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Invited Commentary

Hypertonic Saline or High Volume Normal Saline for Viral Bronchiolitis: Mechanisms and Rationale

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Key words: hypertonic saline; viral bronchiolitis; RSV; mucus clearance; β2 agonist; normal saline.

INTRODUCTION

In recent years and particularly in the last 5 years, there have been substantial advances in our understanding of the mechanisms governing mucus clearance (MC) in health and disease. These have demonstrated the role of hydration of the airway surface liquid (ASL) and the importance of inhaled hypertonic saline for rehyadration and have been recently reviewed.[1–3]

Briefly, it was suggested that MC failure is a dominant factor not only in CF but in most airway diseases and that hydration is the dominant variable governing MC in all airway diseases.[2,3] This was also found to be true even in normal subjects[4] and furthermore, it has been noted, that exacerbations in many airway diseases result from intermittent catastrophic failures of MC due to dehydration of ASL often triggered by viral infections. Thus, therapy to maintain ASL hydration is probably important during viral exacerbations not only in CF patients but in all chronic airway diseases.[2,5]

Issues crucial to understanding the postulated mechanism involving hypertonic saline inhalation treatment in RSV bronchiolitis will be described in more detail here.

POSSIBLE MECHANISMS OF ASL DEHYDRATION IN VIRAL BRONCHIOLITIS

Efficient clearance requires the coordinated interaction of two separate layers: an overlying transported mucus layer (ML) and a separate, distinct environment near the cell surface called periciliary liquid (PCL). ASL comprises both of these layers.[2] Figure 1 is a schematic representation of the proposed mechanisms of ASL dehydration in RSV bronchiolitis (Fig. 1B,C) compared to normals (Fig. 1A) and CF patients (Fig. 1D). Since airway epithelia are water permeable, water moves to equalize electrolyte concentrations following inward active absorption of Na through ENaC thereby causing dehydration of the ASL and outward following Cl transport through both CFTR and Calcium activated chloride channels (CaCC), thus hydrating the ASL.

By activating the A28 receptor (red), adenosine stimulates the CFTR to secrete Cl and to attenuate ENaC activity, thus hydrating the ASL. In vivo, ATP activates the P2Y2 receptor (blue) thus stimulating CaCC to secrete Cl and directly attenuate ENaC action, thus hydrating the ASL. ATP, which reaches only negligible, ineffective concentrations in static tissue cultures, reaches a high concentration in vivo (in moving lungs) and is probably the most important hydrating and compensating stimulus for regulating the ASL water content.[2] This increase in ATP concentration, that occurs only in vivo, is due to a mechanism called mechanotransduction in which cells convert a mechanical stimulus into chemical activity. In this case, the phasic motion of the airway flow (lung inflation/deflation and particularly acceleration and deceleration) produces a shear stress which is

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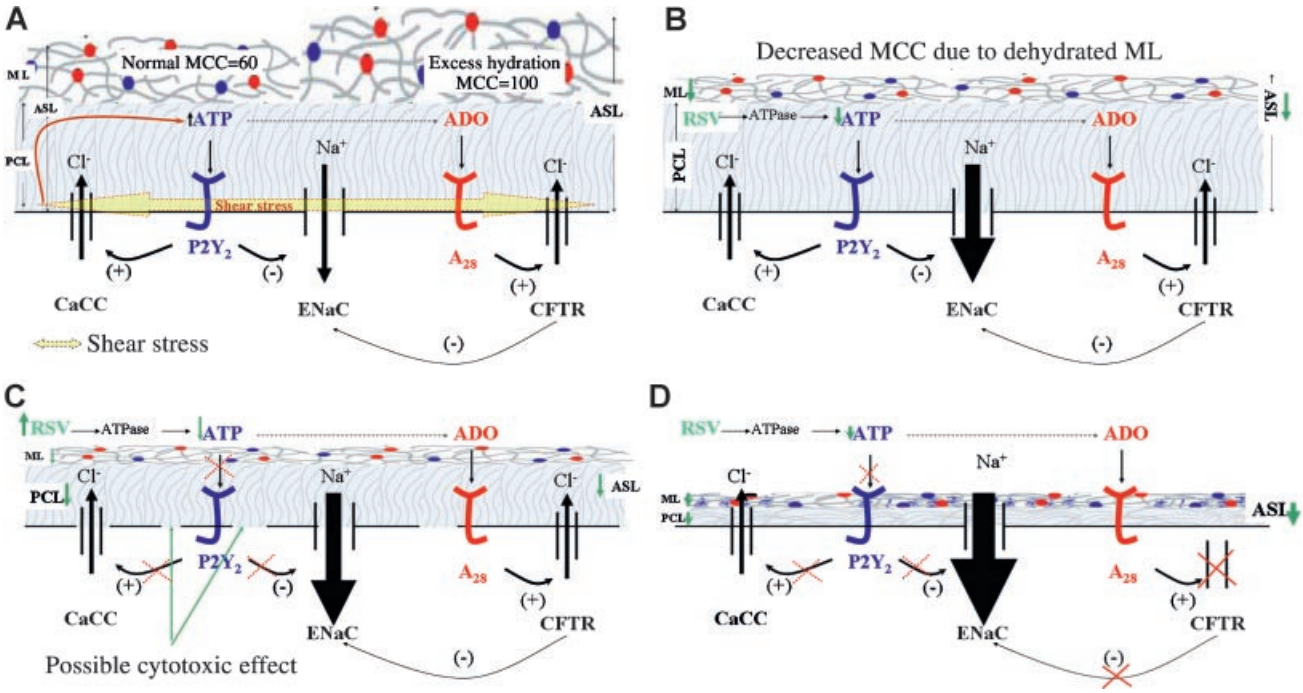

Fig. 1. Postulated mechanism in vivo, explaining ASL dehydration in RSV bronchiolitis as compared to normal and CF: (A) normal, (B) mild RSV bronchiolitis: (C) severe RSV bronchiolitis, (D) during viral infection in CF. This figure was modified particularly for RSV bronchiolitis, with the permission and the courtesy of Randell SH and Donaldson SH, both from the University of North Carolina at Chapel Hill.

tangential to the apical epithelial cell membrane (in contrast to the normal stress that is perpendicular) and causes the epithelial cell to release extra-cellular ATP thus hydrating the ASL (Fig. 1A). This latter mechanism has been shown to be highly vulnerable to viral injury particularly as occurs in RSV infections.[2]

Maintaining normal height of the PCL (around 7 μm) is crucial for maintaining normal airway mucociliary clearance (MCC) so that the moving tips of the cilia will precisely contact the lower margin of the ML. This is maintained by the ML acting as a water reservoir selectively absorbing water in response to excess hydration and increasing the MCC to super-normal rates (Fig. 1A). This super-normal MCC was demonstrated in normal subjects who inhaled hypertonic saline (HS) aerosols.[4] In contrast, it is suggested that when dehydration of the ASL occurs in response to a relatively mild RSV infection, extra-cellular ATP concentrations are depleted, thus dehydrating the ASL. The ML then donates water to preserve at least some MC while maintaining the PCL height close to the normal approximately 7 μm and resulting in ML dehydration ([2] and Fig. 1B). However, when this donor mechanism is exhausted, the ML has no more water to donate, the PCL may start to contract to the point that MCC is impossible (Fig. 1C). As CF epithelium, which lacks CFTR (Fig. 1D), is thus totally dependent on ATP, the PCL contraction occurs early, even in CF airways exposed to relatively minor viral injury in CF exacerbations ([2] and Fig. 1D).

In small babies suffering from severe acute RSV bronchiolitis, the high load of RSV infection in the small bronchioles, probably causes a considerable reduction of extra cellular ATP that is crucial for maintaining ASL hydration in vivo. In addition, the non-specific pathological impact of RSV infection such as the cytotoxic effects on cells, ciliary damage and cytokine release results in mucus plugging of smaller airways. We hypothesize that the protective effects of the ML reservoir and that of the still functioning CFTR in the remaining epithelial cells that were not massively damaged by this RSV inflammation, is probably exceeded, thus depleting not only the mucus layer water content but also damaging the ASL epithelial architecture thus reducing the height, of the PCL and impairing MC. This likely contributes to airway mucus plugging, airway obstruction, hyperinflation and atelectasis that also characterize severe RSV infection.

ABBREVIATIONS

ASL	Airway surface liquid
PCL	Periciliary liquid
ML	Mucus layer
MC	Mucus clearance
MCC	Mucociliary clearance
CS	Clinical score

However, although fairly reasonable as a way of explaining the observations, this latter hypothesis has never been proven in a properly designed placebo-controlled study reflecting the complex interactions that occur in vivo, in the various bronchial and bronchiolar airways in small babies during the evolution of naturally occurring acute RSV bronchiolitis. Though dehydration of the ASL and MC dysfunction undoubtedly occur, at present we do not know to what extent. We can only presume that, at some stage, and in some bronchioles of these more severely affected babies, the impact of RSV infection on the ASL is probably intermediate between Figure 1B and D and between uninfected normal ASL and the very extreme conditions that occur in viral infected CF ASL (Fig. 1A–D).

RATIONALE OF HS AEROSOL TREATMENT IN RSV BRONCHIOLITIS

Infants with acute viral bronchiolitis wheeze but as the pathophysiology of bronchiolitis is quite distinct from that of asthma, these infants are less if at all responsive to bronchodilators[6] or steroids.[7] Bronchiolitis is a viral infection of the bronchial and bronchiolar epithelium, with subsequent peribronchiolar mononuclear infiltration and epithelial cell necrosis, profound sub-mucosal edema, increased secretion of mucus and therefore an increase in mucin/water ratio[8] that causes relative dehydration of ASL.[2] Moreover, RSV, by increasing ATPase levels decreases extra cellular ATP and therefore results in loss of ENaC inhibition (increasing Na absorption) and loss of the attenuation of outward secretion of chloride. Thus, more water will move from the ASL to the sub-mucosa along with these electrolytes (Fig. 1B,C). This will result in more dehydration of the ASL, and a decrease in the height of the mucus layer (Figs. 1B and 2). Thus hypothically, in more severely affected bronchiolar areas, the ASL protective hydrating mechanism can be impaired thus depleting not only the mucus layer's water content but also damaging the ASL, and epithelial architecture while the depleted height of the PCL impairs MC (Fig. 1C). Thus, appropriate therapy must hydrate the ASL, decrease the sub-mucosal edema and improve the mucus rheologic properties (elasticity and viscosity) and thus improve MC. Hypertonic saline may, in theory, reverse some of these pathophysiological abnormalities in acute viral bronchiolitis. In vitro, the addition of hypertonic saline increases airway surface thickness, decreases epithelial edema,[9] improves mucus rheologic properties (elasticity and viscosity), and accelerates mucus transport rates.[9,10] In vivo, hypertonic saline inhalation increases the rate of mucociliary transport even in normal subjects with no evidence of dehydration, mucus hyper-secretion or sub-epithelial edema.[4]

Additional Important Modes of Action of Aerosolized HS Treatments in RSV Bronchiolitis

Whereas hydration of the ASL is considered the main mode of action, additional important mechanisms are attributed to the effect of HS by which HS improves MC by ciliary or cough actions. Hypertonic saline breaks the ionic bonds within the mucus gel. This, in turn, reduces the degree of cross-linking and entanglements,[11] thus improving mucus rheology. HS increases ciliary beat frequency via the release of prostaglandin E2.[5] Addition of hypertonic saline raises the ionic concentration in the mucus and brings about a conformational change by ''shielding'' the negative charges, thereby reducing repulsion. This results in a more compact mucus macromolecule, and more

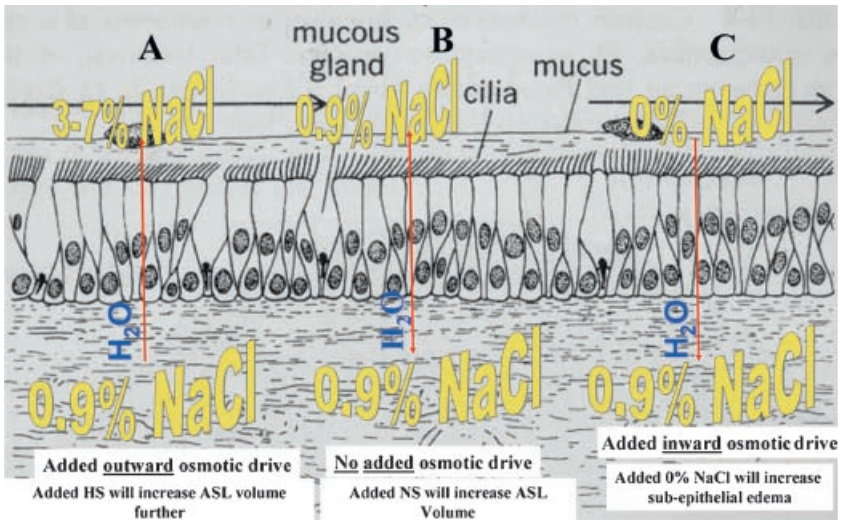

Fig. 2. Simplified scheme assuming only osmotic forces to control water transport.

effective cough-dependent MC.[12] Airway surface liquid hyperosmolarity can release mediators capable of enhancing ciliary activity.[5] Moreover, by absorbing water from the mucosa and sub-mucosa, hypertonic saline solution can theoretically reduce edema of the airway wall in infants with acute bronchiolitis ([13,14] and Fig. 2). Hypertonic saline inhalation can also cause sputum induction and cough, which can help to clear the sputum from the airways and thus improve airway obstruction.[13]

CLINICAL STUDIES USING VARIOUS NaCl CONCENTRATIONS AND DOSES IN RSV BRONCHIOLITIS

Distilled Water (0% NaCl)

Smith et al.[15] used distilled water (0% NaCl) as a ''placebo'' and demonstrated that aerosolized ribavirin considerably reduced the duration of mechanical ventilation and hospitalization compared to ''placebo'' in infants with acute RSV bronchiolitis. Obviously, it was not the ribavirin that improved the treatment group but the adverse effect of the distilled water that had an adverse effect on the ''placebo'' group (Fig. 1). The ''beneficial'' effect of ribavirin could not be duplicated subsequently in previously healthy infants with RSV bronchiolitis and only then was it appreciated that distilled water was not an appropriate placebo and the AAP changed its previous statement from ''ribavirin should be used'' to ''ribavirin may only be considered for children with serious underlying disorders.''[8] This is relevant to our topic in two respects. Firstly, this teaches us that we should not accept without question a ''placebo effect'' even when peer reviewed by a reputable journal.[15] Finally, if distilled water is not appropriate, it appears that there is no really adequate placebo for HS studies. This should be taken into account in the design of future studies.

Hypertonic Saline (3%)

In three randomized double blind placebo controlled studies Mandelberg et al.,[13] Sarrell et al.,[14] and Tal et al.[16] confirmed the efficacy of HS improving the duration of hospitalization and clinical scores, both in ambulatory and hospitalized infants with RSV bronchiolitis. However as stated in a July 2007 review,[3] these studies were all conducted by the same research group and although promising needed to be confirmed by others in a multicenter trial. Since then, Kuzik et al.[17] published a prospective, randomized, double-blind, placebo controlled, multi-center trial (three centers for 3 years) and confirmed the earlier results. In late 2008, Zhang et al.[18] published a Cochrane Database Review to summarize the effect of nebulized HS in these patients. His review included four double blind randomized trials involving 254 infants. Analysis of the pooled data, suggested that therapy with nebulized 3% saline significantly reduced the duration of hospitalization and improved the clinical severity score in infants with acute viral bronchiolitis. The implications for practice of this review were that, given the clinically relevant benefit and good safety profile, nebulized 3% saline used in conjunction with bronchodilators should be considered an effective and safe treatment for infants with viral bronchiolitis.

High Volume Normal Saline (0.9%)

In this issue of the journal, Anil et al.[19] published a randomized double blind placebo controlled study to investigate the effectiveness of nebulized salbutamol, epinephrine and 3% saline compared to high volume normal saline in the treatment of acute mild viral bronchiolitis. All four groups received two inhalations of the treatment drugs in the emergency department (time 0 and 30 min). They showed that CS scores after 30, 60, and 120 min were significantly and progressively better than the baseline values. No nebulized therapy options including 3% saline were more effective than others. However, all treatment modalities included high dose NaCl dissolved in 8 ml (72 mg for the salbutamol, epinephrine and normal saline groups and 240 mg for the 3% saline group).

In view of recent negative results of beta agonist treatment in infants with bronchiolitis,[22] the main added value of this study to the current literature may be that a large mass of NaCl delivered as high volume normal saline inhalations could be sufficient to cause significant improvement in mild acute viral bronchiolitis.

However, Anil's study should not be interpreted as confirmation for a negative effect of hypertonic saline inhalation in acute viral bronchiolitis and was not included in the studies assembled to evaluate the inhaled HS effect for the following reasons: This is a study of very mild bronchiolitis that improved considerably and rapidly (in 120 min) after only two inhalations of 8 ml 0.9% NaCl given in the emergency department. The treatment consisted of a single dose in contrast to the above mentioned studies that continued for 3–6 days.[18] The improvement was so dramatic that all of these children could be discharged home within 2 hr when the CS had improved from 3.6 ± 1 to 1.8 ± 1.4. The O_2 saturation and pulse rate were normal from the start.

Considering this and the fact that 0.9% saline is not a placebo ([4] and Fig. 2), it is evident that, in contrast to the recent literature, hypertonic 3% saline was ''not more effective'' than 0.9% saline. Obviously, there was no further improvement achievable in the clinical score. Moreover, the clinical score was already so low after 0.9% saline that none of the infants required hospital admission and could be sent home. Thus no improvement in more

important outcomes such as a decrease of the rate and duration of hospitalization attributable to hypertonic saline (Cochrane review 2008) was demonstrable.

Indeed, 8 cm^3 of 0.9% saline is not a placebo as pointed out by Sood et al.[4] who showed that the change in ASL depth and therefore, the improvement in mucus clearance after normal saline or hypertonic saline inhalations is not a function of the saline concentration but rather a direct result of the total mass of NaCl added to the airway surface.

Additionally, Sarrell et al.[14] showed that merely 2 cm^3 of nebulized 3% HS solution (=0.06 g of NaCl) was enough to improve CS in relatively mild ambulatory children with viral bronchiolitis. These infants were comparable in severity and age to the present study population. Eight cubic centimeters of 0.9% saline used in this study as a control is equals to 0.072 g of NaCl which is greater than that used by Sarrell. Thus it is obvious that this data could not be interpreted as indicating absence of an effect of hypertonic saline.[18] On the contrary, this data could only be interpreted, as a positive effect of high volume inhalation of normal saline that delivered a mass of NaCl sufficient to treat infants with very mild viral bronchiolitis.

Furthermore since the present study included a total of 186 patients, all of whom received at least 72 mg of NaCl it was, highly powered to detect a clinically significant benefit. Nevertheless, as stated by the authors, and adding the great improvement in all the groups (nothing further to be gained), the study is not powered to detect the lack of a clinically significant difference between the groups (36–39 infants per group).

CONCLUSIONS

Nebulized 3% saline should be considered an effective and safe treatment for infants with viral bronchiolitis. Even in mildly affected infants it is probably faster and more convenient to use a relatively small volume of NaCl as hypertonic saline. Given the recent observations described above, a postulated mechanism explaining hypertonic saline inhalation treatment particularly in RSV bronchiolitis is presented. Further studies to confirm or dispute this hypothesis are warranted.

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