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Posture-induced airflow limitation in asthma: relationship to plasma catecholamines and an inhaled anticholinergic agent

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ABSTRACT: Postural influence on ventilatory function was investigated in thirteen asthmatic subjects on three consecutive days starting at 10.00 am. Lung function was measured in the seated position before and after four hours lying supine. Peak expiratory flow (PEF) was measured every 0.5 h in the supine position. Blood samples for determination of plasma catecholamines were collected before, during and after lying supine. After the initial lung function testing, placebo or ipratropium bromide (0.125 mg) was inhaled. On the third day the whole trial was performed seated, without any drug, as a control experiment. On the placebo day lying supine induced an initial, rapid fall of PEF followed by a progressive decrease during the four hours. The progressive decrease in PEF was apparently caused by bronchoconstriction. Ipratropium bromide prevented this posture-induced bronchoconstriction. On the day seated there was also a tendency towards a decline of PEF though less pronounced than in the supine position on the placebo day. No significant alterations in plasma levels of catecholamines were observed. We conclude that the supine posture is a stimulus to bronchoconstriction in asthma, likely to be involved in nocturnal wheezing. Postural bronchoconstriction is not explained by lowered plasma levels of adrenaline, as has been suggested for nocturnal asthma. The results raise the question of whether cholinergic mechanisms are involved.

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Increased airflow obstruction at night or in the early morning is a common phenomenon in asthma, functioning as a marker of disease activity [1]. The mechanism remains obscure although several pathogenetic factors have been proposed [2]. In particular, circadian fluctuations in autonomic tone, such as nocturnal decrease of plasma adrenaline levels and increase in parasympathetic tone, have been regarded as important [3, 4].

Little consideration has been given to posture although BOUHUYS provided some evidence for its importance 25 yrs ago [5]. MOSSBERG and co-workers observed that ventilatory function recorded upright was significantly decreased after a few hours supine in a sample of patients with asthma and, to a lesser extent, in a sample of patients with moderately obstructive bronchitis [6, 7]. This posture-induced impairment seemed to be due mainly to bronchoconstriction since it was counteracted by a ß-agonist. JÖNSSON and MOSSBERG later demonstrated more systematically that the supine position *per se* may profoundly and progressively decrease airflow in asthmatic subjects, thus making posture likely to be a participating factor in nocturnal asthma [8–10]. The mechanisms for this postural airflow decrease are unknown, but since the effect may at least partly be attributed to bronchoconstriction, it seems possible that it is mediated by an altered autonomic tone as a consequence of the change to a resting position. If this is the case, the alterations in autonomic tone in connection with posture-induced bronchoconstriction might be similar to those claimed to cause nocturnal asthma [3, 4].

The aim of the present study was to investigate the effect of the supine position on ventilatory function and plasma catecholamines in patients with asthma, in order to investigate whether a posture-induced airflow limitation may be linked to an altered adrenergic tone. The influence of an anticholinergic drug, ipratropium bromide, was also studied, in order to obtain information about the role of the parasympathetic system in this phenomenon. Furthermore, the aim was to investigate posture-induced changes on ventilatory function more extensively than before.

Materials and methods

Patients

Thirteen patients (eight women) with a mean age of 59±3 yrs (range 28–73 yrs) participated in the study after informed consent. Clinical data are given in table 1. They all had a history of episodic wheezing and, to some extent, reversible airflow obstruction, thus filling the criteria of bronchial asthma [11]. Duration of the disease was from three to more than forty yrs. All patients had severe disease requiring continuous and multiple drug therapy, including inhaled or oral glucocorticoids. All had on one or several occasions been hospitalized due to an exacerbation of their disease, and had on occasions experienced increased wheezing at night or in the early morning. At the time of the trial all subjects were in a stable phase of their disease and were thus not selected due to ongoing nocturnal asthma. Six of the patients had a history and skin tests suggesting a primarily atopic disease. Three of the patients were smokers and three were ex-smokers. The study had the approval of the local Ethical Committee.

Table 1. - Clinical data on thirteen patients with chronic asthma.

Patient n	Sex	Age yrs	Height cm	Weight kg	FEV_1 %pred.	Current medication
1	M	45	180	78	59	IB,IS
2	F	65	164	58	60	IB,IS
3	F	63	180	38	78	IB,OT,IS,OS
4	F	63	160	80	59	IB,OB,OT,OS
5	F	28	160	55	79	IB,OB,OT,OS
6	F	61	160	63	54	IB,OB,OT,IS,OS
7	F	66	157	58	19	IB,OB,IS,OS
8	M	65	180	62	13	IB,OT,IS,OS
9	M	73	167	70	43	IB,OT,IS,OS
10	M	63	176	87	32	IB,IS,OS
11	M	54	187	101	26	IB,OB,OT,IS,OS
12	F	53	165	59	82	IB,OB,OT,IS
13	F	63	174	75	61	IB,OB,OT,IS,OS
Mean		58.6	170.0	70.3	51.2	
SD		11.6	9.9	13.5	22.9	

IB: inhaled ß-agonist; OB: oral ß-agonist; OT: oral theophylline; IS: inhaled steroid; OS: oral steroid.

Procedure

The patients were investigated on three consecutive days starting at 10.00 am each day. Usual morning medication was taken at 07.00 am in identical doses each day; thereafter no drugs were allowed prior to the investigation. Blood pressure and heart rate were measured and blood samples (10 ml) were collected twice, with an interval of five min, after 30 min resting seated. Thereafter lung function measurements were performed in the seated position. On two of the days the patients then inhaled either placebo or ipratropium bromide, 0.125 mg, in a single-blind manner, seven of the patients receiving placebo on the first day.

After inhalation the patients lay down in the supine position and remained so for four hours. PEF-measurements were performed initially in the upright position, then immediately after lying down and at every half hour in the supine position; the highest PEF-value of three was noted. Blood pressure and heart rate were measured and blood was sampled every hour whilst lying supine.

After four hours the patients sat up, and blood pressure, heart rate and lung function (including PEF) were measured and blood samples collected immediately and at 0.5 and 1.5 h in the seated position. The patients then inhaled 5 mg of salbutamol and a final lung function testing was performed 10 min later.

On one of the three investigation days no drug was administered and the patients remained seated during the whole trial as a control experiment, which was otherwise performed identically to the trials of the other two days. The sequence of the trials was randomized for each patient. The study design is summarized in figure 1.

Measurements

Functional residual capacity (FRC) and specific airway conductance (sGaw) were measured in a volume constant body plethysmograph (PK Morgan Ltd, Chatham, GB) as a mean of three measurements. Airway resistance was measured at a panting frequency of *ca* 2 Hz and an inspiratory flow of 0.5 $l \cdot s^{-1}$. The plethysmograph was also equipped to record flow-volume loops from which the flows at 50 and 25% (*i.e.* $MEF_{50\%}$ and $MEF_{25\%}$) were calculated. Peak expiratory flow (PEF) was measured with a Mini-Wright peak flow meter and forced expiratory volume in

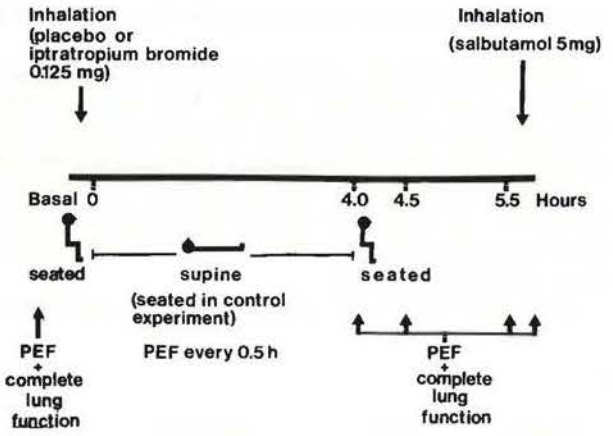

Fig. 1. – Study design. The patients were investigated according to the same basic schedule on three consecutive days. Basal lung function measurements were followed by inhalation of ipratropium bromide or placebo, and on a third day the trial was performed seated as a control experiment, without drug administration. For further details, see text.

one second (FEV1) was measured with a wedge spirometer (Vitalograph).

Blood pressure was measured with an arm cuff connected to an aneroid manometer, and heart rate was recorded during one minute by the palpatory method.

Drugs were nebulized and inhaled from an Aiolos System Inhaler (Karlstads Syrgasfabrik AB, Karlstad, Sweden) which has an output of 0.6 ml·min^{-1} and generates an aerosol in which *ca* 65% of the particles have a size of less than 6.0 μm at a driving pressure of 160 kPa.

Venous blood samples for plasma catecholamine determinations were collected in ice-cold plastic centrifuge tubes containing edetic acid (EDTA) (10 mM final concentration). After centrifugation at 4°C, the plasma was removed and stored at –20°C (for not more than one month) or –80°C before it was analyzed. Plasma catecholamines were determined by microparticulate cation exchange high-performance liquid chromatography (HPLC) with electrochemical detection [12, 13]. This method, which has been validated against a radioenzymatic method, has a sensitivity better than 0.05 nM for noradrenaline, adrenaline and dopamine using 2 ml of plasma.

Statistical analysis

Results are presented as mean values ±SEM. Statistical analyses were performed by analyses of variance (ANOVA), Student's t-test for paired observations and linear regression analysis. $p<0.05$ was considered significant.

Results

Basal lung function did not show any significant differences with regard to any parameter when comparisons were made between the three days of investigation by means of ANOVA (for FEV_1 ($F=0.70$); $p=0.50$ and for sGaw and PEF ($F=1.75$); $p=0.20$). Mean value for basal FEV_1 was 51.1±6.4% of predicted value [14, 15], see table 1.

On the placebo day, lying supine induced an immediate decrease in PEF, from 380±36 l·min^{-1} to 344±35 *l*·min^{-1} ($p=0.002$), followed by a further gradual decrease to 316±29 *l*·min^{-1} ($p=0.068$) after four hours (figs 2 and 3). The minimum PEF occurred during the last hour in the supine position and decrease in PEF exceeded 15% of basal pre-supine value

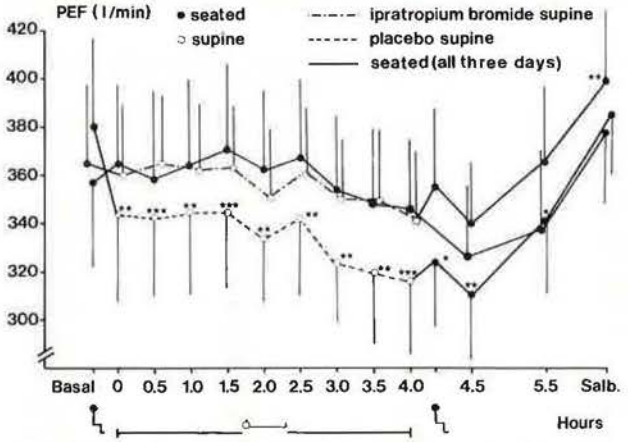

Fig. 2.– Peak expiratory flow (PEF) initially in the seated position, during 4 h in the supine position, during 1.5 h after sitting upright and after a final inhalation of 5 mg of salbutamol. On two of the three consecutive days of investigation there was a presupine inhalation of ipratropium bromide (0.125 mg) or placebo. The third curve represents the control day when the whole trial was performed seated without drug administration *p<0.05; **p<0.01; ***p<0.001 compared to basal presupine values.

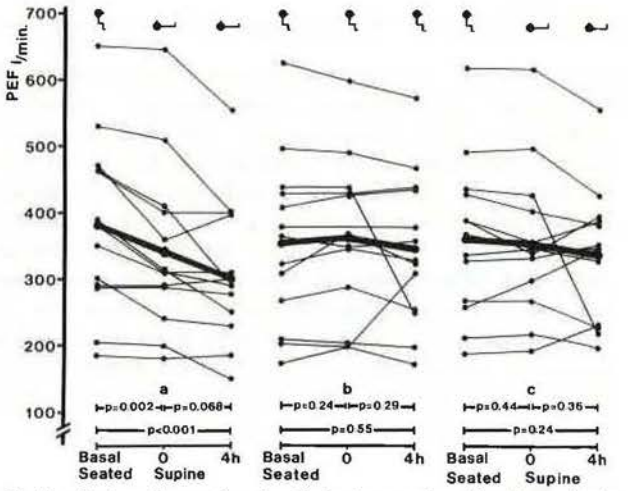

Fig. 3. – Peak expiratory flow basally in the seated position, immediately after lying down, and supine after 4 h on the placebo day (a) and the ipratropium day (c), or seated at corresponding time intervals on the control day (b). Thin lines represent each patient and thick lines mean values. p-values are given in the figure.

in nine and 20% in eight of the thirteen patients. Ipratropium bromide prevented the posture-induced PEF decrease in most patients (fig. 3). On the control day (in the sitting position) there was a slight, but insignificant, decrease in PEF ($p=0.55$). The total decrease in PEF was significantly greater on the placebo day compared to the ipratropium day ($p=0.022$)

and control day (p=0.004), whilst there was no significant difference between the latter two days. Further statistical information is given in figure 3.

The progressive PEF decrease when supine (excluding the initial rapid decrease in PEF on lying down) was slightly but significantly greater on the placebo day compared to the control day, when the coefficients of the regression equations for each patient on the two days are compared by means of Student's t-test for paired observations (p=0.044), but not when compared to the ipratropium day. A tendency towards increased PEF was observed on transition from supine to seated, significant on the ipratropium day only (p=0.033). In the placebo experiment, the PEF values reseated were still significantly lower than the basal, pre-supine values (fig. 2).

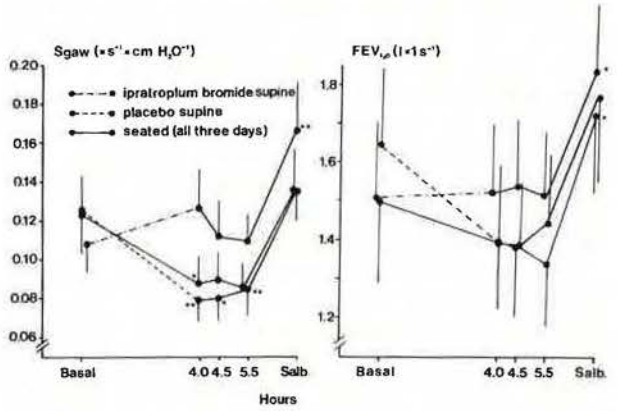

Fig. 4. – Specific airway conductance (sGaw) and FEV_1 measured basally before lying down, seated after 4 h in the supine position (immediately, 0.5 and 1.5 h after sitting upright) and after inhalation of 5 mg of salbutamol. Pre-supine inhalations of placebo and ipratropium bromide (0.125 mg), respectively. The third curve represents the control experiment in the seated position. * p<0.05; ** p<0.01 compared to basal pre-supine values.

There was a significant decrease in sGaw after four hours both on the placebo day (p=0.004) and on the control day (p=0.042, fig. 4), with no significant difference between these two days. On the ipratropium day, the mean post-supine sGaw was even higher than before lying down, but this increase was not statistically significant. There was a decrease in FEV_1 after the period spent lying supine on the placebo day which was more than twice as large as that on the control day, but not significant on either day (fig. 4). Ipratropium bromide completely inhibited the tendency towards a posture-induced decrease in FEV_1 (fig. 4). End-expiratory flows and lung volumes, *i.e.* FRC and TLC, were unaltered on all three days when comparisons were made between pre-and post-supine values. TLC was 6.47±0.51 *l* basally, pre-supine, and 6.55±0.50 *l* (p=0.53) post-supine. After salbutamol inhalation lung function was significantly improved with regard to sGaw, FEV_1 and PEF on all three days (figs 2 and 4).

Lying in the supine position caused a slight, insignificant, decrease in plasma adrenaline and nonadrenaline levels whilst these levels were unaltered or even elevated (p=0.047 for adrenaline) after four hours on the control day (fig. 5). There was no correlation between changes in plasma catecholamine levels and

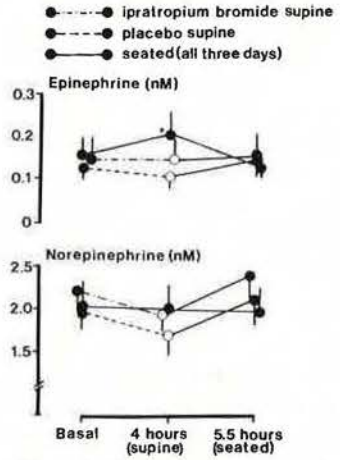

Fig. 5. – Venous plasma levels of adrenaline and noradrenaline basally (seated), after 4 h in the supine position (supine), and 1.5 h after sitting upright. Pre-supine inhalations of placebo and ipratropium bromide (0.125 mg). The third curve represents the control experiment in the seated position. • = upright; o = supine. * p<0.05 compared to basal pre-supine values.

changes in PEF during the time interval in the supine position (r=0.058 for adrenaline).

There was a significant decrease in heart rate on all three days (p<0.02), but no significant differences were found between the days. There was no correlation between the decrease in heart rate and the decrease in PEF on the placebo day. Changes in blood pressure were small and similar on the three days.

Discussion

All patients studied had severe disease requiring continuous and multiple drug therapy. Several had a significant component of irreversible airways obstruction, but since all had a clinical history of episodic wheezing and had responded favourably to bronchodilators and corticosteroids it seems appropriate to classify them as asthmatics. Furthermore, several of them had a history of atopy (6/13) and a few had a history of smoking (three smokers and three ex-smokers). Chronic asthma in a currently stable phase was the only criterion for the selection of patients to the study. This would allow the experiments to be performed without excessive fluctuations in baseline lung function and, at the same time, patients would be unlikely to have a complete clinical remission, abolishing the bronchoconstrictor response to posture. This selection was apparently succesful since the intra-individual day-to-day variation in lung function was small, whilst the bronchial instability was large enough to show deterioration in lung function in nine patients out of thirteen when lying supine (decrease in PEF >15%).

As it was considered unethical to withdraw the morning medication in these patients with severe

disease, it may seem that the deterioration in lung function during the placebo experiment was due to a tapering effect of medication. This was not the case to any large extent, since there was a significantly smaller decrease in PEF on the control day in the upright position than on the placebo day when lying supine, and since only two patients had a PEF decrease > 15% on the control day compared to nine when lying supine on the placebo day.

The present study confirms the earlier findings by JÖNSSON and MOSSBERG [8] that the supine position *per se* induces increased bronchial obstruction in asthmatics. Although in that study there was a significant decrease in FEV_1 as well as PEF recorded upright after the period spent supine, it is again shown that this effect is best revealed by recording lung function, *e.g.* PEF, when the patient remains supine. The PEF decrease observed here did not clearly correspond to decreases in FEV_1 and airway con-ductance, *i e.* lung function parameters measured seated only. Since the transition from supine to upright position may act as a bronchodilator stimulus [8], a posture-induced bronchoconstriction may be more or less masked if lung function is measured in upright position only.

The posture-induced reaction consists of two components: an immediate fall in PEF on transition from upright to supine position, followed by a progressive decrease in PEF when lying supine. In the present study, which included several patients with partly irreversible airway obstruction, the progressive PEF decrease when supine was modest, but the results display the same principal pattern as in the earlier study by JÖNSSON and MOSSBERG [8]. That study was performed on patients with a more completely reversible airflow obstruction, in whom the progressive PEF-decrease in the supine position was somewhat more pronounced. The immediate PEF-decrease on lying down is not unexpected since changing to the supine position also leads to a decrease in airway dimensions and conductance in healthy subjects [16]. The explanation of the further, progressive lung function impairment is more obscure. This decline is directly associated with the asthmatic condition since it does not occur in healthy subjects, in whom little or no bronchoconstriction occurs even overnight [17]. The fact that not all of the patients responded with a PEF decrease when lying down may be due to a temporarily or permanently rather fixed obstruction, or alternatively, to the presence of a remission. It is well known that the pattern of "morning dipping" may disappear when an asthmatic patient either improves or acquires a temporally fixed obstruction [1]. It is also to be noted that the present patients were in a stable phase of their disease without pronounced nocturnal symptoms at the time of the trial.

On resuming the sitting position after four hours lying supine, PEF remains decreased while TLC is unaltered. This indicates that the persistent PEF decrease after sitting upright is a result of a bronchoconstriction rather than just a consequence of an alteration in lung volumes. Furthermore, the finding of a protection against PEF decrease when lying supine offered by ipratropium bromide in the present study and by terbutaline in earlier studies [6, 7] also indicates that the deterioration in ventilatory function actually reflects a bronchoconstriction.

The finding that the supine posture *per se* increases airflow obstruction in asthmatic subjects suggests that posture is an important participating factor in nocturnal asthma. The deterioration in lung function induced by posture during four hours in the daytime in a fairly stable phase of the disease amounted to an average of 17% of basal pre-supine PEF-values in the present material and 25% in the previous study by JÖNSSON and MOSSBERG [8], with large individual variation in both studies (fig. 3). Considering the usually progressive nature of the decrease, it has to be presumed that the deterioration of lung function induced by posture often proceeds far enough to cause overt asthmatic symptoms during a night's sleep, particularly if the disease is in a more unstable phase than in the studies mentioned here and/or if pre-supine lung function is further decreased. This assumption is in good agreement with the finding that the frequency of asthma attacks increases with time during the night [17, 18].

Since circulating noradrenaline does not influence bronchial tone or reactivity [19, 20], the effects of circulating catecholamines on the airways are caused by adrenaline. There is no circadian variation in the response to ß-adrenoceptor stimulation [21], but it has been found that the morning-dip in lung function c oincides with trough values in plasma adrenaline levels and a causal connection between these two phenomena has been proposed [2, 3]. We found in the present daytime experiment no posture-induced alteration in plasma adrenaline levels and no correlation between changes in plasma catecholamine levels and the drop in lung function induced by posture. Therefore, if posture-induced bronchoconstriction also-occurs at night, as we suggest, the nocturnal decrease of plasma adrenaline is not necessary to explain nocturnal bronchoconstriction (although an additive effect remains a possibility). Another argument against the concept that changes in plasma adrenaline levels are of any major importance in nocturnal asthma is the finding of a typical diurnal variation in lung function in an adrenalectomized asthmatic patient [22].

The present finding that an anticholinergic drug prevented posture-induced bronchoconstriction may be related to the observation that asthmatic patients may benefit from such drugs with regard to nocturnal symptoms [23, 24], although currently available drugs may not be sufficiently long-acting. The protective effect observed might possibly be due to bronchodilatation unrelated to variations in cholinergic (parasympathetic) tone, but it seems reasonable to ascribe this protection to an increased cholinergic tone at night, since animal experiments and observations in healthy humans indicate that cholinergic tone is then

increased [25,26]. This may possibly be the case to an even greater extent in patients with obstructive lung disease [27]. Attacks of nocturnal asthma in children have been claimed to be associated with an increased cholinergic and a decreased adrenergic activity on the basis of urinary excretion of cyclic nucleotides [28]. It seems plausible that cholinergic tone also increases when resting in the supine position regardless of the time of day; if this happens to a lesser extent even when resting seated it would help to explain the tendency to bronchoconstriction on the control day in the present study. Since our results are compatible with the concept of cholinergic rather than adrenergic mechanisms operating in posture-induced bronchoconstriction, we suggest that nocturnal asthma is related to an increased parasympathetic tone induced by rest in a horizontal position, resulting in a significant bronchoconstriction if airway reactivity is large enough.

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