammation and bronchoconstriction [15]. Involvement of macrophages in the response to local bronchial provocation was observed by Tonnel et al. [16] who found an increased level of β-glucuronidase after challenge.

Does a cellular mechanism make a patient more likely to develop a late asthmatic reaction to allergen exposure? Using BAL in patients with previously documented dual asthmatic response Mertens et al. [14] showed, 48 h after the immediate response, not only an increased number of neutrophils and eosinophils but also of T-lymphocytes. T-cells were still elevated 48 h later, with a high proportion of helper T-cells. Conversely, in patients with an isolated early asthmatic reaction Gonzales et al. [17] found an increased proportion of suppressor T-cells. These findings suggest that T-lymphocytes play a key role in development of the late asthmatic reaction, possibly by modulating B-lymphocytes to produce and release antigen specific IgE's.

Lavage techniques may provide information on the relationship between cells and mediator release by allowing quantitation of soluble components secreted by inflammatory cells in the bronchial lumen. The presence of a mediator in BAL or BL is not necessarily correlated with the presence of the cells which produce it, because of the time lag between cell influx and mediator release at the site of inflammation. Murray et al. [18] recorded the release of a major mast cell mediator into BAL fluid after local allergen challenge. Nine minutes after challenge a 150 fold mean rise in PGE₂, and an increased concentration of 15-HEPE and β-glucuronidase were observed. Changes between control and postchallenge levels of 5-HETE, LTB₄, LTC₄, LTD₄ and LTE₄ were not detected. Leukotrienes B₄, D₄, and E₄ were observed by Chan-Yeung et al. [19] in BAL from patients with red cedar asthma 2 h after bronchial challenge. An increased concentration of cosinophil cationic protein to albumin ratio in BAL from patients who underwent bronchial challenge has also been reported [12]; again the highest concentrations of this protein were observed for patients with a dual response. Gravelin et al. [20] studied the release of mediators after local exposure to hyperosmolar stimulus and observed a significant increase in the lavage concentration of histamine, PGE₂ and PGF₂α-alpha.

Possible repetitive evaluation of inflammatory cells and their products in the lungs makes the BAL technique useful in understanding the action of anti-asthmatic drugs. Díaz et al. [21] showed that sodium cromoglycate suppressed local accumulation of eosinophils and reduced levels of specific IgE antibodies in allergic asthmatics treated for 28 days. Boschetto et al. [22] showed the efficacy of prednisone in preventing the late asthmatic reaction and airway inflammation induced by toluene disocyanate.

Few studies have evaluated the complications of BL and BAL techniques. Some have reported BAL-induced bronchospasm [23, 24] whilst others observed no significant deterioration of pulmonary function even when BAL was performed after local allergen provocation [14, 25]. We found no significant changes of sensitivity to methacholine in patients with isolated early response or dual response who underwent BL and BAL 72 h after bronchial challenge.

Studies using a combination of BPT and BAL may provide useful information on the pathophysiology of allergic asthma. They should be designed to clarify the complex relationships between the inflammatory cells and their mediators and between these mediators, tissue damage and bronchial constriction. The role of non-specific stimuli and of specific and non-specific pharmacologic antagonists should also be evaluated.

References


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Role of bronchoalveolar lavage in the investigation of cell-mediated defence mechanisms against lung cancer

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Little information is available on the applicability and reliability of bronchoalveolar lavage (BAL) in the evaluation of local cellular defence mechanisms against lung cancer (LC). LC is frequently located in the large airways, whilst BAL allows recovery of cells from the alveolar spaces. Important functional differences may exist between cells obtained by BAL and immunologically competent cells isolated after disaggregation of whole lung tissue specimens, thus BAL does not always sample the pulmonary cell population correctly.

Alveolar macrophages (AM) are thought to play an important role in the host defence mechanism against LC by releasing a variety of cytotoxic and cytostatic substances and by functioning as accessory cells for lymphocytes (LY). The importance of AM is demonstrated by the fact that over 90% of cells recovered from the alveoli by BAL and over one third of cells isolated after disaggregation of LC surgical specimens belong to the monocyte macrophage lineage [1]. These were shown to exert specific cytotoxic activity against autologous LC cells but not against non-malignant tumour targets, hence their toxicity could be related to tumour antigen driven specific responses [2].

Investigations into the differentiation of blood monocytes into AM and association to modifications of tumour killing properties have led to conflicting results. AM from smoking and nonsmoking normals and patients with LC were shown to be more cytotoxic than autologous blood monocytes for various tumour cell lines (including squamous LC) with no differences between study groups [1]. In contrast, Bordignon et al. reported