

## Short papers

## Cardiovascular side effects of inhaled salbutamol in hypoxic asthmatic patients

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## Abstract

**Background**—Beta-2 adrenoceptor agonists have been associated with sudden death in asthma patients but the cause and underlying mechanism are unclear. Animal experiments indicate that the combination of hypoxia and  $\beta_2$  agonists may result in detrimental cardiovascular effects. A study was undertaken to investigate the effect of hypoxia on the systemic vascular effects of salbutamol in patients with asthma who are hypoxic by assessing forearm blood flow (FBF) as a measure of peripheral vasodilatation.

**Methods**—Eight men with mild asthma underwent the following treatments: normoxia + placebo (NP), normoxia + salbutamol (NS), hypoxia + placebo (HP), and hypoxia + salbutamol (HS). The period of mask breathing started at t=0 minutes, lasted for 60 minutes, and at 30 minutes 800  $\mu$ g salbutamol was inhaled. The experiment was completed 30 minutes after the inhalation (t=60 minutes). For the hypoxia treatment the Spo<sub>2</sub> level was 82%. Differences between treatments were sought using factorial ANOVA on percentage change from the pretreatment value.

**Results**—There were no significant differences in blood pressure and potassium levels between the treatments. After 60 minutes the increase in FBF was 13% (95% CI -12 to 39) more for HP treatment than for NP, 21% (95% CI -5 to 46) more for NS than for NP, and 32% (95% CI 7 to 58) more for HS than for HP (p=0.016). The inhalation of salbutamol during hypoxia resulted in a significant increase in FBF of 45% (95% CI 20 to 71) compared with NP (p=0.001).

**Conclusion**—Patients with asthma who are hypoxic and inhale  $\beta_2$  agonists have serious systemic vascular side effects which may be an additional explanation for the association between asthma treatment and sudden death.

(Thorax 2001;56:567-569)

Keywords: asthma; hypoxia;  $\beta_2$  agonists

Beta-2 adrenoceptor agonists ( $\beta_2$  agonists) are the most effective and widely used bronchodilator drugs for treatment of acute exacerbations of asthma. However, ever since their introduction,  $\beta$  agonists have been associated with sudden death in asthma.<sup>1</sup> Many explanations for the association of sudden death and asthma treatment have been proposed and refuted.<sup>2-7</sup> Among the factors that may play an important role are the severity of asthma,<sup>8</sup> treatment intensity,<sup>9</sup> socioeconomic factors,<sup>10</sup> cardiac arrhythmias (due to QT prolongation and/or changes in potassium levels), and the use of  $\beta$  agonists.<sup>5-11</sup> It appears that most of the sudden deaths occur outside hospital.<sup>12</sup> In contrast with the situation outside hospital, clinical treatment of exacerbations of asthma in hospital involves the concomitant administration of  $\beta$  agonists and oxygen. It can be hypothesised that administration of  $\beta$  agonists during hypoxia is potentially detrimental and provides an alternative explanation for the association with sudden death.<sup>13</sup> Experimental studies have shown that  $\beta$  agonists are lethal in dogs when the animals are hypoxic.<sup>14</sup> We have recently shown in volunteers exposed to hypoxia that a similar mechanism may also apply to humans.<sup>15</sup> Furthermore, it has been shown that inhalation of  $\beta$  agonists can worsen hypoxia.<sup>16</sup> The present study was designed to investigate the effect of hypoxia on the systemic vascular effects of salbutamol in patients with asthma who are hypoxic.

## Methods

The study protocol was approved by the medical ethics committee of Leiden University Medical Center. After obtaining informed consent, eight men with mild asthma (aged 21-26 years, using  $\beta$  agonists on demand only) who complied with the international classification of intermittent mild asthma (NNHLBI/WHO Workshop 1995) participated in a double blind, placebo controlled, four way, crossover study. The following interventions were investigated: normoxia and placebo, normoxia and inhaled salbutamol, hypoxia and placebo, and hypoxia with salbutamol inhalation. Each intervention was separated by a one week washout period. During the experiments the subjects breathed ambient air or a variable N<sub>2</sub>/O<sub>2</sub> mixture through a well fitting face mask. The N<sub>2</sub>/O<sub>2</sub> mixture was continuously adjusted

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Received 6 April 2000  
Returned to authors  
18 September 2000  
Revised version received  
4 December 2000  
Accepted for publication  
19 March 2001

Table 1 Mean (SD) values (n=8) for mean arterial pressure (MAP), heart rate (HR), QTc interval, forearm vascular resistance (FVR), and serum potassium levels (K<sup>+</sup>) at baseline (t=0) and at the end of the experiment (t=60)

	MAP (mm Hg)		HR (bpm)		QTc (ms)		FVR (mmHg/%FBF)		K <sup>+</sup> (mmol/l)	
	t=0	t=60	t=0	t=60	t=0	t=60	t=0	t=60	t=0	t=60
NP	81.7 (6.9)	82.4 (9.3)	69.0 (8.1)	64.8 (11.5)	390 (20)	395 (12)	29.3 (14.2)	28.3 (13.6)	4.22 (0.14)	4.10 (0.37)
HP	82.5 (7.2)	82.5 (7.8)	65.0 (9.4)	70.9 (10.9)**	389 (15)	397 (16)	26.2 (11.4)	23.9 (13.6)	3.99 (0.21)	4.01 (0.15)
NS	81.6 (8.1)	83.5 (7.9)	65.1 (8.4)	66.8 (13.3)	393 (14)	398 (12)	25.0 (7.4)	21.1 (8.3)	4.06 (0.28)	4.02 (0.35)
HS	81.8 (3.9)	82.9 (8.6)	62.4 (8.7)	76.3 (9.2)***	384 (18)	409 (23)*	30.9 (9.5)	21.9 (8.9)**	4.08 (0.26)	3.89 (0.17)
p value	0.857		<0.001		0.037		0.034		0.495	

NP = normoxia + placebo; HP = hypoxia + placebo; NS = normoxia + salbutamol; HS = hypoxia + salbutamol.

Significant differences from NP as percentage change from t=0 value: \* p<0.05; \*\* p<0.01; \*\*\* p<0.001.

to obtain a peripheral oxygen saturation (SpO<sub>2</sub>) of 80%. Salbutamol 800 µg and placebo were administered double blind as metered dose aerosols via a spacer device (Volumatic). After obtaining stable baseline haemodynamic values (forearm blood flow (FBF), mean arterial pressure (MAP), and heart rate) the subjects breathed either ambient air (normoxia) or an N<sub>2</sub>/O<sub>2</sub> mixture (hypoxia) for 60 minutes. Salbutamol or placebo were administered after 30 minutes mask breathing. FBF was measured 30 and 60 minutes after baseline using computerised venous occlusion plethysmography.<sup>15</sup> Monitoring of one lead ECG and SpO<sub>2</sub> was done continuously. At regular time intervals blood pressure (oscillometric) was measured and 12-lead ECGs were recorded. Forearm vascular resistance (FVR) was calculated as MAP divided by FBF (in mmHg/%FBF). The interventions were compared using factorial ANOVA (factors subject and treatment) on the percentage change after 60 minutes relative to the baseline value. Contrasts between treatments within the ANOVA model are presented with 95% confidence intervals or by reporting significant contrasts.

## Results

All subjects completed the study without clinically significant adverse events. Subjects could not distinguish whether they had been exposed to hypoxia or normoxia. Hypoxia was easily achieved and maintained at an SpO<sub>2</sub> level of 82 (3)%. In three subjects who were administered salbutamol during hypoxia SpO<sub>2</sub> levels rapidly decreased below 80% (to 60–70%), requiring

cessation of N<sub>2</sub> for several minutes. Salbutamol during normoxia did not influence SpO<sub>2</sub>. Hypoxia did not greatly influence MAP, QTc interval, or potassium levels compared with normoxia (table 1). Salbutamol had no effect on MAP and only a minor effect on QTc (<7% prolongation) and potassium levels (<5% decrease) during both hypoxia and normoxia. After 60 minutes the increase in heart rate was 16% (95% CI 6 to 26) more for hypoxia/placebo than for normoxia/placebo. The increase in heart rate was 9% (95% CI –2 to 19) more for normoxia/salbutamol than for normoxia/placebo, and 13% (95% CI 3 to 24) more for hypoxia/salbutamol than for hypoxia/placebo. After 60 minutes the increase in FBF was 13% (95% CI –12 to 39) more for hypoxia/placebo than for normoxia/placebo (fig 1). The increase in FBF was 21% (95% CI –5 to 46) more for normoxia/salbutamol than for normoxia/placebo, and 32% (95% CI 7 to 58) more for hypoxia/salbutamol than for hypoxia/placebo (p=0.016). Inhalation of salbutamol during hypoxia resulted in a significant increase in FBF of 45% (95% CI 20 to 71) compared with normoxia/placebo (p=0.001).

## Discussion

This study has shown that patients with asthma who were hypoxic and inhaled salbutamol at a relatively low dose experienced significant and potentially detrimental cardiovascular effects because of substantial vasodilatation and possibly pulmonary shunting. The 45% increase in FBF (or 30% decrease in FVR) is of the same order of magnitude as that observed after vasodilators such as 0.6–0.9 mg sublingual nitroglycerin (35% decrease in FVR)<sup>17</sup> or 10 mg oral felodipine (30% increase in FBF).<sup>18</sup>

The conclusion that salbutamol during hypoxia may have caused pulmonary shunting was based upon the observation that, in three of the eight subjects, SpO<sub>2</sub> levels declined rapidly after inhalation. Obviously, this prompted immediate cessation of breathing of N<sub>2</sub> and made it impossible to test formally whether or not this observation was related by chance to the combination of hypoxia and salbutamol. Nevertheless, the observation seems to confirm previous data showing that β<sub>2</sub> agonists can induce pulmonary shunting.<sup>16</sup>

This study therefore provides an additional explanation for the association between the use of β agonists and sudden death in asthma. Salbutamol did not greatly influence the QTc interval or potassium level. This is in agreement with previous studies showing that, with

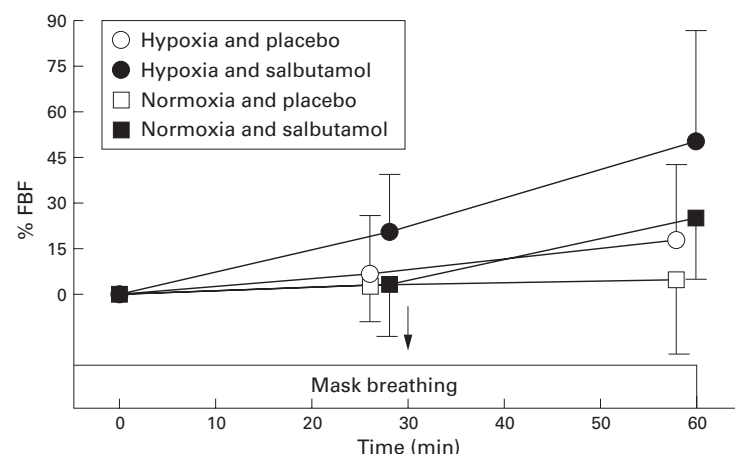


Figure 1 Mean (SD) percentage change in forearm blood flow (FBF) induced by placebo (normoxia + placebo), hypoxia (hypoxia + placebo), salbutamol alone (normoxia + salbutamol), and hypoxia with salbutamol (hypoxia + salbutamol). The arrow indicates inhalation of placebo/salbutamol.

the salbutamol dose used in this study, only minor or no changes in these parameters occurred.<sup>19</sup> It was found that both hypoxia and inhalation of salbutamol induced peripheral vasodilatation, but these effects hardly reached statistical significance. In contrast, the combination of salbutamol and hypoxia resulted in profound cardiovascular effects evidenced by a significant increase in FBF, reflecting a reduction in peripheral vascular resistance. Such a mechanism may result in a diminished venous return, especially when the patient is in the upright position, eliciting the Bezold-Jarisch reflex and subsequent cardiac arrest.<sup>20</sup>

In conclusion, inhaled salbutamol during hypoxia causes significant cardiovascular effects that can be detrimental in compromised patients. Asthmatic patients in respiratory distress should be given  $\beta_2$  agonists and oxygen concomitantly whenever possible.

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Thorax 2001;56:569–571

## Prevalence of asthma among schoolchildren in Patras, Greece: three surveys over 20 years

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Received 11 August 2000  
Returned to authors  
21 October 2000  
Revised version received  
15 January 2001  
Accepted for publication  
26 February 2001

### Abstract

**Background**—The aim of the present study was to compare the prevalence of asthma among schoolchildren in 1978, 1991, and 1998 in Patras, Greece.

**Methods**—The study populations of the three comparable cross sectional surveys comprised third and fourth grade public school children in Patras, Greece. Sample sizes in 1978, 1991, and 1998 were 3735, 2952 and 3397 children and response rates were 80.4%, 81.9%, and 90.6%, respectively. Prevalence of current, non-current, and lifetime asthma or recurrent wheezing was determined by parental questionnaire. Personal communication with the parents of asthmatic children in 1991 and 1998 provided data on lost schooldays.

**Results**—Prevalence rates of current asthma or wheezing in 1978, 1991, and 1998 were 1.5%, 4.6%, and 6.0%, respectively (1978–91:  $p=0.01$ , 1991–98:  $p=0.02$ , 1978–98:  $p=0.03$ ). Lifetime prevalences of asthma or wheezing in 1991 and 1998 were 8.0%

and 9.6%, respectively ( $p=0.03$ ). Current diagnosed asthma increased proportionally to diagnosed wheezing during 1991–98. The number of schooldays lost in the previous 2 years because of asthma did not change ( $p>0.1$ ) between 1991 (0.31 per child) and 1998 (0.34 per child).

**Conclusions**—Our results support a true increase in the prevalence of current and lifetime asthma in the last 20 years among pre-adolescent children in Patras, Greece.

Thorax 2001;56:569–571

Keywords: asthma prevalence; wheezing; childhood

Although unequivocal evidence is lacking,<sup>1</sup> a large body of data supports the impression that the prevalence of asthma has increased in the last decades.<sup>2–4</sup> Data from Greece on the prevalence of asthma are scarce<sup>5</sup> and there are no longitudinal data published to date. In 1978 a cross sectional survey estimated the prevalence of asthma among schoolchildren in the city of



Table 1 Total number and prevalence (%) of current, non-current and lifetime asthma, hospital admissions, and lost schooldays due to asthma or wheezing in 1978, 1991, and 1998 surveys

	1978 (n=3003)	1991 (n=2417)	1998 (n=3076)
Current asthma or wheezing	45 (1.5%)	112 (4.6%)	184 (6.0%)
Non-current asthma or wheezing	—	82 (3.4%)	112 (3.6%)
Lifetime asthma or wheezing	—	194 (8.0%)	296 (9.6%)
Ever hospitalised for asthma or wheezing	—	57 (2.4%)	91 (3.0%)
Mean number of lost schooldays due to asthma or wheezing in the last 2 years:			
Total sample	—	0.31	0.34
Current asthmatics	—	6.75	5.70

Patras.<sup>6</sup> In the present study, using identical methodology, we have compared the data of that survey with that of two surveys conducted in 1991 and 1998 in order to determine possible changes in the prevalence of asthma over the last 20 years.

### Methods

The target populations of all three surveys were schoolchildren in the third and fourth grade of primary public schools—that is, children aged 8–10 years—in the city of Patras, Greece. In the 1978 survey there were 3735 children from 43 schools,<sup>7</sup> in the 1991 survey there were 2952 children from 42 schools, and in the 1998 survey there were 3397 children from 44 schools. Forty schools were common in all three surveys and the rest were situated in neighbouring areas. Study populations included over 80% of the target populations. No school sample consisted of more than 10% from non-Greek ethnic origin groups.

The following standard parental questionnaire was distributed in all three surveys: (1) Has a physician stated that your child had asthma in the last 2 years? (2) Has a physician stated on two or more separate occasions that your child had wheezing in the last 2 years? (3) Has a physician stated that your child had asthma prior to 2 years ago? (4) Has a physician stated on two or more separate occasions that your child had wheezing prior to 2 years ago? Note: If in doubt about your answer, please check “NO”. Questions 3 and 4 were not included in the 1978 survey. Two collection attempts were made in each survey. In 1991 and 1998 the answers were confirmed by personal communication of one of the investigators with all parents who had a positive response to at least one question, all parents who returned questionnaires with missing values, and with 350 randomly selected controls (negative responses to all questions). During personal communication, additional information was obtained on hospital admissions for asthma and/or wheezing from all positive responders and on the number of school days lost because of asthma and/or wheezing during the previous 2 years from current asthmatic subjects. Prevalence was calculated for current (positive answer to questions 1 and/or 2), non-current (positive answer to questions 3 and/or 4), and lifetime asthma (positive answer to any of the four questions). All surveys were conducted in the months of January and February for comparability.

Confidence intervals and prevalence differences were calculated and significance tests

were made using the  $\chi^2$  test for comparison of two proportions.

### Results

The response rates after the second collection of questionnaires in 1991 and 1998 were 81.9% (76.1–92.8%) and 90.5% (78.2–96.5%) respectively. Missing values represented less than 2% of returned questionnaires. After personal communication no missing values occurred. Seventy three of 77 positive responders to question 1 in 1991 (94.8%) and 126 of 131 in 1998 (96.2%) also responded positively to question 2. Respective values for questions 3 and 4 were 43 of 45 (95.5%) and 83 of 85 (97.6%).

The prevalence of current and lifetime asthma in 1978, 1991, and 1998 is shown in table 1. There were significant consecutive increases in the prevalence of asthma. Statistical significance of differences (D) and 95% confidence intervals (95% CI) between surveys were as follows:  $D_{\text{current 1978-91}}$ : 3.1% (95% CI 2.6 to 4.0),  $p=0.01$ ;  $D_{\text{current 1991-98}}$ : 1.4% (95% CI 0.2 to 2.6),  $p=0.02$ ;  $D_{\text{current 1978-98}}$ : 4.5% (95% CI 3.6 to 5.4),  $p=0.03$ ;  $D_{\text{non-current 1991-98}}$ : 0.2% (95% CI –0.8 to 1.2),  $p>0.1$ ;  $D_{\text{lifetime 1991-98}}$ : 1.6% (95% CI 0.1 to 3.1),  $p=0.03$ .

The ratio of “current physician diagnosed asthma” over “ $\geq 2$  episodes of current physician diagnosed wheezing not identified as asthma” was 2.2 (77/35) and 2.5 (131/53) in 1991 and 1998, respectively ( $p>0.1$ ). Respective ratios for “non-current physician diagnosed asthma” over “non-current physician diagnosed wheezing” were 1.2 (45/37) and 3.1 (85/27), ( $p=0.04$ ).

History of “ever been hospitalised” (lifetime asthma) did not change significantly between 1991 and 1998 (D: 0.6% (95% CI –0.26 to 1.46),  $p>0.1$ ). The mean number of school days lost because of asthma in the previous 2 years among current asthmatics and in the total sample did not change significantly between 1991 and 1998 (D: 1.05 (95% CI –1.7 to 3.8),  $p>0.1$  and D: 0.03 (95% CI –0.6 to 0.6),  $p>0.1$ , respectively).

### Discussion

Large sample sizes and high response rates were achieved in the three surveys. The four schools that varied between the surveys did not differ in social or environmental aspects. The age group sampled remained constant and the racial, socioeconomic, and cultural structure of the samples remained essentially unchanged.

The prevalence of current asthma or wheezing has increased in Patras approximately threefold in the 1978–91 period from 1.5% to 4.6% (mean yearly rate 0.24%). It continued to increase until 1998 to 6.0%, albeit at a slower rate (0.20% per year).

A standard questionnaire was used in the three surveys. Written questionnaires are probably the method of choice for comparing prevalence.<sup>7</sup> Others have shown that questions on physician diagnosed lung disease are exceptionally specific.<sup>8</sup> The labelling of two or more episodes of wheezing as asthma will tend to overestimate asthma prevalence, but less so

among current asthmatics. Our results may be subject to bias because of the increasing awareness of both asthma and wheezing in the community and could be influenced by parental recall or acceptance of these labels, access to health services, and physician attitudes. We expect that the last sentence of our written questionnaire and the fact that there were no questions on recurrent or persistent cough have significantly limited false positive answers.<sup>9</sup> This is supported by the fact that the majority of physician diagnosed asthmatic subjects were also recurrent wheezers. Access to health care is unrestricted to all children and changing consultation patterns are unlikely to have influenced trends of physician diagnosed asthma since paediatricians have remained, almost exclusively, the primary and secondary care physicians of children during the last 20 years in Greece. Other studies have shown increasing prevalence of objective parameters of the disease.<sup>2</sup> The cause for this worldwide increase is unclear<sup>2-4</sup> and the present study did not address this issue.

An increase in true current asthma is supported by the essentially unchanged ratio of "current physician diagnosed asthma" over "current physician diagnosed wheezing not identified as asthma" during the period 1991–8. These results counter the concern about diagnostic transfer from bronchitis to asthma. The ratio of "non-current diagnosed asthma" over "non-current wheezing not identified as asthma" significantly increased during 1991–8. This should probably be interpreted as increased labelling of wheezing of younger children (under 6–8 years) by physicians as asthma as "total" non-current asthma (diagnosed asthma plus wheezing not identified as asthma) did not change over the same period.

The mean number of lost school days due to asthma during the previous 2 years decreased by approximately one day (15.5%) among current asthmatics and increased by 9.7% in the general population during the period 1991–8. These differences, however, were not significant.

In conclusion, our results show a continuing increase in the prevalence of asthma over a 20 year period and support a true increase in the prevalence of current asthma. Physicians may have become more willing to diagnose wheezing as asthma in younger children during the period 1991–8. There has been no change in the burden of asthma among asthmatics and in the general population during this period in the city of Patras, although hospital admissions for asthma or wheezing have become more common in recent years.

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