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Original articles

Reduced subjective awareness of bronchoconstriction provoked by methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale

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Abstract

Background **Asthma death rates are rising, with the greatest rise and highest death rates in old age. A reduced cardiovascular response in the elderly may lead to the underestimation by physicians of the severity of acute asthma attacks. This would be compounded if elderly patients had reduced awareness of bronchoconstriction.**

Methods **Methacholine provoked bronchoconstriction was compared in 34 elderly (17 asthmatic, 17 normal; age 60–83, mean 68 years) and 33 young subjects (16 asthmatic, 17 normal; 20–46, mean 30 years). None were smokers. All underwent inhaled methacholine challenge by the Newcastle dosimeter method, monitored by maximal expiratory flow-volume loops (MEFVL). The endpoints were a 35% fall in forced expiratory flow at 50% vital capacity or cumulative inhalation of 6·4 mg methacholine. The one second forced expiratory volume (FEV_1) was derived from MEFVL. After challenge and before bronchodilatation subjects graded awareness of respiratory discomfort from 1 (no symptoms) to 4 (pronounced symptoms needing immediate treatment).**

Results **Despite a greater fall in FEV_1 in elderly asthmatic patients (mean (SE) 27·4% (2·2%)) than in young asthmatic patients (21·5% (1·7%)) elderly patients were less aware of bronchoconstriction (awareness score 2·00 (SE 0·15) than young patients (3·06 (0·11)). Similar differences in awareness score were seen between elderly normal subjects (1·53 (0·17)) and young normal subjects (2·76 (0·22)), despite no difference in degree of bronchoconstriction.**

Conclusions **Reduced awareness of moderate acute bronchoconstriction in old age may delay self referral in acute asthma and contribute to higher asthma mortality in the elderly.**

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The death rate from asthma is highest in old age and continues to rise, despite diagnostic and therapeutic advances.[1–3] Acute attacks of asthma in older people with chronic asthma may be very rapidly fatal[4] and have been said to have a poorer prognosis than in the young.[5] Of the many potential reasons for the higher mortality from asthma in old age, the possibility of impaired awareness of the severity of an acute asthmatic attack by the elderly patient, his physician, or both has been little investigated. Petheram *et al*[6] showed that during acute exacerbations of asthma elderly patients have less pronounced pulsus paradoxus and tachycardia than younger patients with similar airway obstruction and blood gas abnormalities. They argued that this might theoretically result in undertreatment of the elderly asthmatic patient during an acute attack. Treatment might also be inadequate if the severity of the attack were also underestimated by the patient. This may indeed be the case in the elderly. Elderly asthmatic patients tend to deteriorate for longer periods at home before admission,[6] and when challenged with inhaled methacholine they do not report dyspnoea or wheeze to be troublesome despite a minimum fall in one second expiratory volume (FEV_1) of 20%.[7] A recent case report has shown an elderly asthmatic patient to be symptomless during a 40% fall in peak expiratory flow.[8] There has, however, been no controlled comparison of awareness of acute bronchoconstriction between elderly and young subjects.

Acute bronchoconstriction may be provoked in asthmatic and in many normal subjects by the inhalation of histamine or cholinergic agonists such as methacholine.[9–11] Asthmatic patients, however, require less agonist than normal individuals to produce the same degree of bronchoconstrictive response.[9–10] Thus the aim of the present study was to compare awareness of acute bronchoconstriction provoked by inhaled methacholine in elderly asthmatic and elderly normal subjects with awareness of similar degrees of methacholine provoked bronchoconstriction in young asthmatic and young normal subjects. In addition, the study provided the opportunity to assess the possible relation between awareness of bronchoconstriction and airway responsiveness to

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methacholine. To accomplish these goals a simplified awareness score was used and its reproducibility verified.

Methods

SUBJECTS AND INCLUSION CRITERIA

Subjects were recruited in four separate categories: (1) elderly asthmatic patients aged 60 years and over; (2) elderly normal individuals aged 60 years and over; (3) young asthmatic patients aged 18–50 years; (4) young normal individuals aged 18–50 years. Asthma was defined as a history of spontaneous wheezing with documented variability in FEV_1 of at least 15%. Normal subjects were defined as those with no present or past history of respiratory disease and with baseline FEV_1 within the normal range. Individuals were excluded if they had smoked any form of tobacco within 10 years or had a history of total cigarette consumption of 10 pack years or more. The following were also exclusion criteria: pregnancy; cognitive impairment; cardiac disorder; current treatment with β adrenergic antagonists or with oral β adrenergic agonists, calcium antagonists, or angiotensin converting enzyme inhibitors; past or present thyroid disorder; treatment with systemic corticosteroids in the previous six weeks; respiratory tract infection in the previous six weeks; baseline FEV_1 less than 60% of predicted or less than 1 litre.

STUDY DESIGN

The study was part of a larger project (unpublished) examining the relation between bronchial responsiveness and mononuclear cell β adrenoceptor parameters, for which all subjects underwent two methacholine challenges on separate, non-consecutive days within a seven day period. The selection criteria for this larger project were identical to those described above and all subjects participated in both studies. All tests were performed between 10 am and 4 pm, and for each subject tests were performed at the same time of day (± 2 hours). Before being included all potential subjects were screened by full history and examination, and a serum pregnancy test was performed where appropriate. All subjects were asked to abstain from drinks containing caffeine and from all oral medications for 24 hours before each challenge (48 hours for "sustained release" preparations), and from all inhaled medications for 12 hours before each challenge.

Methacholine challenge testing was performed by a dosimeter technique using a computer controlled Newcastle dosimeter[11] and Acorn System 22 Turbo nebulisers (Medic-Aid Ltd, Pagham, Sussex), the output of which was controlled at 10 μl (standard deviation less than 2·5%) per inhalation. Bronchoconstriction was monitored by maximal expiratory flow-volume loops on a Gould 5000 IV pulmonary function unit with a System 21 pulmonary work station (Gould, Dayton, Ohio, USA). Baseline FEV_1 was taken as the best of six technically satisfactory measurements performed immediately before challenge. After baseline measurements has been made sequential doubling doses of buffered methacholine chloride were administered at five minute intervals by inhalation, beginning with a dose of 1·5625 μg. A single technically satisfactory flow-volume loop was recorded immediately before each dose. Alternative end points were a minimum 35% fall in forced expiratory flow at 50% of vital capacity (FEF_{50}) or administration of the maximum cumulative dose of 6·4 mg of methacholine. As not all subjects achieved a 35% fall in FEF_{50} bronchial responsiveness results were expressed in terms of the simplified slope of the FEV_1 dose-response curve[12] derived from the flow-volume loop.

Immediately after the challenge had been completed, and before reversal of bronchoconstriction, subjects were asked, on both challenge days, to rank their awareness of chest tightness, discomfort, or breathlessness on a four point scale (1—no symptoms; 2—equivocal or mild tightness, discomfort, or breathlessness, requiring no treatment; 3—mild to moderate tightness, discomfort, or breathlessness, not needing immediate treatment; 4—pronounced tightness, discomfort, or breathlessness, needing *immediate* treatment). The reason for this exercise was not discussed with the subjects, nor were they aware of the percentage fall in FEV_1 or FEF_{50}. The sensation of bronchoconstriction was described to normal subjects (before methacholine challenge) as "chest tightness, discomfort, or breathlessness." All subjects were instructed to rank their overall respiratory discomfort (that is, the scale was deliberately subjective and non-specific) but were asked to ignore non-respiratory side effects of methacholine (such as salivation and flushing).

All subjects gave written informed consent to participation in the protocol, which was approved by human subjects committee of the University of Washington and the research and development committee of the Boise Veterans' Affairs Medical Center.

DATA ANALYSIS

Awareness scores for different groups of subjects were compared by χ^2 analysis. Unpaired t tests were used to compare the degree of bronchoconstriction produced in the groups of subjects. To assess whether awareness of bronchoconstriction was related to the total dose of methacholine administered in each age group, total cumulative doses of methacholine were ranked in three previously defined categories,[13] as follows: less than 50 μg, 50–<400 μg, and 400–6400 μg. χ^2 analysis was then performed to compare this ranking with awareness scores in each age group. Rank correlation was used to assess reproducibility of awareness scores on the two days. A paired t test was used to check that the maximum fall in FEV_1 was similar on the two days. Data are expressed as mean (SE) values. Statistically significant differences were defined as those where p was below 0·05.

Results

Sixty seven subjects were recruited—17 elderly

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asthmatic patients (10 male and seven female, aged 60–83 (mean 68·5) years), baseline FEV_1 (day 1) 62–102% (mean 78·3%) predicted; 17 elderly normal individuals (seven male and 10 female, aged 60–76 (mean 67·2) years), baseline FEV_1 (day 1) 88–130% (mean 109·5%) predicted; 16 young asthmatic patients (four male and 12 female), aged 20–46 (mean 30·6) years), baseline FEV_1 (day 1) 85–115% (mean 104·0%) predicted; 17 young normal individuals (10 male and seven female, aged 20–36 (mean 28·1) years), baseline FEV_1 (day 1) 82–128% (mean 105·3%) predicted. All recruited subjects completed the study.

None of the subjects had ever received β adrenergic antagonists; one subject (age 23) had taken oral β adrenergic agonists, but these had been discontinued six weeks before the study. Other medications are shown in table 1.

Non-specific bronchial responsiveness results for the four groups are given in table 2.

The following results are for day 1, very similar and equally significant results being obtained for day 2.

Normal subjects The mean percentage fall in FEV_1 for normal subjects was 15·0 (SE 1·1), with no difference between elderly (16·3 (1·3)) and young normal subjects (13·7 (1·7)). The mean awareness score in elderly normal subjects was lower (1·53 (0·17)) than in young normal subjects (2·76 (0·22); $p = 0·004$).

Asthmatic subjects The mean percentage fall in FEV_1 for asthmatic patients was 24·6 (1·5). Elderly asthmatic patients had somewhat greater percentage falls (mean 27·4 (2·2)) than young patients (21·5 (1·7); $p < 0·001$). Despite this, elderly asthmatic patients had much lower awareness scores (2·00 (0·15)) than young patients (3·06 (0·11); $p < 0·001$).

There was no relation between awareness scores (day 1) and the total cumulative dose of methacholine administered either overall or in the subgroups of elderly or young subjects.

Table 1 Subjects' use of medication

	No of subjects	
	Elderly	*Young*
Intermittent β agonist inhaler (less than once a day)	4	8
Regular β agonist inhaler	9	5
Inhaled corticosteroids	4	0
Theophyllines	7	3
Cromoglycate	5	1
Diuretics	4	0
Ipratropium	0	3
Oral contraceptives	0	3
Hormone replacement	4	0
Vitamins	5	2
Clonidine or methyldopa	3	0

Table 2 Bronchial responsiveness to methacholine (simplified slope of FEV_1 dose-response curve) on day 1

Group	*Simplified slope (% fall/mg methacholine)*	
	Geometric mean	*Range*
Elderly normal	48·6	1·86–679
Young normal	2·84	0·68–6·64
Elderly asthmatic	4465	435–5626
Young asthmatic	179·3	7·07–19629

There was no relation between awareness scores and duration of asthma in either asthmatic patients overall or in elderly or young asthmatic patients.

Rank correlation showed good agreement between awareness scores on days 1 and 2, whether in all subjects (rho = 0·82, $p < 0·001$), normal subjects (rho = 0·89, $p < 0·001$), or asthmatic patients (rho = 0·64, $p < 0·001$) or in the four subgroups ($p < 0·001$, all cases).

Discussion

This study has shown that, despite equivalent or greater percentage falls in FEV_1 in the elderly, older subjects were less aware of acute bronchoconstriction than the young. This difference was independent of the presence of asthma. There was no relationship, either overall or within age groups, between the dose of methacholine needed to provoke bronchoconstriction to a defined endpoint (an index of the presence and severity of asthma[9 10 14–16]) and the degree of awareness. Furthermore, awareness was unrelated to duration of asthma, either in asthmatic patients overall or in the subgroups of elderly or young asthmatic subjects.

The difference in awareness between the elderly and the young was maintained on day 2, and thus is unlikely to be due to "over-reporting" of discomfort due to anxiety by young non-asthmatic subjects who had no prior experience of bronchoconstriction. Moreover, the difference in awareness between young and old was also seen in asthmatic patients, who are familiar with bronchoconstriction whatever their age. Furthermore, there is no evidence that the old would complain less than the young about distressing symptoms if sensory input were intact. Indeed, the opposite may be true.[17]

The awareness score we used was chosen to be as simple as possible for elderly patients and deliberately to reflect a subjective and non-specific awareness of respiratory symptoms associated with bronchoconstriction rather than an attempted objective assessment by the physician. It was shown to be reproducible both overall and in all groups of subjects.

The possible causes of reduced awareness of bronchoconstriction in the elderly are many and varied. Sensory input from the lungs is transmitted by three types of receptor—the stretch receptor, the irritant receptor, and the J receptor.[18 19] J receptors primarily react to increased pulmonary capillary pressure,[19] and are thus unlikely to play a part in awareness of bronchoconstriction provoked by irritants. Stretch receptors may produce termination of deep inspiration. Their stimulation also produces tachycardia and they are responsible for the Hering-Breuer reflex.[19] As both the tachycardic response to bronchoconstriction and the Hering-Breuer reflex diminish with age,[6 20] conceivably impaired awareness of bronchoconstriction may result from a reduced number or activity of stretch receptors in old age. Their blockade, however, increases rather than decreases dyspnoea during the breathing of gases enriched with carbon dioxide.[21]

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Irritant receptors are one route by which methacholine produces bronchoconstriction.[19] As methacholine responsiveness is not impaired in old age—indeed, it may be enhanced[22]—reduced activity of irritant receptors seems unlikely to be important in impaired awareness of bronchoconstriction, even though they help to produce unpleasant respiratory sensations.[19 23] This is consistent with our finding of no association between bronchial responsiveness and awareness.

Reduced sensitivity of chemoreceptors to hypoxia in the elderly[24] may be relevant. We did not estimate blood gas tensions, but bronchial challenge may produce arterial desaturation.[25]

Elderly people have impaired perception of externally applied resistive and elastic respiratory loads,[26 27] perhaps because of impaired perception of joint movement or tactile sensation,[28-30] and such abnormalities may be also relevant to the present study, as may age related abnormalities in central processing.[31-33]

Further research is needed to establish the mechanism or mechanisms of reduced subjective awareness of bronchoconstriction in old age. Whatever the mechanism, however, this observation has important implications. Mortality from asthma not only is highest in the elderly but is rising most in this age group.[1-3] Possibly the disproportionate rise in deaths from asthma in the elderly results partially from a shift in diagnostic labelling from chronic obstructive airways disease to asthma,[34] and whether excessive asthma mortality in the aged result from primary uncomplicated asthma or from other age associated conditions is not clear. There is evidence, however, that chronicity of asthma is a risk factor,[5] and the excessive asthma mortality in the aged is likely to be multifactorial. Impaired awareness of bronchoconstriction may contribute by leading to delayed self referral during acute asthmatic attacks. The problem merits wider recognition and should be a further stimulus to precise diagnosis, improved education of patients, and effective treatment and monitoring of asthma in old age.

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