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Evidence for a dual effect by beta-adrenoceptor antagonists on post-exercise airway calibre

K.E. Berkin*, G. Walker**, N.C. Thomson*

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ABSTRACT: The effect of selectivity of beta-adrenoceptor antagonists on resting and post-exercise airway calibre in normal subjects was studied. Eight normal subjects were given atenolol 50 mg, propranolol 80 mg and placebo orally, in random order, double-blind. Specific airways conductance and flow-volume curves (partial and complete) were recorded before, 2 hours after drug administration and after exercise. Neither beta-adrenoceptor antagonist had a measurable effect on lung function tests at rest. The post-exercise increase in flow rates measured from partial flow volume curves was inhibited by propranolol but not by the beta-1-selective adrenoceptor antagonist atenolol, whereas both drugs caused a decrease in specific airways conductance after exercise. Beta-adrenoceptor antagonists may have a dual effect on airway calibre. Firstly, a direct effect on the beta-2 receptors in airway smooth muscle may occur. Secondly, beta-adrenoceptor blockade may, in the large airways, inhibit vagal pre-junctional beta-1 receptors which normally inhibit acetylcholine release at the nerve ending, thereby permitting vagally-induced airway narrowing.

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* Department of Respiratory Medicine, Western Infirmary, Glasgow.
** Institute of Physiology, University of Glasgow, Glasgow.

Correspondence: K.E. Berkin, Respiratory Medicine, General Infirmary, Great George St, Leeds LS1, UK.

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Beta-adrenoceptor antagonists can cause airway narrowing in asthmatic patients [1, 2]. In normal subjects some workers have found no evidence for such an effect [3, 4] but several studies have demonstrated small reductions in resting airway calibre [2, 5]. However, airway narrowing with beta-adrenoceptor antagonists appears to be more pronounced after exercise [1], with a time course similar to that of exercise-induced asthma [6].

The mechanism by which beta-adrenoceptor antagonists cause airway narrowing is not established. One obvious explanation is that the beta-adrenoceptor antagonist could be acting directly on the beta-2 receptor in airway smooth muscle antagonizing the beta-2 (bronchodilator) effects of adrenaline [5]. Although basal concentrations of circulating adrenaline are probably not important in the control of airway calibre in normal subjects [7], increased adrenaline concentrations, such as those found during moderate exercise [8, 9], can influence airway calibre [7, 9, 10]. Thus a direct antagonistic effect on beta-2 receptors may be evident when circulating adrenaline concentrations are elevated above basal. An alternative mechanism might be indirect, involving the vagus nerve, as the bronchoconstriction induced by beta-adrenoceptor antagonist administration can be inhibited by anticholinergic drugs [2, 5]. This latter mechanism would be therefore expected to operate on the large (central) airways which are supplied by the vagus [11–13]. In contrast, the small airways appear to be sparsely innervated by the vagus nerve [12–15] but have an abundance of beta-2 receptors [16].

Thus, to investigate further the mechanisms by which beta-adrenoceptor blockade causes airway narrowing we compared the effects on airway calibre of a beta-1-selective adrenoceptor antagonist, atenolol, which is relatively lacking in beta-2 effects [17], with a non-selective agent, propranolol, which has both beta-1 and beta-2 blocking properties. Any airway changes induced by beta-adrenoceptor antagonists in normal resting subjects are small, so airway changes were also assessed after exercise, which may amplify the effect of beta-adrenoceptor blockade [1, 6]. Several different tests of lung function were used in an attempt to distinguish between effects on large and small airways. Specific airways conductance is thought to reflect large airway calibre in normal subjects [18], whereas flow rates at 25% of vital capacity are probably determined by small airway calibre [19, 20] in the absence of concomitant major changes in large airway calibre.

Methods

Eight normal non-atopic subjects gave informed consent for the study which had been approved by the Hospital Ethical Committee. The subjects, mean age 24 yr (range 21–27 yr) were non-smokers, had no history of chest disease and had not had a respiratory infection within the preceeding six weeks. All had forced expiratory volume in 1 s and vital capacity values within the predicted normal range.

Airway resistance and thoracic gas volume were measured simultaneously in a constant-volume body plethysmograph (Fenyves and Gut) using a computerized data collection and analysis system [21] based

on the methods of Du Bois *et al.* [22]. The results were expressed as specific airways conductance (sGaw), which is the reciprocal of airway resistance per litre of thoracic gas volume. The mean of eight values recorded was taken as sGaw.

Partial and complete expiratory flow volume curves were obtained using a 12 *l* dry rolling-seal spirometer with a flow/volume differentiator (P K Morgan Ltd.) and recorded using an X-Y plotter (Rikadenki 201T). After 30 s of normal tidal breathing, a forced maximal expiration from end-tidal inspiratory volume to residual volume was performed to obtain the partial flow-volume curve. The patient then inspired from residual volume to total lung capacity and performed a second forced maximal expiration to residual volume to obtain the complete expiratory flow-volume curve. Three curves were recorded at intervals of 90 s for each reading. Flow rates at 25% of vital capacity were measured from the partial ($\dot{V}_{25}$(p)) and complete $\dot{V}_{25}$(c) flow-volume curves. Measurements from the complete flow-volume curve may be less sensitive in detecting changes in airflow resistance than from the partial flow-volume curve [19] because an inspiration to total lung capacity may transiently reduce bronchomotor tone [23], thus partially obscuring changes in airway calibre.

Subjects attended the laboratory at 9 am on three separate occasions at least a week apart, having had a light breakfast with no tea, coffee or cola. After a 15 min rest period, baseline lung function tests were performed. Following this, either atenolol 50 mg, propranolol 80 mg or placebo was administered orally in a double-blind, random-order fashion. After 2 hours, to allow peak drug concentrations to be reached [17, 24], the lung function tests were repeated. The subjects then underwent symptom-limited graded treadmill exercise (Bruce protocol) with continuous electrocardiogram (ECG) monitoring. Lung function tests were repeated at 2 min after completion of the exercise to allow adequate equilibration of the body plethysmograph. Further lung function tests were recorded 10 min after completion of the exercise, at which time airway calibre changes are present in exercise-induced asthma [25]. Heart rate and blood pressure were recorded regularly during the experiment.

Results (expressed as mean (SEM)) of the lung function tests at baseline, 2 hours after drug administration, 2 and 10 min post-exercise on each beta-adrenoceptor antagonist were compared with those on placebo using Student's paired t-test, with a modification for multiple comparisons [26]. The results for sGaw were logged prior to statistical analysis [27].

Results

Respiratory

Propranolol and atenolol caused small reductions in $\dot{V}_{25}$(p) and $\dot{V}_{25}$(c) 2 hours after dosing (figs 1A and B) but these did not achieve statistical significance. Two min after completion of exercise on placebo $\dot{V}_{25}$(p) increased from 1.97 (0.11) $l \cdot s^{-1}$ (2 h post dose) to 2.38 (0.18) $l \cdot s^{-1}$; and $\dot{V}_{25}$(c) increased from 2.30 (0.10) to 2.66 (0.08) $l \cdot s^{-1}$. These increases in $\dot{V}_{25}$(p) and $\dot{V}_{25}$(c) were inhibited by propranolol ($p < 0.01$ at 2 min post-exercise) but not by atenolol (figs 1A and B). Two min after completion of exercise on atenolol, $\dot{V}_{25}$(p) increased from 1.87 (0.14) to 2.24 (0.26) $l \cdot s^{-1}$, $\dot{V}_{25}$(c) increased from 2.18 (0.12) to 2.59 (0.16) $l \cdot s^{-1}$. Ten min after completion of exercise, values were returning towards resting levels and there were no statistically significant differences between placebo, atenolol and propranolol. The changes in $\dot{V}_{25}$(p) were closely mirrored by those in $\dot{V}_{25}$(c), although the latter were numerically larger. Statistical significance occurred at the same time points for both measurements.

Neither beta-adrenoceptor antagonist had a significant effect on resting sGaw (fig. 1C). However, 2 min after completion of exercise on placebo mean sGaw increased from 1.56 (0.18) $s^{-1} \cdot kPa^{-1}$ (2 h post dose) to 1.69 (0.19) $s^{-1} \cdot kPa^{-1}$, whereas on atenolol post-exercise sGaw fell from 1.49 (0.20) to 1.23 (0.11)

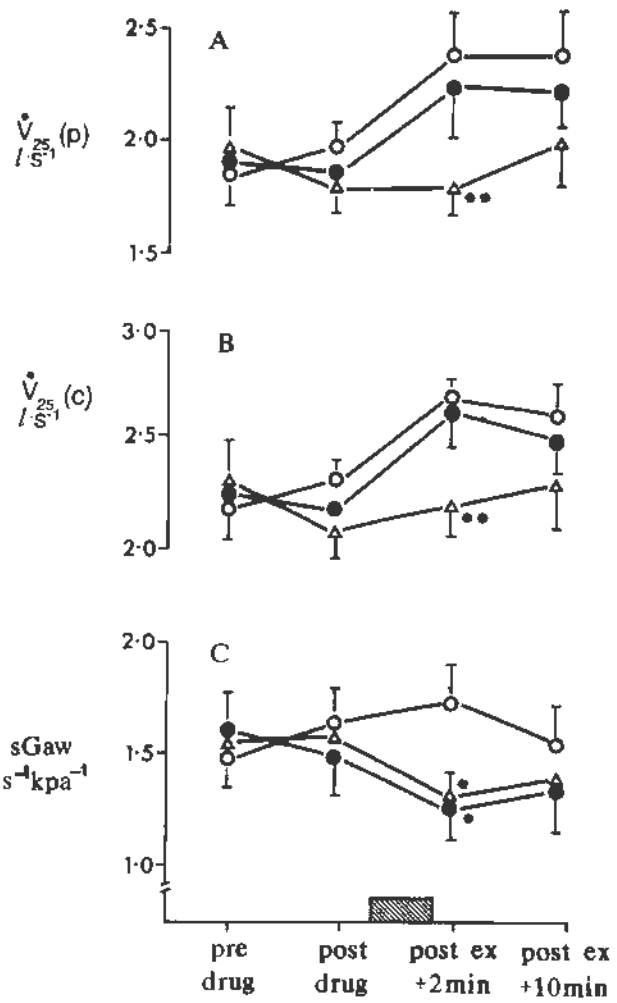

Fig. 1. Mean (SEM) $\dot{V}_{25}$(p) (panel A), $\dot{V}_{25}$(c) (panel B), and sGaw (panel C) before and after drug administration and after exercise on placebo (○), atenolol (●) and propranolol (Δ). *: $p < 0.05$; **: $p < 0.01$.

$s^{-1} \cdot kPa^{-1}$ and on propranolol from 1.55 (0.16) to 1.29 (0.13) $s^{-1} \cdot kPa^{-1}$ ($p < 0.05$). Ten min after completion of exercise, values were returning towards resting levels and there were no statistically significant differences between placebo, atenolol and propranolol.

Cardiovascular

Heart rate and systolic blood pressure after drug administration and during each stage of exercise were similarly reduced by both atenolol and propranolol when compared to placebo. Peak heart rate during exercise on placebo (193 (4) beats per min) was significantly reduced ($p < 0.05$) by both atenolol (146 (7) beats per min) and propranolol (138 (8) beats per min). Mean exercise time (17.2 (0.9) min, placebo) was significantly reduced by propranolol (14.6 (0.6) min; $p < 0.05$), but not by atenolol (16.8 (1.0) min).

Discussion

The doses of propranolol and atenolol used had equipotent cardiovascular beta-blocking effects in this study. The exercise-induced increases in heart rate and blood pressure after placebo were attenuated to the same extent by the two antagonists during each stage of exercise and also at peak exercise. As expected, exercise time was reduced by propranolol but not by atenolol when compared with placebo, because propranolol has beta-2 blocking effects on the peripheral circulation and skeletal muscle metabolism. These observations are consistent with previous work [28].

The reductions in resting measurements of $\dot{V}_{25}(p)$, $\dot{V}_{25}(c)$ and sGaw were small after administration of propranolol and atenolol, and in this group of eight normal subjects did not achieve statistical significance. These findings are in agreement with most [3, 4] but not at all [5] studies in normal subjects. Inadequate dose or time interval after dosing are unlikely explanations of the apparent lack of effect since the change in post-exercise lung function was clearly seen, as was an effect on exercise heart rate. Airway smooth muscle possesses large numbers of beta-2 receptors and responds to circulating adrenaline when concentrations are elevated within the physiological range by low-dose infusion [7, 9], with a preferential effect in the small airways [7]. The lack of a significant effect of beta-adrenoceptor antagonists on resting airway calibre in this study suggests that basal concentrations of circulating adrenaline play little part in the control of resting airway tone in normal subjects.

Two minutes after completion of exercise on placebo and atenolol a significant increase in $\dot{V}_{25}(p)$ and $\dot{V}_{25}(c)$ was observed. This increase was inhibited by the non-selective propranolol. The increase in $\dot{V}_{25}(p)$ and $\dot{V}_{25}(c)$ after exercise on atenolol occurred despite a concomitant reduction in large airway calibre as assessed by a decrease in sGaw. The reduction in sGaw would tend to diminish any increase in $\dot{V}_{25}$ values. This result indicates that the increases in $\dot{V}_{25}$ values were true observations, and is in keeping with the changes in $\dot{V}_{25}$ measurements being generated from airways other than the large airways, *i.e.* from small airways [19, 20].

Exercise time was reduced by propranolol compared to atenolol and placebo. It is unlikely that this influences the differential effect of atenolol and propranolol on the small airways since no such differential effect was observed in the large airways. Moreover, longer exercise, which in this study would be at greater work loads, would tend, if anything, to cause larger falls in airway calibre, as observed in asthmatic patients [25]. The reverse was observed in this study; the reduction in airway calibre occurred with propranolol, despite the shorter exercise time.

The bronchodilation in the small airways is probably mediated by the beta-2 effects of the increased concentrations of adrenaline which occur during vigorous exercise [8, 29] and which have been shown to cause similar bronchodilation in the small airways when infused [7, 10]. The differential effect of the selective and non-selective beta-adrenoceptor antagonists on the post-exercise bronchodilation in the small airways is compatible with the presence of beta-2 receptors and probable lack of beta-1 receptors on airway smooth muscle [16].

A slight increase in large airway calibre (sGaw) was seen 2 min after completion of exercise on placebo, although the increase was not statistically significant. However, both beta-adrenoceptor antagonists caused a reduction in sGaw at 2 min post-exercise. Atenolol is relatively lacking in beta-2 blocking properties [17], and this effect on the large airways may be mediated therefore by the beta-1 blocking properties which both drugs have in common. The mechanism is likely to be indirect because airway smooth muscle does not appear to possess beta-1 receptors [16]. The large airways are vagally innervated [11-13], whereas the small airways receive only sparse vagal innervation [14, 15]. The vagus possesses pre-junctional inhibitory beta receptors [30, 31] and clinical studies have shown that beta-adrenoceptor blockade can cause increased cardiac vagal tone [32]. The receptors have been shown recently in dogs to be beta-1 receptors [33]. Why should blockade of these receptors allow the vagus to mediate airway narrowing after exercise but not at rest? Firstly, vagal tone to the airways is reduced during exercise, permitting bronchodilation [6], but returns when exercise is stopped. A beta-adrenoceptor antagonist, by antagonizing the beta-1 receptors which would normally counter-balance vagal return after exercise, would allow vagal tone to return more rapidly, and possibly excessively for a short while, thus causing airway narrowing. Secondly, in asthmatic patients exercise is a potent stimulus to bronchoconstriction [34]. In normal subjects, exercise may provoke airway narrowing in the presence of the altered vagal control mechanisms induced by beta-adrenoceptor blockade.

The effect of atenolol on post-exercise sGaw but

not $\dot{V}_{25}$ measurements is not explained by loss of cardioselectivity which can occur with higher doses of the drug [35]. No effect of atenolol was seen on the small airways which have been shown to have large numbers of beta-2 adrenoceptors.

The underlying mechanism by which beta-adrenoceptor antagonists can cause profound airway narrowing in asthmatic patients is not established. Although a direct effect on airway smooth muscle beta-2 reecptors by a non-selective beta-adrenoceptor antagonist may be a partial explanation [2], selective beta-adrenoceptor antagonists can also cause bronchoconstriction in some asthmatic patients [36, 37]. This is usually explained by the lack of complete selectivity of so-called 'selective' drugs. However this study suggests that vagal mechanisms may also be involved. There is indirect evidence to suggest that vagal activity is increased in asthma [13], and this enhanced vagal tone may therefore be more dependent on pre-junctional inhibitory beta-1 receptor control. The effect of a beta-adrenoceptor antagonist in such patients would therefore be to permit vagally-induced airway narrowing. In support of the involvement of the vagus, the bronchoconstrictor response to beta-adrenoceptor antagonists can be inhibited by anti-cholinergic drugs [2, 5].

The results of this study suggest that beta-adrenoceptor antagonists possibly have a dual effect on the airways. Inhibition of vagal pre-junctional inhibitory beta-1 receptors may permit vagally-mediated airway narrowing under certain conditions. In addition, a non-selective beta-adrenoceptor antagonist may have a direct effect on airway smooth muscle beta-2 receptors.

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RÉSUMÉ: Nous avons étudié l'effet de la sélectivité des antagonistes des bêta adréno-récepteurs sur le calibre des voies aériennes au repos et après l'effort chez des sujets normaux. Huit sujets normaux ont reçu 50 mg d'aténolol, 80 mg de propanolol et du placebo par voie orale en ordre randomisé et selon la technique du double anonymat. La conductance spécifique des voies aériennes et les courbes débit-volume (partielle et complète) ont été enregistrées avant et 2 h après l'administration de la drogue et après l'effort. Aucun antagoniste des bêta-adréno-récepteurs n'a eu d'effet mesurable sur la fonction pulmonaire au repos. L'augmentation des débits après l'effort, mesurée par la courbe débit-volume partielle était inhibée par le propanolol mais pas par l'antagoniste adréno-récepteur bêta-1 sélectif aténolol, alors que les deux drogues entrainaient une diminution de la conductance spécifique des voies aériennes après l'effort. Les antagonistes des bêta-adréno-récepteurs peuvent avoir un effet biphasique sur le calibre des voies aériennes: d'abord un effet direct sur les bêta-2 récepteurs du muscle lisse des voies aériennes; en second lieu, un blocage des bêta adréno-récepteurs peut, au niveau des grandes voies aériennes, inhiber les bêta-1 récepteurs pré-jonctionnels vagaux qui, normalement, inhibent la libération d'acétylcholine à la terminaison nerveuse, permettant ainsi un rétrécissement des voies aériennes, d'origine vagale.