Plasma exudation in the airways: Mechanisms and function

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ABSTRACT: Inflammatory challenges of tracheobronchial and nasal mucosa produce prompt extravasation or exudation of plasma from the well developed microcirculation just beneath the epithelial base. Plasma exudation is not an exaggeration of the normal capillary exchange of fluid and solutes but a specific inflammatory response of post-capillary venules. The exuded plasma may not produce oedema. By a rapid, undirectional, unfiltered and yet non-injurious process, plasma exudates cross the mucosal lining to appear on the airway surface at the site of challenge. In vitro data suggests the possibility that a slightly increased hydrostatic pressure moves the acellular exudate through valve-like openings between epithelial cells. By the venular-mucosal exudation mechanism all the potent protein systems of circulating plasma will operate in respiratory defence on the surface of an intact mucosa. A further inference is that exudative indices obtained from the airway surface quantitatively reflect the intensity and time course of mucosal/submucosal inflammatory processes. Irrespective of which particular cellular mechanism happens to fuel the inflammation. Mucosal exudation of plasma characteristically occurs in health and disease also when there is no airway oedema, no epithelial disruption, and no increased absorption ability. However, exuded plasma and its derived peptide mediators potentially contribute to several pathophysiological characteristics of inflammatory airway diseases.


The intriguing pathophysiology and pharmacology of airway plasma exudation, the potential physical effects of plasma exudates in and on the airway mucosa, and the exudate’s content of inflammatory plasma-derived peptides are factors which may account for the attraction of the plasma exudation hypothesis of asthma as it was originally proposed [1]. In two reviews [2, 3] that followed, I added several pieces of circumstantial evidence in support of the ‘hypothesis’. It was extremely exciting to discover that the literature of the past contained many widely scattered data, collected by astute observers, that could support my notion. I was surprised to learn that no one else had come forward with a similar hypothesis previously. The technique of using ‘historic’ material to support a novel hypothesis has its problems. The established views on the mucosal crossing of plasma may not be true. The data collected by my group several years ago suggested to me that the luminal entry of plasma exudates only occurs when a marked airway oedema has been produced and that the mucosal passage of proteinaceous exudate disrupts and causes shedding of the epithelial lining. Third, luminal entry of plasma macromolecules, has been taken as firm evidence of a general “hyperpermeability” with increased mucosal penetration and absorption of airway surface material. Since these ideas have prevailed, the role of mucosal exudation in respiratory defence has not received any attention.

The ‘established views’ on the mucosal crossing of plasma may not be true. The data collected by my group several years ago suggested to me that the luminal entry of plasma exudates basically has a “primary role in airway defence” [1, 3]. Further work in guinea-pig tracheobronchial and human nasal airways (fig. 1) carried out in Lund [4-13] have now confirmed that the plasma exudation process may not produce or necessarily be associated with three reputed characteristics of asthmatic and rhinitic airways.

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Oedema may not be induced because bulk plasma exudate readily enters the airway lumen. Epithelial disruption is not produced because the mucosal crossing of even unfiltered plasma exudates is a non-injurious process. Absorption is not increased because the mucosal exudation of plasma turns out to be a unidirectional flux of macromolecular solutes into the lumen.

Luminal entry of Plasma exudates

The luminal entry of plasma at mucosal provocations simply reflects the extravasation process of the subepithelial microvessels. Over the entire dose-response range mediators, allergen and other inflammatory factors applied on the airway surface thus do not selectively increase plasma exudation into the airway tissue [5, 14]. The persistent luminal entry of exudate has been observed with acute, biphasic as well as sustained inflammatory responses (fig. 2). Plasma exudation can thus occur without producing airway oedema. This may raise some doubt as to the presence of airway oedema in inflammatory airway diseases. As a matter of fact, quantitative data demonstrating airway oedema in asthma and rhinitis are scarce or lacking. Perhaps the inflamed airway mucosa may be thickened by the accumulation of cells, by fibrin formation, by collagen depositions and fibrosis rather than by the presence of plasma-derived oedema fluid.

Separation between inward and outward airway permeabilities

By employment of techniques for controlled tracheobronchial distribution of solutes and tracers in guinea-pigs ERJEFALT and Persson [5, 10] and Greiff et al. [11] have demonstrated that absorption of luminal solutes may not have been affected by allergen, neurogenic stimuli and mediator provocations. Even...
during the acute exudation phase when plasma tracers such as albumin, fibrinogen, and large dextrans enter the lumen without being filtered, there was no increased absorption of small or large solutes from the lumen. Also, during prolonged histamine-induced plasma exudation into human nasal airways there was no change in the rate of absorption of a small-sized tracer \(^{(12)\text{Cr-EDTA}}\) [12]. The separation between exudation-and-absorption-processes agrees with the fact that there is now compelling supporting evidence that plasma exudation does occur in asthma, rhinitis, and bronchitis whereas no increase in airway mucosal absorption, however attractive the hypothesis, has been demonstrated in these diseases [15-18] (fig. 3). The latter possibility seems to me to be a subject where the attraction of a hypothesis has received greater weight than actual data.

Epitrochlear venules (fig. 4). This is an active cellular response because receptors for mediators and autacoids are present on the endothelial cells [19]. Unfiltered plasma is moved through the mediator-induced holes in the venular wall by the hydrostatic pressure gradient between the venular compartment and the interstitial space. The venular endothelial cells have a strong ability to spontaneously close the venular holes. Hence, a plasma exudation response normally lasts for only a few minutes.

**Neurogenic extravasation/inflammation**

In 1981 ERJEFALT et al. [20] originally reported that local application of substance P increases the total amount of albumin (bound to Evan's Blue dye) in airway tissue. During the 1980's several other authors have measured the total airway tissue amount of Evan's Blue dye in work suggesting that substance P or a similar tachykinin mediates neurogenic inflammation ("oedema", "plasma leak" etc.) in the airways of guinea-pigs and rats. However, it is not sufficient to measure the tissue dye content. The extravasated amount of plasma in the airway tissue can be assessed only if both the total amount and the intravascular plasma pool are known [14]. The first work that quantitated actual neurogenic extravasation in rodent airways was carried out by ERJEFALT [14, 20] and the experiments demonstrating neurogenic exudation of plasma into the airway lumen (guinea-pigs) were also carried out by ERJEFALT [4, 5]. The possibility that nerves mediate a mucosal exudation response is highly intriguing but its importance must be based on human observations.

The available data suggest that neurogenic tachykinin-mediated inflammatory exudation occurs exclusively in rodent and not in human airways [20, 21].
in human subjects concerns nicotine, which is a potent exudative agent in guinea-pigs [22]. This neural stimulant, even in doses which cause significant pain, are without exudative effects in human airways [21]. The attraction of the hypothesis of neurogenic exudative inflammation in airway disease has clearly created an imbalance between belief and actual support of human data.

Mediators of extravasation

A wide range of non-neural mediators and factors emerging from cells and the plasma itself may account for plasma exudation in human nasal and tracheobronchial airways [3]. Many mediators will affect both blood flow and extravasation. In theory, the plasma exudation response is regulated by blood flow in addition to the increased vascular permeability. However, the airway mucosa/submucosa seems so well perfused with blood that pharmacologically induced changes in blood flow may not have a great influence on the exudation process [14, 22]. Even a large dose of a topical vasoconstrictor, that would reduce mucosal blood flow by 50%, has not reduced inflammatory stimulus-induced airway exudation of plasma [22].

Increased subepithelial hydrostatic pressure may move plasma exudates across the mucosa

Plasma extravasated from the abundant subepithelial microvessels will multiply its solutes and expand in volume. It surrounds the basolateral aspects of the epithelial cells and, by increasing the hydrostatic pressure, the exudate may compress the sides of these cells (fig. 4). At a certain pressure the tight junctions at the apical pole of the epithelial cells would also separate. Thus an intercellular pathway may be created through which the plasma exudate can flow in bulk into the lumen. When the interstitial pressure is again reduced towards normal values, epithelial tight junctions would be re-established immediately (fig. 4). The following findings support the reasoning above: in guinea-pig isolated tracheal tubes a subepithelial hydrostatic pressure increase of only 5 cm H2O is sufficient to produce significant luminal entry of macromolecular tracers [7]. Such pressure-induced epithelial passages are reversible and reproducible [7].
However, this action awaits confirmation in human airways. In complex disease conditions the important anti-exudative effect may rather reflect inhibition of earlier and crucial steps of the inflammatory process (fig. 5) than direct vascular actions.

**Glucocorticoids inhibit airways plasma exudation**

![Diagram of glucocorticoids inhibiting airways plasma exudation](image)

Fig. 5. - When glucocorticoids reduce plasma exudation in human airways this probably reflects inhibition of cellular mechanisms that fuel the inflammatory process (above) rather than a direct vascular anti-permeability effect (below).

**Plasma exudates on the intact mucosa in airway defence**

Plasma exudation across airway endothelial-epithelial barriers is largely an unfiltered flow of the various-sized plasma solutes. Hence, circulating immunoglobulins and other proteins with significant capacity to bind, catabolize, and neutralize offending factors will be abundant on the surface at the very site of mucosal provocation. This would be a major defence mechanism [20, 23, 24].

At exudation the plasma proteins come in contact with activating factors such as negatively charged surfaces and an abundance of potent plasma-derived peptides are produced. Accordingly, the exudation response would allow potent plasma protein systems (kinin-, complement-, coagulation-, fibrinolysis- etc.) to operate on mucosal surfaces at the sites where the challenge has occurred.

Newly formed peptides of the exudate will not only be potent mediators. By osmotic forces the increasing number of these molecules will attract fluid and make the plasma exudate significantly more voluminous after it has been extravasated. The subsequent flow of exudate into the lumen could wash away allergen and other factors which have penetrated between epithelial cells. A large volume of fluid may contribute significantly to humidification of inhaled dry air. When the demand is high, as during the hyperpnoea of exercise, the dry air may itself evoke mucosal exudation responses. The elimination of luminal exudate would be by mucociliary transport and, if needed, coughing.

Inflammatory stimulus-induced plasma exudation usually goes on for only a few minutes, apparently because the mechanisms for closure of the vascular leak are strong. Even in the continuous presence of an inflammatory mediator a spontaneous closure takes place. In most instances the defence reaction will thus be a brief localized burst of plasma exudate into the lumen. However, when required the exudative defence is an "inexhaustible" source of a potent armamentarium [20, 23, 24]. It seems unfortunate that the current literature on respiratory defence has ignored the possibility of a contribution of the mucosal exudation mechanism.

**Plasma exudation into the lumen as an index of mucosal inflammation**

Inflammatory cells may be in the airways for trivial or unknown reasons, and should be there for tissue repair. It is, therefore, difficult to accept the view that inflammation can be equated with the presence of these cells, unless it can also be demonstrated that they are fuelling an inflammatory process. Indeed, markers are needed to show to what extent the tissue itself is affected by active inflammation.

Airways inflammation may be associated with a great number of tissue responses. Most of these are nonspecific exaggerations of normal airway functions. Thus bronchial tone, secretions, mucociliary transport, cough/sneezes, blood flow, and blood pooling may be altered by both inflammatory and non-inflammatory stimuli. In contrast, the plasma exudation response is not an exaggeration of the normal capillary exchange of solutes but a specific defence/inflammatory response of subepithelial post-capillary venules. Particularly in human airways the exudative tissue response is not induced by irritant agents which merely evoke neurogenic actions [20, 21]. The plasma exudation response is graded in terms of the number of venular leaky sites and by the amount of exuded plasma per unit time [19]. The prompt and non-injurious luminal entry of the extravasated plasma indicates further that increased airways vascular permeability can be monitored just by sampling and analysing mucosal surface material [4, 5]. Animal tracheobronchial data thus show excellent correlation between luminal and tissue exudative indices for immediate, biphasic, and sustained airways inflammation and for dose-response to inflammatory challenges [5, 14].

The unfiltered nature of the mucosal exudate [4, 5, 10, 25] suggests that large proteins, which are not normally transuded or secreted, may be preferable surface indices of airways plasma exudation. This aspect seems particularly valid for bronchoalveolar lavage (BAL) studies. BAL harvests material which has accumulated for an unknown period of time on a mucosal surface area which cannot be well defined and which includes the alveolar lining. The small plasma
Asthma is a tracheobronchial and not pulmonary disease. Hence, although it may be increased in asthma [26, 29] albumin may not be well suited as an exudative index in BAL fluid.

The distinction between pulmonary microvascular-alveolar indices and bronchial microvascular-mucosal indices is particularly important in studies of bronchial diseases such as asthma (fig 6). In accordance with the thought that the large plasma proteins may better reflect bronchial mucosal exudation, GRÖNBERG et al. [26] have demonstrated allergen-induced exudation of fibrinogen (MW 340000) rather than albumin (MW 69000) in BAL fluids from asthmatic subjects.

In BAL fluid obtained from symptomatic non-allergic asthma MATTOLI et al. [27] have demonstrated elevated levels of fibronectin (MW >400000) and VAN DE GRAAF et al. [28] have found reduced levels of large plasma proteins in BAL fluids obtained after prolonged treatment of asthmatic subjects with an inhaled glucocorticoid. Similarly, SVENSSON et al. [30] demonstrate glucocorticoid-induced inhibition of fibrinogen in allergic rhinitis. In the human nose, where prior saline lavages can provide a low base-line and where airway specificity and distribution of the lavage fluid are well controlled, albumin is a useful exudative index along with fibrinogen, α1-macroglobulin and other large proteins.

Conclusion

Inflammatory stimulus-induced plasma exudation into the airway lumen can occur as a brief and directed response that does not compromise the integrity of the epithelial lining as a barrier to luminal material. In co-operation with the mucociliary apparatus, exuded plasma protein systems thus act on the surface of the intact airway mucosa to neutralize offending factors. The airways plasma exudation is induced by mediators which produce transient holes in the venular wall by actively separating endothelial cells. It appears that the plasma exudate itself, by increasing the hydrostatic pressure in the subepithelial space, creates pathways for its luminal entry. Anti-exudative drugs may act on the microvascular wall or the may inhibit earlier and crucial events in the inflammatory process. Glucocorticoids are potent anti-exudative agents in airway disease but this may only in a small part reflect direct effects on the vascular wall.

Exuded plasma containing an abundance of peptide mediators potentially contributes to several patho-physical and pathophysiological characteristics of the airway tissue and surface in inflammatory airway diseases [1-3]. However, the plasma exudation process is not necessarily associated with airway oedema, epithelial disruption, or increased mucosal absorption. This is important because plasma exudation may be a consistent feature of airways diseases such as asthma and rhinitis whereas the other three alterations are not.

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References

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**Exudation plasmurique dans les voies aériennes: mécanismes et fonction. C.G.A. Persson.**

Des provocations inflammatoires de la muqueuse trachéobronchique et nasale provoquent une extravasation rapide ou une exudation du plasma à partir de la micro-circulation qui est bien développée immédiatement sous la membrane basale de l'épithélium. L'exudation plasmurique n'est pas une exagération de l'échange normal de liquide capillaire et des solutos, mais une réponse inflammatoire spécifique des veines post-capillaires. Le plasma exsudé peut ne pas produire d'oedème. Les exsudats plasmuriques traversent le revêtement muqueux au cours d'un processus rapide, unidirectionnel, non filtré et dès lors non idéal, pour apparaître à la surface de la voie aérienne au siège de la provocation. Les données *in vitro* suggèrent la possibilité qu'une pression hydrostatique égérément accrue déplace l'exsudat au travers d'ouvertures du type valvulaire entre les cellules épithéliales. Par le mécanisme d'exudation muqueuse au niveau des veines, tous les systèmes protéiques puissants du plasma circulant agiront sur les défenses respiratoires à la surface d'une muqueuse intacte. Une conséquence ultérieure est que les indices exsudatifs obtenus à partir de la surface de la voie aérienne reflètent quantitaivement l'intensité et le découvrant dans le temps du processus inflammatoire muqueux ou sous-muqueux. Et ceci se produit indépendamment du mécanisme cellulaire particulier qui intervient pour nourrir l'inflammation. L'exudation muqueuse de plasma se produit de façon caractéristique dans l'asthme et la rhinite, même lorsqu'il n'y a pas d'oedème de la voie aérienne, pas de destruction épithéliale, et pas d'augmentation de la capacité d'absorption. Toutefois, l'exudation plasmurique et ses peptides médiateurs dérivés contribuent potentiellement à la plupart, si pas à la totalité, des caractéristiques physiopathologiques et physio-pathologiques des maladies inflammatoires des voies aériennes. *Eur Respir J.*, 1991, 4, 1268–1274.