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Vascular volume expansion and thermally induced asthma

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ABSTRACT: To determine whether a relationship exists between intravenous infusion of isotonic fluid and reactivity to hyperpnoea, eight normal and eight asthmatic subjects underwent rapid intravascular administration of approximately 2 *l* of warm normal saline, by itself and before and after hyperventilation of cold air.

In the asthmatic subjects, saline infusion mirrored the obstruction seen with hyperventilation; whereas, in normal subjects saline produced more bronchial narrowing than hyperventilation. When the two stimuli were given together, the timing of the infusion altered the asthmatic subjects' responses. Giving fluid early in the hyperventilation challenge blunted obstruction, whereas giving it later amplified the airway narrowing. Similar findings, but on a smaller scale, occurred in normal subjects.

These data demonstrate that sudden elevations in intrathoracic vascular volume with warm saline produce airway obstruction that is quantitatively similar to that seen with hyperventilation in asthmatic individuals. They also demonstrate that these two stimuli interact together in such a manner that a common mechanism may exist to account for the decrease in airflow.

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Data have accumulated over the past several years suggesting that the airway obstruction which develops in asthmatic individuals, following the thermal bronchoprovocations of exercise and hyperventilation, may be related to vasodilation and oedema of the bronchial wall [1–7]. Initially, these postulates were based only upon studies which manipulated the heat content of the inspired air in the immediate recovery period [1, 5–7] but, later, they were expanded by actually measuring the temperature fluxes in the intrathoracic airways of asthmatic and normal subjects during and after hyperpnoea [2, 3]. These last experiments showed that asthmatics rewarmed their airways twice as fast as normals in the immediate post-hyperpnoea period, and demonstrated an enhanced flow of heat to the walls of the tracheobronchial tree at a time concomitant with the onset of obstruction [2]. That this post-hyperpnoea increase in heat was due to hyperaemia, was subsequently supported by first rapidly moving blood into the thorax from the legs and recording an increase in airstream temperature [8], and then by locally constricting the blood vessels in the airway wall with an alpha-agonist and observing a reduction in the magnitude of the end hyperpnoea temperature gradient [9]. Moreover, in conjunction with topical alpha-agonist administration, responses to both exercise [10] and isocapnic hyperventilation have been attenuated [9, 11].

To further explore the potential relationship between the airway vasculature and thermally-induced asthma, we reasoned that if the two phenomena were related, it should be immaterial as to how intrathoracic vascular volume is increased. To provide data on this possibility, we contrasted the effects of hyperventilation of frigid air on pulmonary mechanics with those seen with the rapid infusion of normal saline. We then studied the effects of both stimuli together. Our observations form the basis of this report.

Methods

Subjects

Eight asthmatics (5 men and 3 women; mean age 26±2 (SEM) yrs) and 8 normals (5 men and 3 women; mean age 27±2 yrs) served as our subjects. No participant had a history of cardiovascular disease, smoked cigarettes, or had experienced a recent upper respiratory tract infection. All were clinically mild asthmatics who required, in the main, only aerosolized $beta_2$-agonists for control of their disease. None had

been taking cromolyn or glucocorticoids in the 6 weeks preceding the investigation, or routinely used sustained release bronchodilator preparations. All participants refrained from use of any medication for 12 h before each study. Informed consent was obtained from each subject, and the study was approved by the Institutional Review Board for Human Investigation of University Hospitals.

Study design

The participants underwent a four part study with each investigation performed on a separate day. Each subject completed all parts of the protocol. In trial 1, each volunteer performed 4 min of isocapnic hyperventilation (HV), whilst breathing cold air through a heat exchanger [1–3]. The water content of the inspirate was <1 $mgH_2O \cdot l^{-1}$, which for the purposes of this study was considered to be zero. Recovery took place on room air. The temperature and humidity of the air in the laboratory were measured by standard techniques.

As in former studies, expired air was directed away from the heat exchanger into a reservoir balloon, which was being constantly evacuated through a calibrated rotameter [3, 8]. The subjects were coached to respire to keep the balloon filled and, in so doing, minute ventilation ($\dot{V}_E$), could be controlled at any desired level. End-tidal CO_2 concentrations during hyperventilation challenges were monitored with a Beckman LB-2 analyser, and sufficient CO_2 was added to the inspiratory port of the exchanger to maintain this parameter at eucapnic levels.

The ventilation used in the asthmatics was at a level previously determined to produce a 15–25% fall in forced expiratory volume in one second (FEV_1). In order to maximize the effects of the thermal stimulus, $\dot{V}_E$ for the normals was set at the highest level which each subject could sustain comfortably for 4 min.

In trial 2, an 18 gauge angiocatheter was inserted into a large antecubital vein in each arm of the subjects and 30 $ml \cdot kg^{-1}$ body weight of normal saline, at 37°C, was infused over a 15–20 min time period [12–14]. The total volume infused was approximately 2 *l* (table 1).

In trial 3, the same hyperventilation challenge used in trial 1 and the same fluid loading used in trial 2 (with the exception of one subject) were administered simultaneously, such that the infusion was completed 5 min after the cessation of hyperventilation. This time was chosen to coincide with the point at which maximum obstruction from thermal stimuli generally develops [3]. Our purpose was to attempt to accentuate any vasocongestion and/or oedema which might be induced by hyperventilation. In trial 4, the saline infusion protocol was completed prior to the onset of the hyperventilation challenge. Hyperventilation commenced at the end of the infusion.

In one subject, the fluid load was decreased to 20 $ml \cdot kg^{-1}$ in trials 3 and 4. At 30 $ml \cdot kg^{-1}$, this individual developed such severe airway obstruction (59% reduction in FEV_1) that we were afraid to combine this stimuli with hyperventilation. Consequently, in subsequent experiments, the lower volume of saline was used. This infusion, in itself, produced a 17% reduction in FEV_1.

Trials 1 and 2 were performed first but in a random fashion. Trials 3 and 4 were also randomized. However, in order to characterize the responsivity of each subject to hyperventilation and fluid infusion, and to minimize the risk of severe airway obstruction being induced by the combination of these stimuli, the latter two trials were always undertaken after both of the single stimulus protocols had been completed.

Blood pressures and pulse rates were measured prior to and after each fluid infusion study. Maximum forced exhalations were performed in triplicate using a waterless spirometer before and serially after each

Table 1. – Baseline mechanical and challenge data

	Trial 1 HV	Trial 2 FLUID	Trial 3 HV+FLUID	Trial 4 FLUID+HV
Asthmatics				
FEV_1 *l*	3.50±0.25	3.30±0.27	3.32±0.26	3.33±0.24
$\dot{V}_E$ $l \cdot min^{-1}$	50±8	–	50±8	50±8
Ti °C	-12±2	–	-9±2	-9±2
Saline cc	–	1905±125	1855±148	1855±148
Time min	–	18±1	18±1	18±1
Normals				
FEV_1 *l*	4.19±0.25	4.18±0.25	4.16±0.28	4.19±0.27
$\dot{V}_E$ $l \cdot min^{-1}$	75±4	–	75±4	75±4
Ti °C	-9±4	–	-12±3	-11±3
Saline cc	–	2048±128	2048±128	2048±128
Time min	–	19±1	19±1	19±1

Data are presented as mean±SEM. FEV_1: baseline forced expiratory volume in one second; $\dot{V}_E$: minute ventilation; Ti: inspired air temperature; saline: volume of fluid infused; time: time for fluid infusion; HV: 4 min isocapnic hyperventilation; FLUID: fluid infusion; HV+FLUID: fluid infusion before, during, and after HV; FLUID+HV: fluid infusion prior to HV.

of the four trials. The curve with the largest FEV_1 was chosen for analysis.

The data were analysed by paired and unpaired t-tests and one factor analysis of variance. Statistical significance was defined as a p value ≤ 0.05.

Results

The baseline mechanical and challenge data for the four experimental trials, for both subject groups, are contained in table 1. Baseline FEV_1 prior to trial 1 (HV) was 3.50±0.25 *l* (mean±SEM) (90±7% of predicted) and 4.19±0.25 *l* (109±9% of predicted) for the asthmatic and normal subjects, respectively. There were no significant within-group differences for any of the trials for this parameter. Similarly, for all trials in which hyperventilation was performed, there were no significant differences in minute ventilation ($\dot{V}E$) or inspired air temperature (Ti), within groups.

In the fluid infusion study, trial 2, the asthmatic subjects received 1,905±125 ml of normal saline over an 18±1 min time period. The normal subjects were given 2,048±128 ml of fluid in 19±1 min, and there were no differences among the various fluid trials or subject groups for these variables. Similarly, there were no differences or significant changes between baseline and post-infusion pulse rates and blood pressures between groups or among the three infusion trials.

Figure 1 compares the individual data for the maximum changes in FEV_1 in the asthmatic and normal subjects produced by hyperventilation and fluid. These data are plotted independent of time. In the asthmatics, hyperventilation at 50±8 $l \cdot min^{-1}$ of -12±2°C air resulted in a maximum decrease in FEV_1 of 0.63±0.07 *l*, ($p<0.001$). The saline infusion resulted in an equivalent decrement in lung function, with FEV_1 falling 0.65±0.16 *l* ($p<0.01$). There were no differences between the maximal responses to those two stimuli. The mechanical consequences of both of these stimuli were significantly less in the normals, despite this group receiving a greater thermal burden and similar volumes of fluid. Hyperventilation at 75±4 $l \cdot min^{-1}$ of air at -9±4°C produced a maximum fall in FEV_1 of only 0.09±0.02 *l*. Unlike the asthmatics, administration of saline in the normal population produced significantly greater decrements in lung function than hyperventilation ($p<0.01$). In this instance FEV_1 decreased 0.33±0.04 *l* ($p<0.001$). However, this was approximately half of the effect which FLUID produced in the asthmatic subjects ($p<0.05$).

The time course of the mechanical response to both stimuli in both groups is shown in figure 2. In the asthmatic subjects, no significant difference between HV and fluid were found at any time. In the normal participants the changes following fluid administration remained statistically greater than HV until 60 min, at which point the response equalized.

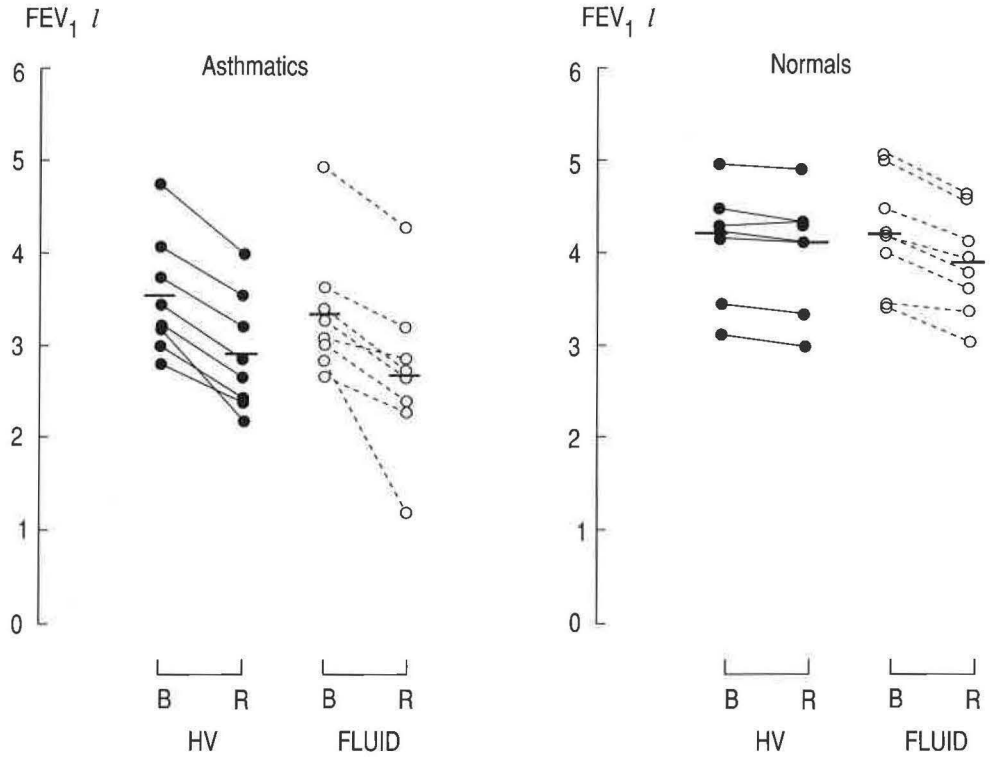


Fig. 1. – The maximum change in forced expiratory volume in one second (FEV_1) prior to and following isocapnic hyperventilation (HV) (●——●), and saline infusion (FLUID) (○---○), in the asthmatic and normal subjects. The data points are individual values and the bars indicate the mean. B: baseline; R: maximum response.

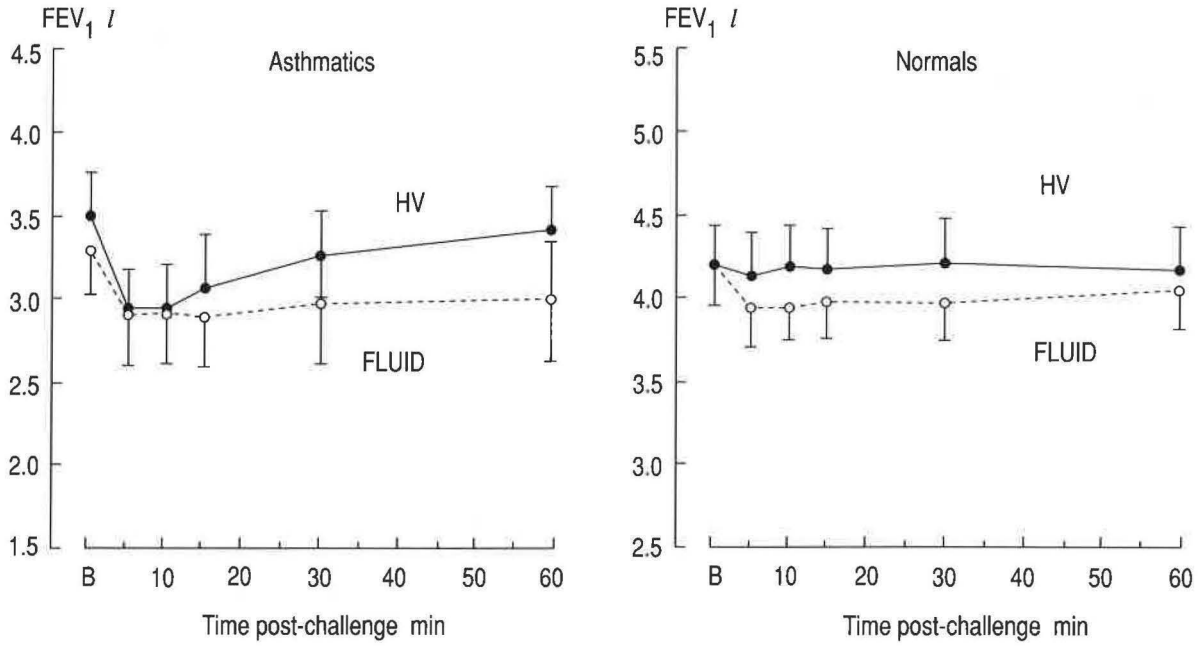


Fig. 2. – The mechanical effects of hyperventilation (●—●) and saline infusion (○···○) in asthmatic and normal subjects as a function of time. The data points are mean values and the brackets represent 1 standard error of the mean. For abbreviations see legend to figure 1.

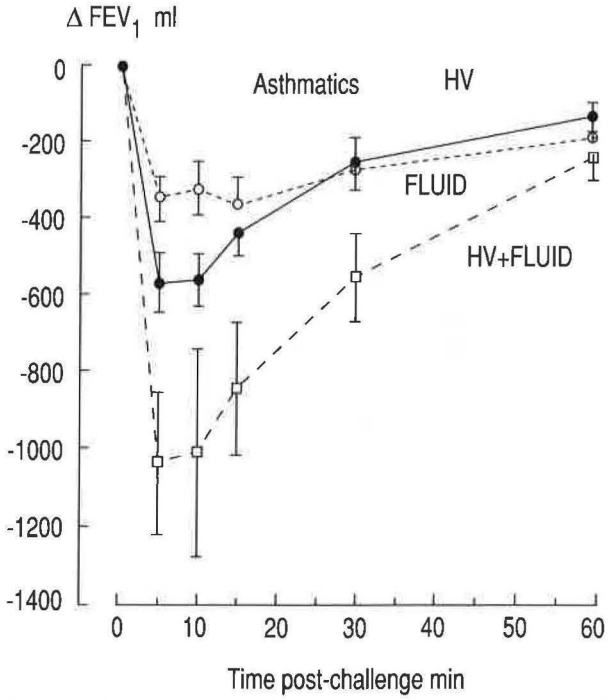


Fig. 3. – The effects over time of hyperventilation (HV) (●—●), fluid (○···○) and this combination of HV+FLUID (□- - -□) on lung mechanics in the asthmatic subjects. The data points are mean values and the brackets represent 1 standard error of the mean. Δ FEV_1: change in forced expiratory volume in one second. For the FLUID trial, the first data point occurs 5 min after completion of the infusion. For the HV trial, the first data point occurs at 5 min post cessation of hyperventilation. In the HV+FLUID trial, the initial data point is also 5 min post cessation of hyperventilation, which is the point at which all fluid had been infused.

Figure 3 contrasts the mechanical effects over time in the asthmatics, of HV, FLUID and the combination of these stimuli (HV+FLUID). The latter was performed in such a fashion that the cessation of hyperventilation preceded completion of saline administration by 5 min. The HV data are the same as in figure 2. The fluid data, however, differ from this figure in that they include the data from the subject who received 20 ml·kg^{-1} of saline. When HV and FLUID were given together, this combination resulted in significantly greater obstruction than either challenge alone for the first 30 min post-challenge. The effect was gone by 60 min. In this trial, the maximum decrement in FEV_1 of 1.18±0.26 *l* approximately doubled that seen with each stimulus alone ($p<0.05$).

A different pattern of mechanical changes over time was produced by these same three trials in the normal volunteers (fig. 4). Unlike the asthmatic subjects, in the first 30 min post-challenge, FLUID resulted in significantly greater falls in FEV_1 than HV, and at no time did the combination of stimuli produce greater effects than FLUID alone. Additionally, the maximum fall in FEV_1 engendered by HV+FLUID was only 0.35±0.08 *l*, one-third the decrement produced by this combination in the asthmatics ($p<0.01$).

In an attempt to discern whether the airflow limitation produced by vascular volume expansion was predominately due to an obstructive or a restrictive mechanical process, we measured FEV_1/forced vital capacity (FVC) ratios prior to and following HV, FLUID, and the combination HV+FLUID. There were

no differences between the baseline FEV_1/FVC ratios for the three trials in either group. As expected, following cold air hyperventilation in the asthmatic subjects, this parameter fell significantly from a baseline value (B) of 0.75±0.05 to a response value (R) of 0.66±0.04 ($p<0.001$), indicating the development of airway obstruction. Saline administration also significantly reduced the FEV_1/FVC ratio, and there was no difference in the degree of fall in this parameter produced by the HV and FLUID trials (FLUID B = 0.71±0.04; R = 0.65±0.04). Moreover, when vascular volume expansion continued during the recovery period from hyperventilation, the FEV_1/FVC ratio fell from a baseline value of 0.72±0.04 to 0.58±0.03 ($p<0.01$), a decrement significantly greater than that produced by either challenge alone ($p<0.05$). Unlike the asthmatic subjects, the normal group showed no change in the FEV_1/FVC ratio following any one of these three trials (FEV_1/FVC post-HV = 0.85±0.02; post-fluid = 0.85±0.02; post-HV+FLUID = 0.85±0.02).

In contrast to the accentuated obstructive response to HV, which was observed when saline was administered at the end of hyperventilation (HV+FLUID), the effect of hyperventilation upon lung mechanics was significantly attenuated when intrathoracic vascular volume was expanded prior to the onset of hyperventilation (FLUID+HV).

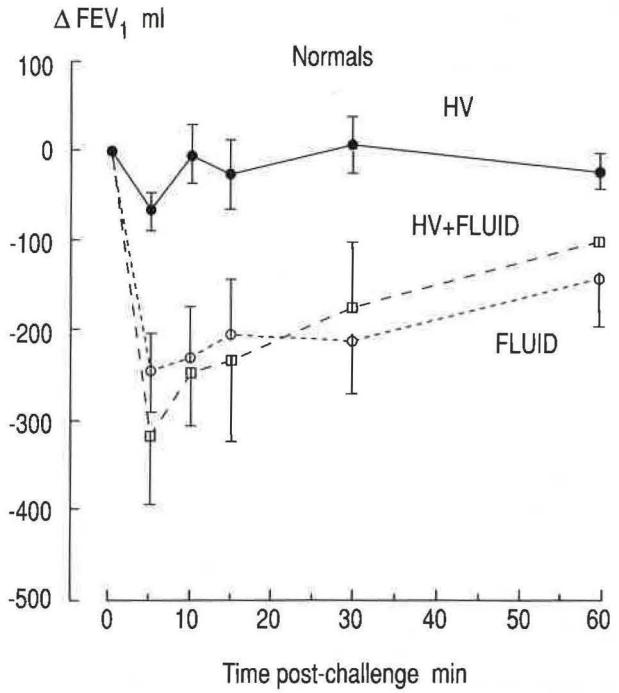
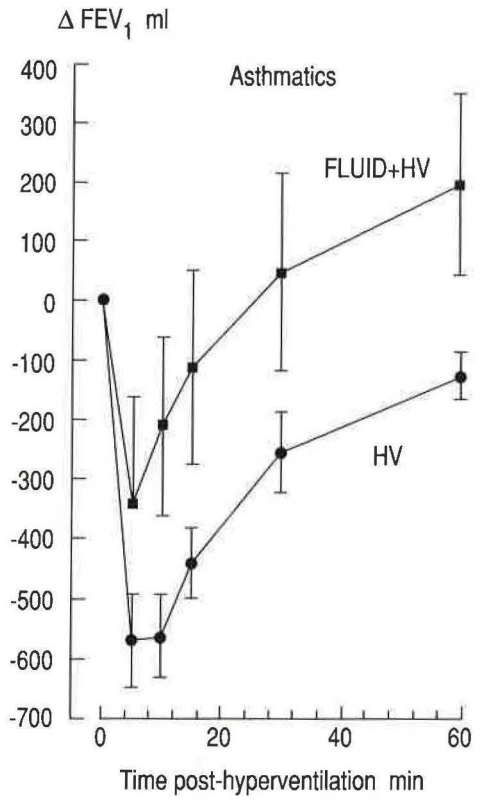


Fig. 4. – The effects of hyperventilation (HV) (●——●), fluid (○- - -○) and the combination of HV+FLUID (□- -□), on lung mechanics over time, in the normal subjects. The format and abbreviations are the same as for figure 3.



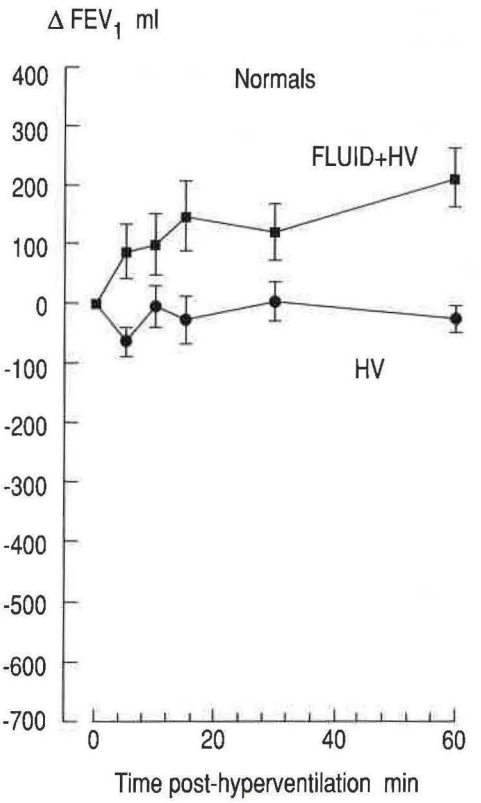


Fig. 5. – The mechanical effects over time of hyperventilation alone (HV) (●——●), and hyperventilation performed after vascular volume expansion was complete (FLUID+HV) (■——■), in the asthmatic and normal subjects. The data points are mean values and the brackets represent 1 standard error of the mean. Δ FEV_1: change in forced expiratory volume in one second. The initial data point for both conditions is at 5 min post cessation of hyperventilation. However, in the FLUID+HV trials, all data points are calculated from the end-infusion FEV_1.

In this experiment, fluid alone significantly reduced the FEV_1 0.43 *l* from 3.32±0.24 to 2.89± 0.22 *l* ($p<0.001$) in the asthmatic group. As can be seen in figure 5, when calculating the effect of HV on FEV_1 from the end of infusion, significantly less obstruction occurred at 10 min after completion of the cold air challenge ($\Delta FEV_1 HV=0.57\pm0.07$; FLUID+HV=0.22±0.15 *l*, $p<0.02$), and at each point thereafter ($p<0.05$) when saline was administered before hyperventilation took place than when hyperventilation was performed alone. Similarly, for the normal group, FEV_1 was significantly higher at each observation point when hyperventilation followed fluid infusion than when it was the sole stimulus ($p<0.05$).

In an effort to determine if the relative magnitude of the response to the combined effects of HV+FLUID and FLUID+HV was not an artifact due to a shift in baseline, we compared the time course of mechanical changes (fig. 6) and the maximum response for both sequences (fig. 7) using the FEV_1 value before each of the combined challenges was undertaken. Once again, giving fluid during the recovery period produced significantly greater airway obstruction than when fluid was infused prior to the onset of hyperventilation. Baseline FEV_1 for the HV+FLUID trial was 3.32±0.26 *l* and following this combination of stimuli, the FEV_1 fell maximally to 2.14±0.81 *l* ($p<0.02$) (% Δ FEV_1= 34±6%). In the FLUID+HV trial, the FEV_1 before the onset of either stimulus was 3.32±0.24 *l*. After the sequence of FLUID+HV, the maximum response was a decrement in FEV_1 to 2.52±0.20 *l* ($p<0.01$) (% Δ FEV_1=24±4%). There was no significant difference in the baselines prior to either set of experiments; however, following HV+FLUID, the % change in FEV_1 was significantly larger than that following FLUID+HV ($p=0.05$).

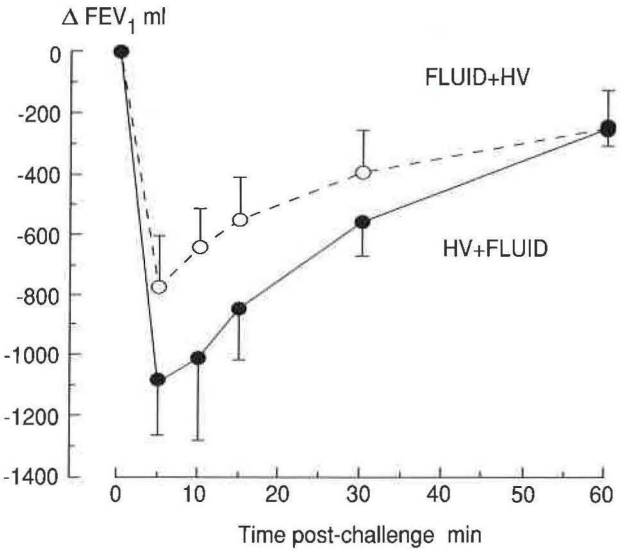


Fig. 6. – The effects over time of FLUID+HV (○- - -○) and HV+FLUID (●——●) on lung mechanics, in the asthmatic subjects. The baseline for these data, in both circumstances, is the pre-infusion and pre-hyperventilation FEV_1. The data points are mean values and the brackets 1 standard error of the mean. Δ FEV_1: change in one second forced expiratory volume. The first data point for both trials is 5 min post-cessation of hyperventilation.

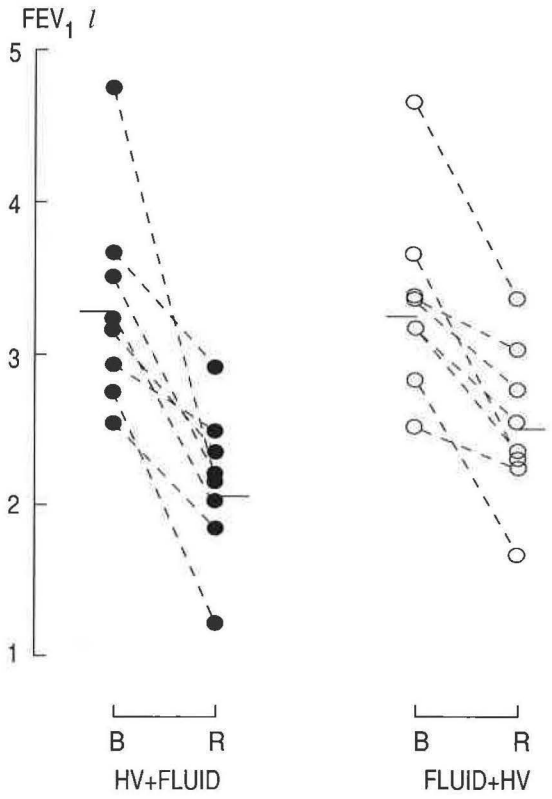


Fig. 7. – The maximum change in forced expiratory volume in one second (FEV_1) after the completion of both fluid infusion and hyperventilation. The solid circles represent individual data when fluid was infused prior to, during, and following isocapnic hyperventilation (HV+FLUID), and the open circles represent individual data when fluid was completely infused prior to the onset of hyperventilation (FLUID+HV). B: the baseline FEV_1 prior to the onset of any stimulus; R: maximum response.

Discussion

The results of these studies illustrate that the intravenous administration of approximately 2 *l* of normal saline within a 20 min time period can produce profound decrements in lung function in asthmatic subjects. The magnitude and duration of the mechanical changes induced by fluid infusion (fig. 1 and 2) were of the same quantitative and qualitative pattern as the changes caused by moderately severe hyperventilation that was designed to mimic exercise at approximately 60% of maximum oxygen consumption [3, 15]. The changes in the normal subjects following fluid infusion, although significant when compared to their baseline, were considerably smaller. When vascular volume expansion was coupled with hyperventilation, in the asthmatic subjects, the effects of the thermal challenge on pulmonary function appear to be dependent upon whether fluid infusion was completed prior to (figs. 5–7), or following the cessation of hyperventilation (fig. 3, 6, 7). In the former situation, the obstruction was attenuated; whereas, in the latter, the response was amplified. In the normal subjects, the combination of HV+FLUID did not produce any effects that were greater than FLUID alone; however, in the converse

experiment, FLUID+HV, obstruction did not develop at all.

The mechanism for the development of airway obstruction with saline administration and its interaction with hyperpnoea is unknown, however, a number of possibilities exist. In addition to its direct effect on intrathoracic vascular volume (*vide infra*), salt loading also influences vascular homeostasis and, through this, evokes a series of events that could influence airway smooth muscle tone. For example, plasma atrial natriuretic peptide (ANP) rises [16, 17] and plasma catecholamines fall [18, 19]. A decrease in catecholamine concentration could conceivably increase airway bronchomotor tone; whereas, an increase in ANP could result in bronchodilation [20].

The effects of salt loading on catecholamine concentrations are small and the plasma levels do not fall below the normal range [18]. Hence, it is unlikely that this factor, *per se*, produced the obstruction with the saline infusion, although it may have had a permissive effect. Although infusion of ANP has been shown to result in enhancement of lung function in moderately obstructed asthmatics [20], and thus may account for the inhibition of hyperpnoea-induced airway obstruction when fluid is administered prior to hyperventilation (FLUID+HV), this effect occurs at ANP plasma concentrations 25 times baseline [20]. Although, we have no direct measurements of plasma ANP in our own subjects, administration of 500 ml of normal saline in healthy volunteers increases the concentration of this hormone 1.8 times baseline [17]. If this percentage of increase occurred with each 500 ml administration, our own protocol would have been expected to produce only a ten-fold increase in ANP.

Although it is conceivable that rapid volume expansion may produce a vagal reflex, there is nothing to suggest that this possibility played any role in the present study. Blood pressure and pulse pre- and post-infusion did not change and bladder distention did not occur. (The subjects did not begin to diurese for hours after the infusion was completed). Finally, we know from previous studies that rapid expansion of intrathoracic blood volume, *per se*, in man with shock trousers, does not alter airway mechanics [8].

The most likely cause for the bronchoconstriction induced by the large saline load that we employed is through its effect on intrathoracic vascular volume. It has long been observed that the pulmonary venous hypertension, which occurs with elevated left atrial pressure, can produce wheezing and obstructive decrements in pulmonary mechanics. These abnormalities presumably develop *via* a combination of external airway compression from a dilated pulmonary circulation and internal bronchial narrowing secondary to mucosal oedema from an overloaded bronchial vascular bed [21–26]. While we did not directly measure central haemodynamics in the present investigation, several studies employing rapid administration of intravenous saline, similar to our protocols, have demonstrated intravascular volume expansion to occur without alterations in systemic blood pressure or heart rate [13, 27]. In these studies, general and pulmonary blood volumes rose 14 and 12%, respectively [27]. More importantly, investigations employing only half of the volume load that we used produced increases in mean pulmonary artery and pulmonary capillary wedge pressures of approximately 8 and 7 mmHg, (1.1 and 0.9 kPa) respectively [27]. These haemodynamic changes could only be accounted for by vasocongestion and not pulmonary vasospasm or increases in cardiac output [27]. Consequently, our protocols most certainly resulted in pulmonary vascular engorgement.

If the fluid had produced its effects on lung mechanics purely through engorgement of the pulmonary vasculature with external compression of the airways and with a decrease in compliance, we would have expected lung volumes, as reflected by the vital capacity, to have fallen in proportion to the reduction in FEV_1, such that the FEV_1/FVC ratio would have remained constant. This only occurred in the normal subjects and not the asthmatics, suggesting that the decrements in lung function observed in the latter group derived from airflow limitation and not simply volume loss. Based upon the anatomy of the bronchial and pulmonary circulations, it is possible that at least some of the obstruction could be attributable to congestion of the vessels in the airway wall. These two vascular beds anastomose freely [28] and part of the bronchial system drains into the left atrium [29], consequently, any elevation in left atrial and/or pulmonary venous pressures induced by the fluid infusion would be transmitted backward to the airways.

Precedents for our reasoning for a role for the bronchial circulation in the obstructive responses seen with the fluid experiments in trials 2 and 3 can be found in the literature. For example, fluid infusion increases airway reactivity in normal subjects [14], and airway vasocongestion has been implicated in the production of the bronchial hyperresponsivity which has recently been demonstrated in patients with cardiomyopathies [30] and left-sided valvular disorders [31]. Treatment of these cardiac conditions, as well as the inhalation of alpha-agonists free of bronchodilating properties, reverses the abnormalities [30, 31], suggesting that the changes in pulmonary mechanics are not due to contraction of airway smooth muscle, but rather to vascular effects from an engorged bronchial circulation.

Why should fluid infusion produce so much obstruction in the asthmatics relative to the normals? It is possible, that part of the answers lies in the fact that asthmatics have a larger and leakier capillary bed in their airway walls, presumably secondary to their chronic inflammatory state [32, 33]. Thus, they might be at exaggerated risk for the development of obstruction due to vascular dilation with mucosal thickening. In addition, if the microcirculation in the airway walls had a propensity to leak when thermally stimulated, this could help explain why the combination of HV+FLUID produced more obstruction than either stimulus alone. In this experiment, the timing of the infusion was such that saline was administered

before, during and after HV was completed. This last section may have been quite important. For if the fluid enlarged the volume of the capillary bed and if HV altered vascular permeability, then the continuous administration of saline beyond this point might have accelerated the formation of submucosal oedema and airway narrowing [34].

Why then do the mechanical responses appear to differ when HV begins after the saline infusion stops? One possibility is that the significant obstruction induced by the infusion mechanically limited the ability of the airways to respond to the HV challenge. While the data presented in the present paper cannot substantiate or refute this point, there is nothing to suggest that this factor, *per se*, accounted for our observations. In fact, computation of the data using the prechallenge FEV_1 and the maximum response for the HV+FLUID and FLUID+HV experiments totally removes this issue (fig. 7), and yet the analysis still shows significantly less obstruction in the latter experiment (HV+FLUID; % Δ FEV_1=34±6%; FLUID+HV; % Δ FEV_1=24±4%; p=0.05). Furthermore, from a purely mechanical standpoint, addition of a second provocative stimulus to already narrowed airways would be expected to have deleterious and not protective effects. Such negative interactions are seen with cold air hyperpnoea and SO_2, [35] for example.

Additionally, one cannot implicate that the vascular and/or bronchomotor effects of volume expansion were waning in the FLUID+HV *vs* HV+FLUID studies, and thus accounting for the attenuation of obstruction in the former case. Figure 2 demonstrates that the mechanical decrements which occur from fluid infusion persist at an equivalent level for at least 1 h. Moreover, when pulmonary capillary blood flow has been measured following completion of intravenous administration of 2 *l* of normal saline, the observed rise in blood flow seen at the end of the infusion persists for 3 h [36].

One manner in which fluid and HV could have interacted is through the sequential effects of both stimuli on respiratory heat exchange. In the FLUID+HV protocol, unlike HV+FLUID, there was nothing to augment the consequences of HV and the saline may have had a protective effect. Capillary dilation and/or oedema induced by the warm saline would have increased the heat content of the tissues, and so potentially have caused the temperatures in the airways to remain higher than usual during the subsequent hyperpnoea. This phenomenon would have resulted in a diminution of the magnitude of the thermal gradient at the end of hyperventilation and so the severity of the obstruction to HV. Such behaviour has been predicted from mathematical models of airway thermal transport [34] and now has been observed with repetitive exercise [37].

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