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Hyperosmolarity-induced increases in airway responsiveness and late asthmatic responses

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ABSTRACT: Airway responsiveness to inhaled methacholine was assessed before and after bronchial challenge with ultrasonically nebulized hyperosmolar saline (UNHS), and these changes were correlated with the development of late asthmatic responses (LAR). Sixteen subjects with mild to moderate asthma had two consecutive methacholine challenges before and one after a cumulative-dose challenge with UNHS. Twelve of these subjects also had a single-dose hyperosmolar challenge to document the occurrence of LAR and determine if UNHS had a significant cumulative-dose effect. If a LAR was observed, a control day without challenge completed the study. Responsiveness to methacholine was similar on the 2 baseline methacholine challenges with a provocative concentration producing a 20% fall in forced expiratory volume in one second (PC_{20}) (mean±SEM) of 1.11±0.94 and 1.16±0.94 mg·ml^{-1} (r: 0.98). However, it was significantly increased after the inhalation of UNHS with a PC_{20} (mean±SEM) of 0.57±1.00 mg·ml^{-1} ($p<0.001$). Two subjects developed a late fall in forced expiratory volume in one second (FEV_1) of 19 and 46% after hyperosmolar challenge. In this last subject, the LAR, not reproduced on the control day, was associated with a marked post-UNHS change in PC_{20}, going from a baseline of 4.4 to 0.7 mg·ml^{-1} after UNHS. The % fall in FEV_1 following the dose-response hyperosmolar challenge and the single-dose hyperosmolar challenge were not different, with mean values ±SEM of 34.9±2.2 and 35.8±4.1, respectively, ($p>0.5$). In conclusion, airway responsiveness to methacholine may increase following hyperosmolar saline inhalation, often unrelated to LAR.

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Inhalation of hyper- or hypo-osmolar solutions may induce a bronchoconstriction in asthmatic subjects [1–3]. The development of airway hyperosmolarity has been proposed as a mechanism of exercise-induced asthma [4, 5]. Previous observations support this hypothesis. There is a correlation between the intensity of the bronchospasm induced by exercise and hyperosmolar solutions. Both exercise and hyperosmolarity-induced bronchospasm may be inhibited by the same drugs. Finally, a refractory period may occur in both cases [6–9].

Non-allergic airway responsiveness (NAAR) does not usually change after non-sensitizing stimuli. We and others have shown that exercise does not change bronchial response to histamine even when repeated at regular intervals [10–13]. MALO and co-workers [14, 15] have reported that, in most cases, cold air and sawdust exposure do not modify methacholine responsiveness. However, recent reports have suggested that some "nonspecific" stimuli such as ingestion of ice or ultrasonically nebulized distilled water may, at least transiently, modify airway responsiveness [16–18]. Furthermore, although SMITH *et al.* [19] have reported that hyperosmolar solutions do not change airway response to methacholine, others have suggested that it could [20].

Increases in NAAR following stimuli such as antigens or occupational substances are usually associated with the development of late asthmatic responses (LAR) and airway inflammation [21–23]. However, exercise may induce late asthmatic responses without changes in NAAR [24]. Furthermore, MATTOLI *et al.* [25]have reported LAR after the inhalation of distilled water and although an increase in airway responsiveness was documented during the few hours following the challenge, it did not persist after recovery from the LAR. Study of the relationship between changes in NAAR and LAR after inhalation of hyperosmolar solutions would help in distinguishing differences in airway response to nonspecific stimuli compared to sensitizing agents.

In order to determine whether inhaled hyperosmolar saline might change NAAR and if this is related to the development of LAR, we studied airway responsiveness to methacholine before and after bronchial challenge with ultrasonically nebulized hyperosmolar saline (UNHS) and

Table 1. – Subject characteristics

Subject no.	Sex	Age yrs	Atopic status	Medication	FEV_1 (% pred)	FVC (% pred)	PC_{20} ($mg \cdot ml^{-1}$)
1	M	23	+	β	92	94	0.4
2	F	22	+	β, Be	91	108	0.16
3	F	34	0	β, Be, T	89	109	2.12
4	F	19	+	β	96	112	4.42
5	F	25	+	β	78	82	0.56
6	F	25	+	β	108	108	0.49
7	F	21	+	β	74	92	0.17
8	F	23	+	β, T	67	90	0.33
9	M	34	+	β, T, I	77	81	2.55
10	F	21	+	β	98	97	10.6
11	M	27	+	β	107	106	6.23
12	F	28	+	β, Be	90	98	1.41
13	M	27	+	β, Be, T	75	97	0.37
14	M	31	+	β	90	94	1.21
15	F	22	0	β, T	82	86	0.89
16	F	21	+	β	91	111	6.51

+: ≥1 positive respose to a battery of 20 common airborne antigens; β=β_2-agonist; Be: inhaled beclomethasone; T: theophylline; I: ipratropium; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; PC_{20}: provocative concentration producing a 20% fall in FEV_1.

looked at the occurrence of LAR after this stimulus. We were also interested in documenting whether UNHS had a cumulative-dose effect.

Materials and methods

Subjects

Sixteen subjects (11 F, 5 M), aged 19–34 yrs (mean 25.2 yrs), volunteered to take part in the study. All had a diagnosis of asthma as defined by the American Thoracic Society [26]. Their asthma was mild to moderate with PC_{20}, the provocative concentration of methacholine giving a 20% fall in FEV_1, varying from 0.16 to 10.6 $mg \cdot ml^{-1}$ (geometric mean = 1.12 $mg \cdot ml^{-1}$) (table 1). Mean baseline values for forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were 3.11 and 4.14 *l* (88 and 98% predicted) respectively. All had previously reported symptoms of exercise-induced bronchospasm. Asthma symptoms had been stable and no subject had any evidence of respiratory infection within one month prior to the study. They were not currently exposed to antigens to which they were sensitized. All subjects used an inhaled β_2-agonist on demand to control symptoms, 6 inhaled beclomethasone (dose <800 μg per day), and 4 a theophylline. Fourteen subjects were atopic, as shown by the presence of at least one positive reaction (>2 mm wheal diameter) on skin prick tests with a battery of common airborne allergens. This study was approved by the Laval Hospital Ethics Committee and all subjects signed an informed consent form.

Study design

The subjects attended the laboratory on three occasions over a period of 2 wks. Visits were at least 48 h apart and were made at the same time of the day. Before the tests, β_2-agonists were withheld for 8 h and long-acting theophyllines for at least 48 h. At each visit, the baseline FEV_1 had to be greater than 60% of predicted, otherwise the test was postponed. At each visit, three reproducible measurements of expiratory flows were obtained with a Vitalograph spirometer S-Model (Cat. no. 20-600). At the first visit, methacholine responsiveness was determined in duplicate, to assess the repeatability of this measurement, according to the method described by COCKCROFT *et al.* [27]. The second test (MIT_2) was started when FEV_1 had recovered to at least 90% of the baseline of the first methacholine inhalation test (MIT_1) or when 60 min had elapsed since the end of the last inhalation.

On the second visit, a dose-response hyperosmolar challenge was performed according to a method developed in our laboratory [3]. As soon as the FEV_1 was back to at least 90% of the baseline value, or when 60 min had elapsed since the end of the last inhalation, a methacholine challenge was done (MIT_3).

On the third visit, a single-dose hyperosmolar challenge, using the concentration which caused a 20% fall in FEV_1 on day 2, was performed and the FEV_1 measured at regular time intervals up to 8 h. If a fall in FEV_1 >15% between 2 to 8 h after challenge occurred, a control day without challenge was done within the next 72 h.

Methacholine inhalation tests

After the measurement of baseline FEV_1 and FVC, the subject inhaled a solution of control saline 0.9% followed by doubling concentrations of methacholine (0.03 to 8 $mg \cdot ml^{-1}$) in order to obtain a 20% fall in FEV_1. FEV_1 was measured at 30, 90 and 180 s and repeated if necessary every 2 min until it started to increase. Methacholine was inhaled for 2 min at 5 min intervals, and the bronchial response, expressed as the PC_{20} FEV_1, was

obtained by interpolation of the last two points of the dose-response curve. Aerosols were generated by a Wright nebulizer operating at 50 PSI and 7 $l \cdot min^{-1}$ in order to get a constant aerosol output of 0.13 $ml \cdot min^{-1}$.

Hyperosmolar challenges

Aerosols of hyperosmolar saline were generated by a $MistO_2gen$ ultrasonic nebulizer (model EN143) operating at 3.6 $l \cdot min^{-1}$, calibrated to produce an aerosol output of 2.0±0.3 $ml \cdot min^{-1}$. Hyperosmolar saline was prepared by dilution from commercial sterile preservative-free saline of 3% or 14.6%. Aerosols were inhaled *via* a face mask for periods of 5 min, at 5 min intervals. After the measurement of baseline FEV_1 and FVC, the subjects inhaled solutions of sodium chloride 0.9, 1.8, 3.6, 7.2, and 14.4% as required. The bronchial response to these solutions was determined by measuring FEV_1 at 30, 90, and 180 s after the inhalation, or every 2 min until it started to increase.

The test was stopped when a 20% fall in FEV_1 was obtained or after the highest concentration of saline (14.4%). The osmolarity causing a 20% fall in FEV_1, (PO_{20}), was determined by interpolation of the last two points of the log dose-response curve. On the third visit, the last dose of saline inducing a 20% fall in FEV_1 on day 2 was administered for 5 min. This was followed by repeated measurements of FEV_1 over the next 8 h.

Statistical analysis

Results are expressed as mean±SEM. Mean baseline FEV_1 before MIT_1 and UNHS or before MIT_2 and MIT_3 were compared by paired t-test. Mean baseline FEV_1 before MIT_2 and MIT_3 are compared separately by paired t-test and not by analysis of variance with MIT_1 and UNHS because these tests were started as soon as FEV_1 was at 90% of the baseline value observed before MIT_1 and UNHS. Logarithmically transformed mean PC_{20} obtained after methacholine on the first visit (MIT_1, MIT_2) and after UNHS (MIT_3) were compared first by analysis of variance for repeated measures followed by Student-Newman-Keuls test for multiple comparisons [28]. The difference between mean fall in FEV_1 after UNHS on days 2 and 3 was determined by paired t-test. A value of $p<0.05$ was considered as statistically significant.

Results

All 16 subjects completed visits 1 and 2. Twelve came back to the laboratory for the third visit, to document possible late response to UNHS. Two subjects had a late fall in FEV_1 >15% between 2–8 h post-challenge. These two came back for a control day, to document spontaneous changes in expiratory flows during the day.

Mean baseline FEV_1 before MIT_1 (87.9±2.9%) and UNHS (89.1±2.7%) were not statistically different

Table 2. – Baseline FEV_1 before each test and bronchial response to methacholine tests (PC_{20}) and to dose-cumulative UNHS (PO_{20})

Subject	Baseline FEV_1 (% pred)				PC_{20} ($mg \cdot ml^{-1}$)			PO_{20} (mosmol)
no.	MIT_1	MIT_2	UNHS	MIT_3	MIT_1	MIT_2	MIT_3	UNHS
1	92	93	101	96	0.4	0.33	0.21	734
2	91	89	85	83	0.16	0.2	0.06	743
3	89	87	99	97	2.12	2.0	2.26	1673
4#	96	101	100	98	4.42	6.74	0.7	1348
5	78	75	84	75	0.56	0.67	0.16	746
6	108	98	98	101	0.49	0.57	0.21	779
7	74	70	80	75	0.17	0.28	0.11	707
8#	67	68	76	66	0.33	0.31	0.38	1437
9	77	73	71	66	2.55	2.9	3.19	873
10	98	94	98	94	10.6	7.72	4.79	1537
11	107	84	108	100	6.23	6.8	3.63	1207
12	90	76	81	81	1.41	1.22	0.44	1211
13	75	72	79	66	0.37	0.31	0.24	657
14	89	84	89	77	1.21	0.81	0.67	810
15	82	80	81	74	0.89	0.84	0.34	1364
16	91	93	93	91	6.51	9.19	3.4	1313
Mean	88	84	89	84	1.11	1.16	0.57	1020
SEM	2.9	2.6	2.7	3.2				
95% confidence interval					(0.30, 4.30)	(0.31, 4.37)	(0.14, 2.28)	(736 1413)

* MIT: methacholine inhalation test; UNHS: ultrasonically nebulized hyperosmolar saline; #: late response to UNHS; PO_{20}: osmolarity causing a 20% fall in FEV_1. For other abbreviations see legend to table 1.

(p=0.48), neither were those before MIT_2 (83.7±2.6%) and MIT_3 (83.9±3.2%), p=0.89. The two baseline PC_{20} of visit 1 (MIT_1 and MIT_2) were similar (1.11±0.94 and 1.16±0.94 $mg \cdot ml^{-1}$, p>0.5) (table 2). Since all subjects responded to hyperosmolar saline with a >20% reduction in FEV_1, the PO_{20} could be determined in all cases. After hyperosmolar challenge, airway responsiveness to methacholine was significantly increased compared to mean baseline values obtained on visit 1. The mean PC_{20} post-hyperosmolar challenge was significantly reduced (0.57±1.00 $mg \cdot ml^{-1}$) compared to the mean baseline PC_{20} (mean±SEM: MIT_1 = 1.11±0.94, p<0.001), (fig. 1). However, these subjects reported no increase in asthma symptoms on the evening or days following the tests.

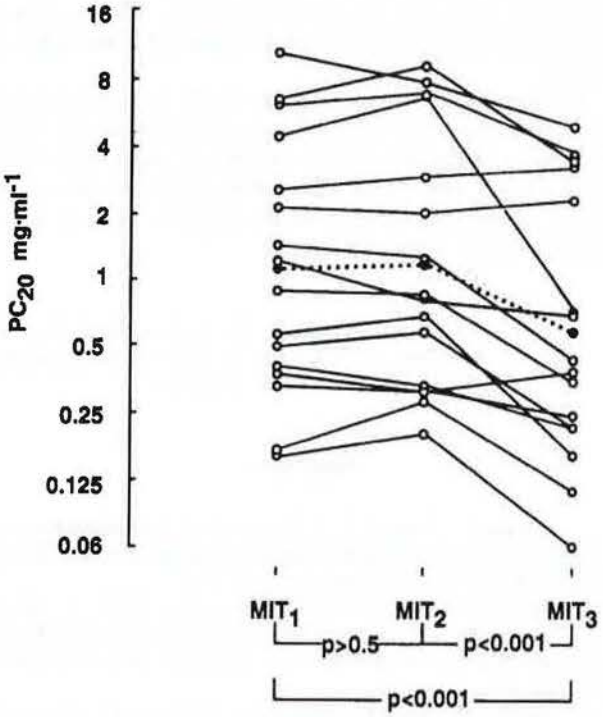

Fig. 1. – The PC_{20} measured after MIT_1 and MIT_2 were not significantly different. However, the PC_{20} following hyperosmolar challenge was significantly reduced compared to that of MIT_1 andMIT_2.

Of the 12 patients studied on visit 3, 2 had a fall in FEV_1, >15% between 2–8 h post-challenge with a maximal fall of 19.0% from baseline in subject no. 4 and of 45.7% in subject no. 8. In both cases this followed the inhalation of 7.2% sodium chloride. On the control day, the maximal fall in FEV_1 up to 8 h after baseline reached 3.2% in subject no. 4 and 38.2% in no. 8. Subject no. 4 had the largest increase in airway responsiveness after hyperosmolar challenge, the PC_{20} going from 4.42 (baseline) to 0.70 $mg \cdot ml^{-1}$ after UNHS.

The % fall in FEV_1 following the dose-response hyperosmolar challenge (visit 2) and the single-dose hyperosmolar challenge (visit 3) was not statistically different, with a mean fall in FEV_1 of 34.9±2.2 and 35.8±4.1, respectively (p>0.5). Figure 2 presents individual values for the two challenges.

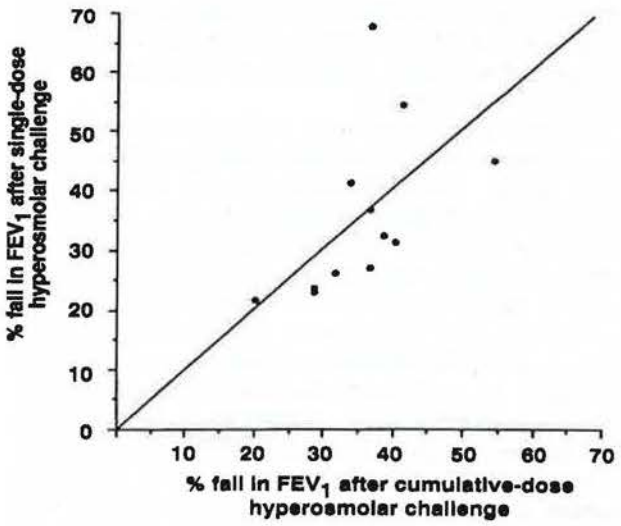

Fig. 2. – The fall in FEV_1 following single-dose and cumulative-dose hyperosmolar challenge were not significantly different.

Discussion

These observations suggest that the inhalation of hyperosmolar solution can increase airway responsiveness to methacholine, at least in the period immediately following the challenge. Although the fall in PC_{20} was variable from one subject to the other and the overall magnitude of this change was small, it was statistically significant. In 8 subjects, the change in PC_{20} was greater than the limits of the reproducibility of the test. The fact that this change was not associated with persisting or worsening symptoms of asthma is probably related to its short duration.

A late fall in FEV_1 was observed after the inhalation of hyperosmolar saline in only two subjects. It seemed specific to UNHS challenge in one case while in the other it probably reflected a spontaneous diurnal fluctuation of expiratory flows. Therefore, the increase in NAAR was not usually associated with LAR. However, the subject (no. 4) with a LAR, not reproduced on control day, had the largest change in methacholine responsiveness after UNHS.

To document the occurrence of LAR, in 12 subjects, expiratory flows were followed for up to 8 h after the single dose UNHS challenge. Although these measurements were not done after the cumulative-dose challenge, it is unlikely that the pattern of bronchial response differs from the single-dose test, as the stimulus (UNHS) and the magnitude of the early response are not different.

We do not believe that the observed increase in NAAR following UNHS could be related to a lack of repeatability of methacholine challenges since PC_{20} were not significantly different on visit 1. It also cannot be attributed to a reduction in airway calibre after the hyperosmolar challenge, as there was no difference between baseline FEV_1 before second tests (MIT_2 and MIT_3). Moreover, it cannot be explained by the between-day variability of the methacholine inhalation tests: firstly, methacholine inhalation tests are known to be

reproducible over a short period of time, and secondly, if such between-day variability occurred, airway responsiveness should have increased in some subjects and decreased in others [29].

Our data differ from those of SMITH *et al.* [19] who found no increase in NAAR after challenge with nebulized 4.5% saline. This difference may be related to the concentration of saline nebulized. In their study, they used a fixed concentration of 4.5% saline administered at different volumes, while we used progressive concentrations of saline (up to 14.4%) administered for fixed periods of time. O'HICKEY *et al.* [20] have also observed an increase in methacholine responsiveness after UNHS challenge. They proposed that all individuals become relatively hyporesponsive to UNHS after a first challenge and that the response to a second UNHS test is dependent of the increase in NAAR. Heterogeneity of subjects in relation to the occurrence of refractoriness after UNHS could therefore explain the differences between our results and those of SMITH *et al.* [20].

Our observations suggest that the effects of hyperosmolar solutions may have some similarity with those of hypo-osmolar solutions; both induce a bronchospasm and increase NAAR in asthmatics. These stimuli seem to differ from other so-called "nonspecific stimuli", such as exercise or cold air inhalation, which do not increase bronchial responsiveness [10, 11, 14]. The exact time-course and significance of this increase in NAAR remains however to be documented. There was no increase in asthma symptoms or medication needs in our subjects in days following inhalation of UNHS, suggesting that this effect is of short duration. This is contrary to the sometimes prolonged increase in NAAR following antigenic or occupational exposures [29].

The mechanisms responsible for the transient increase in NAAR are unknown. A short-lived cellular inflammatory process may occur after the inhalation of hyperosmolar solutions, or may be due to the release of mediators able to transiently change airway responsiveness. SILBER *et al.* [30] have recently demonstrated the release of inflammatory mediators in nasal secretions after challenge with hyperosmolar solutions. This confirms that osmotic variations at the airway surfaces may be a stimulus for *in vivo* mediator release and cell activation. This could explain why sodium cromoglycate can inhibit the bronchospasm induced by hyperosmolar inhalation [8, 18].

As proposed by SMITH *et al.* [19], using distilled water inhalations, increased responsiveness to methacholine after UNHS could also be due to increased airway permeability. This may allow easier access of methacholine to the bronchial smooth muscle. Furthermore, damage to respiratory epithelium by eosinophil mediators has often been proposed in the physiopathology of NAAR.

After specific sensitizing agents, such as antigens or occupational substances, there is a close relationship between the increase in NAAR and the occurrence of LAR. In those conditions the link between NAAR and LAR is in association with airway inflammation [21–23]. Our results suggest that increases in methacholine responsiveness following UNHS are not necessarily associated with LAR although when a LAR occurs, UNHS seems to induce marked, although probably transient, changes in airway responsiveness. Our observations are in keeping with those of MATTOLI *et al.* [25] who reported increases in NAAR in the few hours following a distilled water challenge, although PC_{20} returned to baseline values after recovery from LAR. The mechanisms underlying the changes in airway responsiveness following non-isosmolar solutions remain however to be explored.

Finally, we observed no significant difference in the bronchial response to the single or cumulative-dose hyperosmolar tests for the whole group of subjects. However, in some of those, we could not entirely exclude a small cumulative effect, as the single-dose test produced a slightly lesser fall in FEV_1. We found no significant tachyphylaxis to the inhalation of hyperosmolar saline.

In conclusion, airway responsiveness to methacholine increases after inhalation of hyperosmolar saline. This increase is often unrelated to LAR but when associated with a LAR may be of larger magnitude. Furthermore, there is no cumulative dose-response effect after hyperosmolar saline inhalation.

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Augmentation de la réactivité des voies aériennes induite par l'hyperosmolairité, et réponses asthmatiques tardives. S. Bussieres, H. Turcotte, L.P. Boulet.

RÉSUMÉ: La réactivité des voies aériennes à l'inhalation de methacholine a été étudiée avant et après une provocation bronchique au moyen de solution saline hyperosmolaire nébulisée (UNHS), et ces modifications ont été mises en corrélation avec le développement de réponses asthmatiques tardives (LAR). Seize sujets, atteints d'un asthme léger à modéré, ont eu 2 provocations consécutives à la methacholine avant, et une après une provocation à dose cumulative de UNSH. Douze de ces sujets ont eu également une provocation hyperosmolaire à dose unique pour démontrer le développement de LAR et pour déterminer si UNHS avait un effet significatif à dose cumulative. Si l'on observiat un RAR, un jour de contrôle sans provocation complétait l'étude. La réponse à la methacholine a été similaire lors des deux provocations de base à la methacholine, avec un PC_{20} (moyenne±SEM) de 1.11±0.94 et de 1.6±0.94 mg·ml^{-1} (r:0.98). Toutefois, elle était significativement accrue après l'inhalation de UNHS, avec une PC_{20} (moyenne±SEM) de 0.57±1.00 mg·ml^{-1} ($p<0.001$). Deux sujets ont développé un abaissement tardif du VEMs, atteignant respectivement 19 et 46% après provcoation hyperosmolaire. Dans le dernier cas, la réaction asthmatique tardive, que ne s'est pas reproduite le jour contrôle, a été associée à une modification marquée du PC_{20} après UNHS, celui-ci partant d'une valeur de base de 4.4 à 0.7 mg·ml^{-1} après UNHS. Le pourcentage de chute du VEMs après la provocation hyperosmolaire dose-reeponse et la provocation hyperosmolaire à dose unique ne s'avèrent pas différents, les valuers moyennes±SEM étant respectivement de 34.9±2.2 et de 35.8±4.1 ($p>0.05$). En conclusion, la réactivité des voies aériennes à la methacholine peut augmenter à la suite d'inhalation de solution salien hyperosmolaire, et souvent sans relation avec les réactions asthmatiques tardives.

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