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# Effect of Polymorphism of the $\beta_2$ -Adrenergic Receptor on Response to Regular Use of Albuterol in Asthma

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## Key Words

Asthma ·  $\beta_2$ -Adrenergic agonists ·  $\beta_2$ -Adrenergic receptor · Albuterol

## Abstract

**Background:** Regular use of inhaled  $\beta$ -adrenergic agonists may have adverse effects in some asthma patients. Polymorphisms of the  $\beta_2$ -adrenergic receptor ( $\beta_2$ -AR) can affect its regulation; however, results of smaller studies of the effects of such polymorphisms on response to  $\beta$ -agonist therapy have been inconsistent. **Methods:** We examined the possible effects of polymorphisms at codons 16 ( $\beta_2$ -AR-16) and 27 ( $\beta_2$ -AR-27) on response to

albuterol by genotyping 190 asthmatics who had participated in a trial of regular versus as-needed albuterol use. **Results:** During the 16-week treatment period, patients homozygous for arginine (Arg/Arg) at  $\beta_2$ -AR-16 who used albuterol regularly had a small decline in morning peak expiratory flow (AM PEF). This effect was magnified during a 4-week run-out period, when all patients returned to as-needed albuterol only. By the end of the study, Arg/Arg subjects who had used albuterol regularly had an AM PEF  $30.5 \pm 12.1$  liters/min lower ( $p = 0.012$ ) than Arg/Arg patients who had used albuterol as needed only. Subjects homozygous for glycine at  $\beta_2$ -AR-16 showed no such decline. Evening PEF also declined in the Arg/Arg regular but not in as-need albuterol users. No significant differences between regular and as-needed treatment were associated with polymorphisms at  $\beta_2$ -AR-27. **Conclusions:** Polymorphisms of the  $\beta_2$ -AR may influence airway responses to regular inhaled  $\beta$ -agonist treatment.

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## Introduction

We recently addressed the ongoing controversy about the role of  $\beta$ -agonists in treatment of asthma by conducting a multicenter, placebo-controlled double-blind trial that enrolled only patients with mild asthma [1]. One cohort was treated with the inhaled intermediate-acting  $\beta$ -agonist albuterol on a regularly scheduled basis (2–4 puffs 4 times/day) and the other cohort used it as needed only. We found no clinically significant differences in overall asthma control between the two groups but did note greater use of inhaled albuterol in the regular albuterol group.

During the study, a number of polymorphisms of the  $\beta_2$ -adrenergic receptor ( $\beta_2$ -AR) were identified [2] as well as differences in signaling/regulation related to  $\beta_2$ -AR after chronic exposure to  $\beta$ -agonists [2–6]. Two alleles

have been identified for each of the common polymorphisms of  $\beta_2$ -AR at amino acids 16 and 27 [7]. At 16, the possible genotypes are B16-Arg/Arg, B16-Arg/Gly and B16-Gly/Gly. At 27, the possible genotypes are B27-Gln/Gln, B27-Gln/Glu or B27-Glu/Glu.

Results of studies investigating the possible relationship of these polymorphisms to responses to  $\beta$ -agonist treatment have, however, been inconsistent, with differences being associated with either Arg or Gly polymorphisms at codon 16. The short-term nature of many of these studies and/or the enrollment of subjects with asthma of differing severity may have played a part in these inconsistent findings.

We, therefore, genotyped the subjects who participated in our earlier trial and stratified treatment cohort and outcome measures with respect to the most common polymorphisms in the  $\beta_2$ -AR genotype.

**Table 1.** Baseline characteristics of subjects by genotype

Characteristic	B16			B27		
	Arg/Arg (n = 28)	Arg/Gly (n = 89)	Gly/Gly (n = 62)	Gln/Gln (n = 62)	Gln/Glu (n = 87)	Glu/Glu (n = 28)
Male sex	11 (39.3)	45 (50.6)	20 (32.3)	24 (38.7)	43 (49.4)	8 (28.6)
Minority group	10 (35.7)	25 (28.1)	18 (29.0)	27 (43.6)	21 (24.1)	5 (17.9)
Atopy	25 (89.3)	89 (100.0)	59 (95.2)	58 (93.6)	87 (100.0)	26 (92.9)
Age, years	30.4 ± 10.1	27.7 ± 9.1	29.9 ± 9.7	29.3 ± 9.9	28.4 ± 9.5	9.5 ± 8.0
Age < 18 years	3 (10.7)	14 (15.7)	7 (11.3)	8 (12.9)	13 (14.9)	2 (7.1)
AM peak flow <sup>a</sup> , l/min	389.1 ± 84.7	427.7 ± 100.2	395.3 ± 95.3	406.9 ± 92.9	419.6 ± 102.8	389.5 ± 91.0
PM peak flow <sup>a</sup> , l/min	417.4 ± 90.7	444.8 ± 105.1	418.2 ± 91.6	424.9 ± 91.5	441.9 ± 107.7	416.6 ± 87.4
Peak flow variability <sup>a,b</sup> , %	5.1 ± 10.1	3.0 ± 7.3	4.3 ± 9.3	3.4 ± 8.4	4.0 ± 8.4	4.9 ± 8.5
Symptom score <sup>a</sup>	0.35 ± 0.38	0.39 ± 0.37	0.49 ± 0.45	0.39 ± 0.40	0.42 ± 0.42	0.48 ± 0.36
Rescue $\beta$ -agonist use <sup>a,c</sup>	1.2 ± 2.0	1.5 ± 2.4	1.5 ± 1.9	1.6 ± 2.3	1.5 ± 2.2	1.4 ± 1.2
FEV <sub>1</sub> , liters	2.92 ± 0.73	3.24 ± 0.76	3.02 ± 0.70	2.97 ± 0.74	3.25 ± 0.78	3.02 ± 0.56
FEV <sub>1</sub> <sup>d</sup> , % predicted value	88.5 ± 12.8	90.0 ± 12.6	90.0 ± 14.0	90.2 ± 12.1	89.3 ± 14.2	89.4 ± 10.5
Quality of life score <sup>d,e</sup>	2.19 ± 0.88	2.25 ± 0.74	2.41 ± 0.92	2.25 ± 0.80	2.36 ± 0.83	2.34 ± 0.91
PC <sub>20</sub> <sup>d,f</sup> , mg/ml	0.80 (0.38, 2.14)	0.90 (0.31, 2.10)	0.74 (0.24, 3.00)	1.14 (0.43, 3.17)	0.70 (0.25, 1.82)	0.82 (0.28, 3.51)
Reversibility <sup>g</sup>	11.3 ± 10.4	9.4 ± 11.4	10.6 ± 8.8	8.6 ± 8.5	11.4 ± 12.1	10.2 ± 9.2

Values are means ± SD unless otherwise indicated. With the exception of PC<sub>20</sub> (range) figures in parentheses represent percentage. FEV<sub>1</sub> = Forced expiratory volume in 1 s; PC<sub>20</sub> = methacholine concentration required to decrease FEV<sub>1</sub> 20%.

<sup>a</sup> Averages for week 6 (final) of run-in period.

<sup>b</sup> PEF variability calculated as [(PM PEF – AM PEF) / evening PEF] × 100.

<sup>c</sup> Asthma symptoms were graded by patient daily (0 = no symptoms to 3 = incapacitating symptoms).

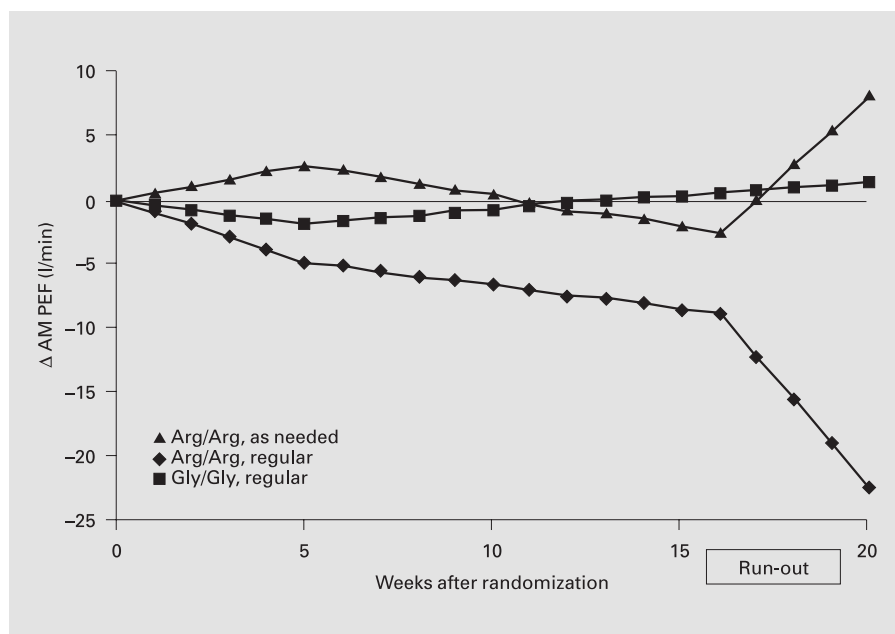
<sup>d</sup> Characteristic measured from week 6 of run-in period.

<sup>e</sup> Patients completed asthma-specific quality-of-life (QoL) questionnaires during clinical center visits (1.0 = no effect on overall QoL; 2.0 = life was ‘a little limited’; 3.0 = ‘some limitation’; 7 = ‘total limitation’).

<sup>f</sup> Geometric mean (interquartile range).

<sup>g</sup> % change in FEV<sub>1</sub> from baseline. Data are from week 4 of the run-in period.

**Fig. 1.** Time course of the change in AM PEF among different B16 genotypes in response to  $\beta$ -agonist treatment. In Arg/Arg patients, the decline in AM PEF with regular  $\beta$ -agonist treatment was  $30.5 \pm 12.1$  liters/min relative to the AM PEF in those with as-needed treatment ( $p = 0.012$ ). Regular treatment in Arg/Arg patients was associated with a  $23.8 \pm 9.5$  liters/min decline in AM PEF relative to AM PEF in B16-Gly/Gly patients ( $p = 0.012$ ).



## Methods

**Inhaled  $\beta$ -agonist trial:** Two well-matched cohorts of patients with mild asthma ( $FEV_1 \geq 70\%$  of predicted,  $PC_{20} \leq 8$  mg/ml using inhaled  $\beta$ -agonists as their only asthma treatment) from five US centers were randomized in double-blind manner to receive regular (2 puffs 4 times/day) plus as-needed albuterol or as-needed albuterol alone. The primary outcome variable was morning peak expiratory flow (AM PEF). Secondary measures are listed in table 1. After 16 weeks of randomized treatment, all patients were switched to regularly scheduled inhaled placebo for 4 weeks ('run-out').

We found no differences in AM PEF in the two groups and no clinically significant differences in other monitored variables, although the regular treatment group used, on average, 7.2 puffs of albuterol/day and the as-needed group used 1.3 puffs/day. Some patients experienced PEF deterioration during the study. After the trial, we collected blood or buccal brushings for genotyping from 190 patients.

Genomic DNA was prepared for analysis by standard techniques, and genotypes were assessed by the amplification refractory mutation system. A mixed-effect linear model was applied for the statistical analysis, which allowed for use of all data. A Bonferroni correction was applied for the three pairwise comparisons.

## Results

Table 2 shows the distribution of the heterozygous and homozygous polymorphisms among the 173 subjects who were genotyped at both loci. All individuals with the B16-Arg/Arg genotype had the B27-Gln/Gln genotype. No significant differences were seen in baseline characteristics

**Table 2.** Number of subjects with each of the potential genotype combinations

Genotype		Subjects observed	Treatment group	
B16	B27		regular	as-needed
Arg/Arg	Gln/Gln	26	16	10
Arg/Gly	Gln/Gln	29	15	14
Gly/Gly	Gln/Gln	7	3	4
Arg/Arg	Gln/Glu	0	0	0
Arg/Gly	Gln/Glu	58	29	29
Gly/Gly	Gln/Glu	27	15	12
Arg/Arg	Glu/Glu	0	0	0
Arg/Gly	Glu/Glu	0	0	0
Gly/Gly	Glu/Glu	26	16	10
Total		173	94	79

of subjects stratified by genotype. Regular albuterol use was associated with a decline in AM PEF in patients with B16-Arg/Arg (fig. 1) but not with any other B16 genotype or with any B27 genotype (data not shown). In B16-Arg/Arg patients, the difference in the change in AM PEF between regular and as-needed treatment over the study period was  $30.5 \pm 12.1$  liters/min ( $p = 0.012$ ) and the difference in mean AM PEF was  $23.8 \pm 9.5$  liters/min greater in patients who received regularly scheduled treatment

( $p = 0.012$ ). The patterns of change were similar for PM PEF. No significant B16 genotype-related differences were seen in any other secondary outcomes monitored, in outcomes related to the B27 genotypes, and in asthma exacerbations and treatment failures among genotypes by treatment (Fisher's exact test).

## Discussion

In our large study of well-defined mild asthmatics, regular use of  $\beta$ -agonists had distinct effects on airway function in patients with specific polymorphisms (B16 Arg/Arg) of the  $\beta$ -adrenergic receptor, reducing response to regular  $\beta$ -agonist use. We found that B16 Arg/Arg patients (~15% of the population) who use  $\beta$ -agonists regularly may be at risk for adverse, or less salutary, effects, especially as they discontinue high-dose therapy. We specifically designed the study with a run-out period because of a concern that the bronchodilating effect of regular  $\beta$ -agonist use might mask a deleterious effect and found that the decline in PEF that occurred in the B16 Arg/Arg group was greatest during the run-out period.

Various studies suggest that B16-Gly expression is downregulated more than B16-Arg by endogenous catecholamine exposure [3–7]. Gly 16 would be downregu-

lated more than Arg16 by endogenous catecholamines during the resting state, and the tachyphylactic effect of regular exogenous  $\beta$ -agonist exposure might be most apparent in Arg16 patients because their receptors have not yet been downregulated. Such models might explain the enhanced bronchodilator response to albuterol in B16-Arg/Arg patients, although an entirely different mechanism may be involved in the effects we noted. For example, the B16-Arg genotype may be in linkage disequilibrium with a nearby, as yet unidentified, polymorphism on the genome. Regardless of the mechanism, the Arg16 polymorphism is a marker for an altered pharmacological response to  $\beta$ -agonists.

Our findings suggest that these B16 homozygotes for arginine may benefit by avoidance of regularly scheduled  $\beta$ -agonists and by earlier intervention with anti-inflammatory agents.

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## Erratum

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The material in *Int Arch Allergy Immunol* 2001;124:183–186 originally appeared in the *American Journal of Respiratory and Critical Care Medicine* with the following original citation:

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