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At least part of the reason for airway narrowing with exercise is due to the exercise-related loss of fluid from the airways. We performed a series of studies to determine if whole body dehydration would affect this response in people known to have asthma. In the first study we tested subjects lung function before and after exercise while fully hydrated and while dehydrated. In those known to have asthma dehydration reduced lung function at rest, but did not worsen the exercise response. In the second study we tested whether breathing water vapor saturated air before exercise would alter this dehydration effect. Pre-breathing water-vapor saturated air had no effect on the response. This work suggests that persons with asthma should pay particular attention to their hydration status for optimal performance. This is particularly true for those for whom dehydration may interact with exercise to cause significantly greater bronchoconstriction than when fully hydrated. Further, the effects of dehydration on asthma can not be ameliorated by pre-breathing warm, humidified air.

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Final Report

Introduction

We have completed the first two parts of the proposed three part study. **It should be noted at the outset that the process for obtaining DOD Human Subjects approval took over 2 years and, in spite of having received an e-mail indicating final approval in July, 2002, we have still not received official notification of final approval.** Completion of this project has been hampered by this bureaucratic process. We proposed to address questions related to **dehydration and asthma** in general and **exercise-induced asthma** (EIA) in particular. There is compelling evidence that EIA is caused by heat and/or water loss from the airways during exercise. Studies completed indicate that total body dehydration may exacerbate asthma and that pre-treating with water vapor saturated inhaled air does not ameliorate this. We will continue studies to identify the effects of a rehydration drink on the prevention of dehydration-induced changes in lung function in people with asthma.

Body

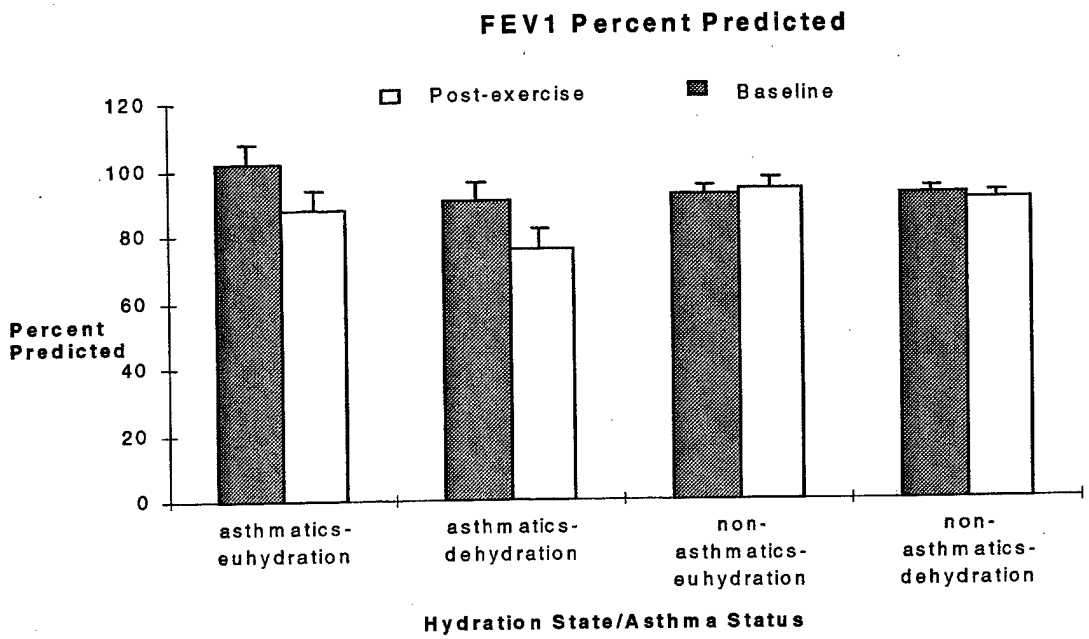
Study 1

Bronchoconstriction is known to be triggered by bouts of intense exercise, but the exact mechanism by which exercise-induced bronchoconstriction (EIB) occurs is unknown. Exercise raises minute ventilation (V_E), increasing the amount of air passing over the airways. This increased volume may cause crucial heat or water loss from the airways. (4) Given that humidity of inspired air is more influential than temperature on EIB, (5, 8, 16, 25), airway water loss is most likely a key trigger to EIB.

If airway dehydration is responsible for EIB, the question then arises whether hydrating the body sufficiently may attenuate exercise or V_E-related airway dehydration. Anecdotal information has suggested that asthmatics who are well hydrated have fewer bronchoconstrictive episodes, whereas those who are dehydrated have more frequent attacks. (2) In studies of non-asthmatics, the effects of systemic dehydration on pulmonary function measures have been inconsistent. (11, 12) These studies have reported a significant decrease in FEV_1 (11) or a significant increase in other pulmonary function measures (12) after dehydration. These conflicting results may be explained by differences in the duration of dehydration and methodology used to dehydrate the participants.

Minimal information exists on the relationship between dehydration and pulmonary function in general, and no studies could be found in which the relationship between hydration level and the incidence of EIB was studied.

The first study compared pulmonary function after 24-hours of "normal" hydration (whatever each individual would normally drink in a given day) with that after 24-hours of fluid deprivation in individuals with known EIB.



The above figure shows that dehydration effected a decrease in % predicted FEV_1 at rest (first solid bar compared to second solid bar) and after exercise (first open bar compared to the second open bar) in asthmatics but resulted in no change in pulmonary function in non-asthmatics (3rd and 4th sets of bars).

Results showed significant decreases in pre-exercise baseline values for FEV_1 and peak expiratory flow (PEF) measurements after dehydration in subjects with known EIA. Exercise then significantly reduced FEV_1, forced expired volume between 25 and 75% of the forced vital capacity ($FEF_{25-75\%}$), and PEF (as expressed in percent of predicted), from the baseline values, but no differences in the exercise-induced changes were observed between hydration states. Individuals with no history of EIA experienced no significant changes pre- or post-exercise.

The results of this first study indicate that dehydration does reduce airflow in persons who have asthma. The airway narrowing associated with dehydration is observed at rest. These data do not show that bronchoconstriction induced by exercise is exacerbated by preexisting dehydration. There were, however, individuals in whom dehydration may have resulted in both a decrement in lung function at rest and a greater decrease in function after exercise when compared to the hydrated condition. These results only partially support our hypothesis that dehydration contributes to EIA. Any contribution of dehydration to EIA may be through a lowering the pre-exercise baseline function. Although the specific pathway by which dehydration influences EIA remains unclear, the water loss possibly creates osmolarity changes in the airway lining fluid leading to neural stimulation or mast cell degradation.

This study suggests that persons with asthma should pay particular attention to their hydration status for optimal performance. This is particularly true for those for whom dehydration may interact with exercise to cause significantly greater bronchoconstriction than when fully hydrated. If the interaction between asthma and dehydration can be eliminated or minimized, military field performance, particularly in warm dry environments, of those with asthma can be

enhanced. The ability to reduce airway problems may be particularly important in personnel who have "silent asthma." This is asthma that may not be diagnosed, but may, under conditions such as dehydration, become severe enough to negatively affect performance.

Study 2

The bronchoconstrictive response to airway cooling and/or heat loss in individuals with EIA may be due to inappropriate conditioning of inspired air (i.e. inadequate warming or humidifying), too little recovery of heat or water on expiration, or unusual sensitivity to the effects of airway cooling or water loss from the airways. (15, 24) When subjects with EIA are exercise-tested under various conditions of inhaled air temperature and humidity, breathing cool, dry air produces more bronchoconstriction than breathing warm, humid air. (5, 20, 23, 24) In most individuals, but not all (1, 3), breathing warm, humid air during exercise (5, 7, 24), or as a pretreatment to exercise (13), or the use of heat- and moisture-exchanging filters (17, 18, 19, 21, 22) diminishes or completely abolishes the response. Breathing cool, moist air during exercise challenge results in similar decreases in pulmonary function as when breathing warm, dry air. (15) Further there is no significant difference between the degree of bronchoconstriction induced by breathing cold, dry air and that induced by breathing warm, dry air, further supporting the contention that water loss is the critical stimulus to EIA. (14) We examined whether breathing warm air with water in the vapor form would attenuate asthma that may be exacerbated by dehydration.

Airway dehydration: Airway dehydration from increased V_E may lead to changes in airway tissue osmolarity. Whether airway dehydration actually occurs and whether it acts as a stimulus in EIA, however, remain controversial. (9, 10) Calculations of fluid availability in the airways show excess water available beyond that necessary to fully saturate the air, rather than showing airway dehydration. (10) By contrast, Daviskas' model (6) suggests that it is likely that water cannot be returned to the airways at a rate equivalent to the rate of the loss, making the periciliary fluid no longer isotonic.

Results:

***Table 1**: Mean age of subjects was 23.67 +_ 2.58. * denotes Asthma medications taken by subjects only when necessary.*

Subject No.	Age (years)	Ht (cms)	Weight (lbs)	Race	Allergies	Medication
1	22	178.5	201.5	Caucasian	Hay	Albuterol *
2	22	187.5	228	Black	None	Ventolin *
3	21	173.5	149	Caucasian	Codeine	Albuterol *
4	25	171.5	140.5	Caucasian	Foods	Albuterol *
5	28	176	219	Caucasian	Seasonal	Albuterol *
6	24	155	102	Caucassian	Dust, Hay	Albuterol *

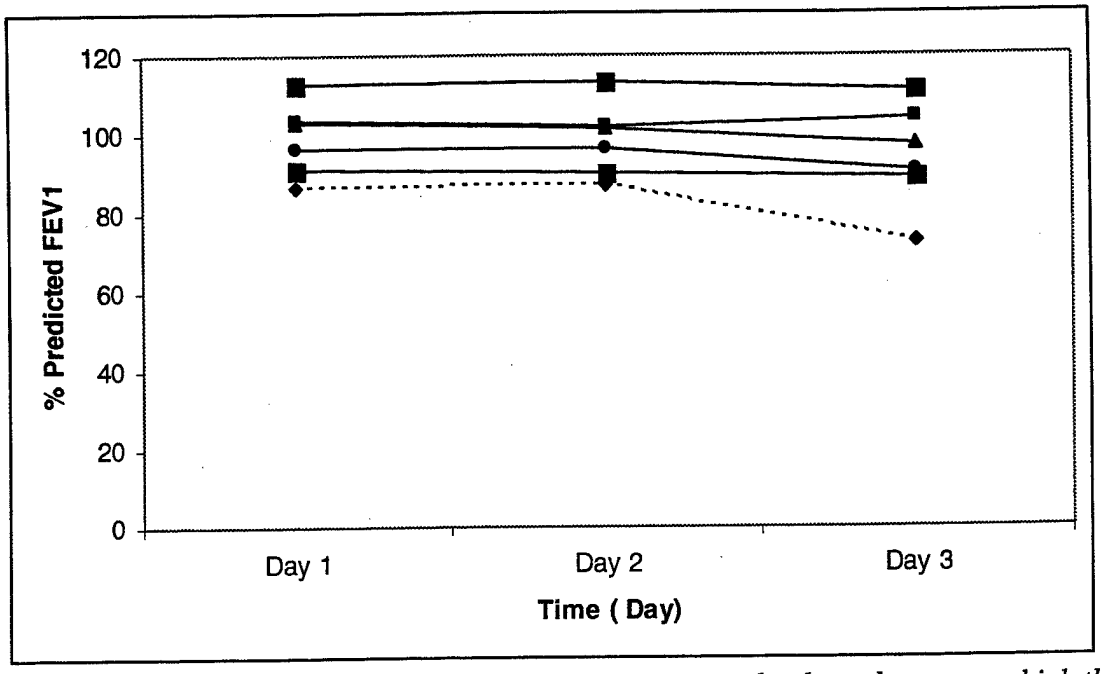


Figure 1: *Daily variability in FEV1. The X-axis represents the three days over which the PFT'S were done. The Y-axis represents the % predicted FEV1.The dashed line represents the FEV1values of one subject who did show a greater than 5 % change in the daily variability.*

Daily Variability: The variability tests were done on alternate days at the same time of the day to prevent the effect of cardinal variation. All but one subject had FEV1 values within 5 % of each other. Subject 1 who showed a greater than 5 % change did complain of a cold on that day.

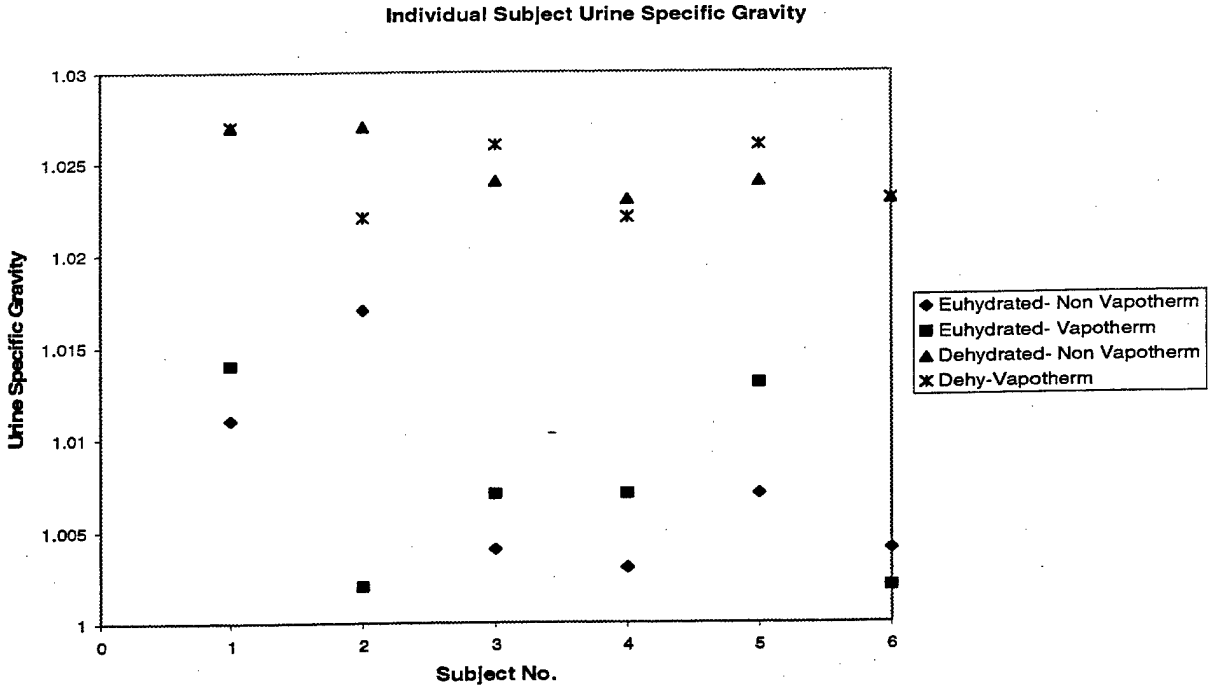


Figure 2: Urine Specific Gravity for each subject. The graph shows all four trials for each subject.

Urine Specific Gravity: There was a statistically significant difference between specific gravity of urine on the euhydration and dehydration days. ($p<0.05$)

Table 2: *Minute Ventilation averaged over last 4 minutes of exercise. There were no significant differences in minute ventilation between euhydration and dehydration days either with or without vapotherm. Values in parenthesis are the standard deviations*

Subject No	Euhydration-Non-Vapotherm	Euhydration-Vapotherm	Dehydration-Non Vapotherm	Dehydratio-Vapotherm
1	69.7(12.23)	63.6(13.28)	61.3(11.48)	65.5(13.46)
2	105.4(20.53)	93.6(14.49)	89(13.54)	83.2(12.25)
3	87.2(14.12)	82.9(10.52)	81.6(7.36)	79(11.33)
4	97(14.70)		91.9(18.41)	94.3(17.64)
5	71.5(9.23)	88.2(7.27)	92.9(10.35)	90.6(7.66)
6	47.9(11.33)	44(12.40)	41.1(10.75)	39.3(11.20)

Minute Ventilation: Minute ventilation was matched to the first trial's minute ventilation. There was no significant difference in the minute ventilation between euhydration and dehydration states both with the vapotherm and non-vapotherm trials for each subject.

Table 3: *Heart Rate averaged over last 4 minutes of exercise. There were no significant differences in the heart rate between euhydration and dehydration days either with or without vapotherm. The values in parenthesis represent standard deviation.*

Subject No	Euhydration-Non-Vapotherm	Euhydration-Vapotherm	Dehydration-Non Vapotherm	Dehydratio-Vapotherm
1	182(13.53)	180(14.98)	178(14.16)	180(14.49)
2	178(13.77)	179(13.58)	185(8.67)	182(11.93)
3	159(10.44)	160(9.71)	156(8.77)	161(10.97)
4	168(7.42)	169(6.50)	180(5.96)	166(6.82)
5	169(10.22)	163(9.38)	155(7.35)	163(6.71)
6	175(22.86)	169(21.70)	175(21.70)	166(25.8)

Heart rate: The heart rate for the first trial was approximately 85-90% of the age predicated maximum heart rate for each subject. There was no significant difference in the heart rate between the euhydration and dehydration states both with the vapotherm and non-vapotherm trials.

	Euhydrated-Non Vapotherm	Euhydrated-Vapotherm	Dehydrated-Non- Vapotherm	Dehydrated-Vapotherm
2 vs 1	0.106	0.115	0.425	0.178
3 vs Previous	0.018*	0.028*	0.124	0.069
4 vs Previous	0.017*	0.017*	0.011*	0.005*
3 vs 1	0.046*	0.011*	0.121	0.05
4 vs 1	0.047*	0.034*	0.068	0.039*
2 vs 4	0.046*	0.035*	0.022*	0.026*
3 vs 4	0.004*	0.008*	0.006*	0.005*

Table 4: p values for within group testing. 1=Pre Vapotherm , 2=Post-Vapotherm, 3=Max Drop, 4=Post Inhaler. stands for statistically significant difference. Repeated measures of ANOVA was done to determine the within group difference.*

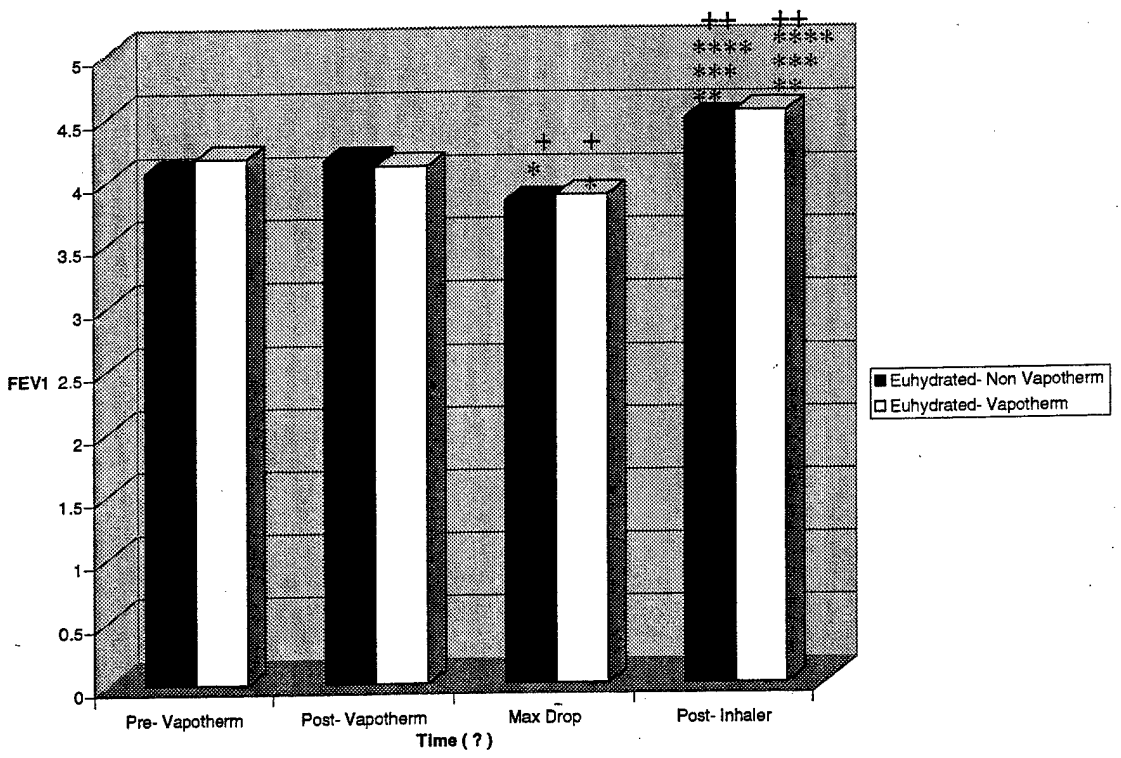


Figure 3: Effect of Vapotherm onFEV1 during Euhydration. The astrix and the plus sign denote statistically significant difference. (p< 0.05)=3 and 1,**=4 and 1, ***=2 and 4 , ****=3 and 4, += Level 3 and Previous, ++ =Level 4 and Previous Euhydrated Non- Vapotherm: *=0.046, **=0.047, ***=0.046, ****=0.004, +=0.018, ++=0.017Euhydrated Vapotherm: *=0.011, **=0.034, ***=0.035, ****=0.008, +=0.028, ++=0.017*

The effect of the vapotherm in the euhydrated state is shown in figure 3. Between groups, there was no statistically significant difference in the FEV1 value between the Vapotherm and the Non-Vapotherm trials at any time point. Within groups, the maximum drop in FEV1post exercise was statistically significant from pre-vapotherm and post vapotherm FEV1and post inhaler FEV1 ($p<0.05$). The pre-vapotherm and the post vapotherm FEV1's were also statistically different from the post- inhaler FEV1 value.($p<0.05$).Five out of the six subjects demonstrated a greater drop in FEV1 after the Vapotherm trial. Subject 2 showed a greater drop in FEV1 following the Non-Vapotherm trial.

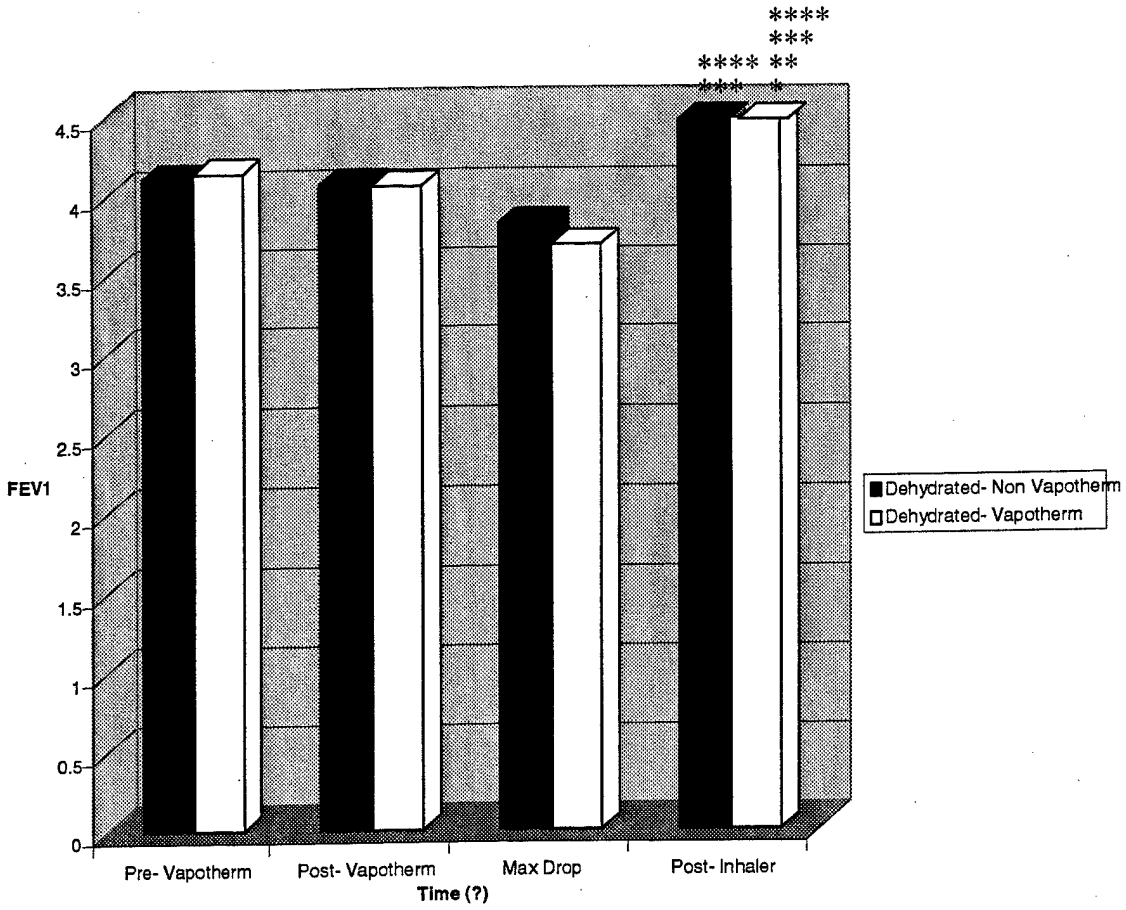


Figure 4: Effect of Vapotherm on Dehydration. The astrix sign denotes statistically significant difference. ($p<0.05$)
= 4 and 1, **= 2 and 4, *=3 and 4, ****=4 and previous.*
*Dehydrated Non- Vaptherm: **=0.022, ***=0.006, ****=0.011*
*Dehydrated Vapotherm: *=0.039, **=0.026, ***=0.005, ****=0.005*

The effect of Vapotherm while dehydration is shown in Figure 4. Between groups, there was no statistically significant difference in the FEV1 value between the Vapotherm and the Non-Vapotherm trials at any time point. Within groups, the maximum drop in FEV1 post inhaler was significantly different from Post- Vapotherm and the maximum drop in FEV1 value. ($p< 0.05$). There was also a statistically significant difference between the pre-Vapotherm and the post Inhaler FEV1's in the Dehydrated Non- Vapotherm group ($p<0.05$). 4 of the 6 subjects demonstrated a greater fall in FEV1 following the Vapotherm trial. Subjects 1 and 3 demonstrated a greater fall in FEV1 following the Non- Vapotherm trial.

Table 5 gives the p values for between group trials. There was no statistically significant difference between groups at any time point during both hydration status -Vapotherm and Non- Vapotherm trials.

Time	p value	Time	p value
Pre 1- Pre 2	.372	Pre 3- Pre 4	.638
Post1- Post 2	.687	Post3- Post 4	.896
Max 1- Max 2	.667	Max 3- Max 4	.168
Inhaler1- Inhaler 2	.662	Inhaler3- Inhaler 4	.822

Table 5: 1=Euhydration- Non Vapotherm, 2=Euhydration- Vapotherm, 3=Dehydration Non-Vapotherm, 4=Dehydration Vapotherm, Pre= Pre Vapotherm, Post= Post Vapotherm, Max= Max Drop post exercise, Inhaler=Post Inhaler FEV1. ($p<0.05$).

Airway dehydration from increased V_E may lead to changes in airway tissue osmolarity. Whether airway dehydration actually occurs and whether it acts as a stimulus in EIA, however, remain controversial. (9, 10) Calculations of fluid availability in the airways show excess water available beyond that necessary to fully saturate the air, rather than showing airway dehydration. (10) By contrast, Daviskas' model (6) suggests that it is likely that water cannot be returned to the airways at a rate equivalent to the rate of the loss, making the periciliary fluid no longer isotonic. The results form the present study indicate that the availability of exogenous fluids in the airways makes no difference in ameliorating the effects of dehydration on airway narrowing.

If airway dehydration is responsible for EIA, the question then arises whether hydrating the body sufficiently may attenuate exercise or V_E-related airway dehydration. Anecdotal information suggests that when subjects ingest large amounts of water, keeping themselves well hydrated, bronchoconstriction from exercise is often eliminated. (2) No studies could be found in which the relationship between hydration level and the incidence of EIA was studied. Previous studies have reported a significant decrease in FEV_1 (11) or a significant increase in other pulmonary function measures (12) after dehydration. These conflicting results may be explained by differences in the duration of dehydration and methodology used to dehydrate the participants.

Key Research Accomplishments

1. Dehydration can exacerbate preexisting asthma and may magnify the effects of exercise-induced asthma.
2. Pre-treatment breathing with water vapor saturated inspired air does not ameliorate the effects of dehydration on asthma.

Reportable Outcomes

Abstracts:

Degrees obtained: One student received her MS degree while working on this project.

Experience and training: Three students gained valuable research experience while working on these projects.

Conclusions

This work suggests that persons with asthma should pay particular attention to their hydration status for optimal performance. This is particularly true for those for whom dehydration may interact with exercise to cause significantly greater bronchoconstriction than when fully hydrated. Further, the effects of dehydration on asthma can not be ameliorated by pre-breathing warm, humidified air.

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