Pulmonary and Cardiac β-Adrenoceptor Density *in vivo* in Asthmatic Subjects

FENG QING, SHAKIL U. RAHMAN, CHRISTOPHER G. RHODES, MICHAEL J. HAYES, SHIRANEE SRISKANDAN, PHILIP W. IND, TERRY JONES, AND J. M. B. HUGHES

Department of Medicine (Respiratory Division), Royal Postgraduate Medical School, and MRC Clinical Sciences Centre, Cyclotron Unit, Hammersmith Hospital, London, United Kingdom

To examine whether there is a primary deficit in β-adrenoceptor density in asthma, pulmonary and cardiac β-receptor density was determined *in vivo* with positron emission tomography (PET) in 10 male asthmatic subjects (36 ± 8 yr of age) and compared with that in 30 age-matched normal male subjects (36 ± 8 yr of age). Pulmonary β-receptor density was 10.3 ± 1.8 pmol/g tissue for the asthmatic group and 10.9 ± 1.9 for the normal group. Cardiac β-receptor density was 9.1 ± 3.3 pmol/g for the asthmatic group and 8.8 ± 2.3 pmol/g for the normal group. There was no difference in either pulmonary or cardiac β-receptor density between the two groups. In addition, an inverse relationship was observed between FEV_1 % predicted and pulmonary β-receptor density in asthmatic subjects. In conclusion, β-receptor numbers are normal in untreated asthmatic subjects. Qing F, Rahman SU, Rhodes CG, Hayes MJ, Sriskandan S, Ind PW, Jones T, Hughes JMB. Pulmonary and cardiac β-adrenoceptor density *in vivo* in asthmatic subjects. AM J RESPIR CRIT CARE MED 1997;155:1130–1134.

Bronchial asthma is characterized by reversible airflow obstruction resulting from a combination of bronchial smooth-muscle constriction and an underlying inflammatory process leading to a thickened, edematous airway lining. Since β-adrenergic-receptor stimulation counteracts both the bronchoconstriction and the response to inflammatory mediators (1), pulmonary β-receptor dysfunction has been suggested as one of the causes of asthma and the accompanying bronchial hyperreactivity (2). Most studies of β-receptor density in asthmatic subjects have relied upon the *in vitro* determination of β-receptor density on circulating lymphocytes (3), making the assumption that lymphocytes reflect the β-receptor status of lung. However, lymphocyte receptors may not necessarily mirror those of the lung (4). Alternatively, lung tissue obtained postmortem has been examined (5), although the premortem condition (high levels of endogenous cortisol and circulating catecholamines) or premortem treatment (possible high doses of corticosteroids and β-agonists) would be expected to influence the results.

With the successful synthesis of the ^{11}C-labeled hydrophilic β-receptor ligand CGP-12177 (6), it is now possible to quantify pulmonary (7) and cardiac β-receptor density (8, 9) *in vivo* in humans using positron emission tomography (PET). In the present study, pulmonary and cardiac β-receptor density was determined *in vivo* using PET on 10 asthmatic subjects who had not been receiving any antiasthma treatment for at least 4 wk prior to the measurements. These were compared with an age-matched normal group of 30 subjects. In addition, pulmonary β-receptor density was compared with lung function (FEV_1 %predicted). The aims of the present study were: (*1*) to determine whether there is any difference in β-adrenoceptor density between asthmatic and normal subjects; and (*2*) to assess whether there is any association between β-receptor density and lung function.

METHODS

Subjects and Treatment

Asthmatic group. Ten male, mildly asthmatic patients with a mean age of 36 ± 8 yr (range: 28 to 55 yr) were recruited. They had taken no β-agonist medication for at least 4 wk prior to the study. This was not a problem, since all subjects used β-agonist inhaler medication infrequently. One subject was taking a low dose inhaled corticosteroid medication, which was withdrawn and replaced by an antimuscarinic inhaler preparation as rescue medication (this was used on a few occasions). All subjects complied with instructions to avoid β-agonist medication.

The asthmatic subjects' mean FEV_1 value was 92 ± 10% predicted, and their mean FVC value was 100 ± 10% predicted. These measurements were made at the time of the PET scan in three subjects and 3 to 5 d earlier in the remainder, while they were off medication. Because no symptoms developed between that visit and the PET scan, the spirometric values were considered representative of those pertaining at the time of the PET scan. Individual patient information is provided in Table 1.

Normal group. Thirty male normal volunteers with a mean age of 36 ± 8 yr (range: 29 to 63 yr) were used as an age-matched comparison group. Their mean FEV_1 value was 100 ± 11% predicted, and their mean FVC value was 101 ± 8% predicted. Subjects with abnormal FEV_1 or FVC values, or with a history of any significant respiratory or cardiovascular illness, were excluded. None were taking any medication at the time of study.

All subjects classified as having asthma had a history of episodic dyspnea with wheezing, relieved by β_2-agonist drugs, and had asthma diagnosed by a physician according to the criteria of the American Thoracic Society (10). The diagnosis was further supported by either peak

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Correspondence and requests for reprints should be addressed to Prof. J. M. B. Hughes, Department of Medicine (Respiratory Division) Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 ONN, UK

TABLE 1
SUBJECTS' CLINICAL INFORMATION

Subject	Age (*yr*)	FEV_1 (L) (% *pred*)	FVC (L) (% *pred*)
Mildly asthmatic			
1	31	3.6 (80)	5.1 (95)
2	35	3.1 (75)	4.7 (93)
3	34	3.1 (93)	3.6 (92)
4	33	3.9 (94)	4.7 (97)
5	33	4.3 (97)	5.4 (101)
6	28	5.0 (109)	6.3 (115)
7	35	3.4 (86)	3.9 (83)
8	41	3.4 (90)	5.1 (112)
9	33	3.9 (93)	5.2 (102)
10	55	3.5 (104)	4.7 (111)
Group	36 ± 8	3.7 ± 0.6 (92 ± 10)	4.9 ± 0.8 (100 ± 10)
Normal controls (n = 30)			
Group	36 ± 8	4.1 ± 0.6 (100 ± 11)	5.0 ± 0.7 (101 ± 8)

flow monitoring showing variability or positive skin prick tests to common allergens (six of the 10 asthmatic subjects were atopic: 4 asthmatic subjects were not tested); all had a positive histamine challenge test. These tests were done on site before recruitment.

Because CGP-12177 is a β-antagonist, all asthmatic subjects were challenged with unlabeled CGP-12177 (3 μg followed by 25 μg unlabeled CGP-12177, as two intravenous injections) on recruitment. A 20% reduction in FEV_1 or FVC during the challenges excluded the subject from the PET study. This challenge induced bronchospasm in only one patient, who did not proceed to the PET scan.

Both asthmatic and normal subjects gave written informed consent to the protocol, which was approved by the Hammersmith Hospital Research Ethics Committee and the United Kingdom Administration of Radioactive Substances Advisory Committee (ARSAC).

Measurement of Pulmonary and Cardiac β-Adrenoceptor Density

A nonselective, hydrophilic β-adrenoceptor antagonist *(S)*-CGP-12177 was used as the β-receptor ligand. This was labeled with the positron-emitting radionuclide carbon-11, which has a half-life of 20.4 min. The preparation of the *(S)*-[^{11}C]CGP-12177, the PET scanning, and the calculation of β-adrenoceptor density were performed as previously reported (7). PET scans were done with an ECAT 931-08/12 15-plane positron tomograph (Siemens/CTI, Knoxville, TN). The protocol comprised: (*1*) ^{68}Ge/^{68}Ga transmission; (*2*) C^{15}O emission; and (*3*) *(S)*-[^{11}C]CGP-12177 dynamic emission scanning to measure total lung and heart density, blood volume, and β-adrenoceptor density, respectively. Measurement of pulmonary β-adrenoceptor density was done with a modification of the double injection method of Delforge and colleagues (11). A high-specific-activity *(S)*-[^{11}C]CGP12177 preparation (~185 MBq *(S)*-[^{11}C]CGP-12177 containing 4.3 ± 0.7 μg unlabeled *(S)*-CGP-12177) was given intravenously over 2 min, followed 30 min later by a second injection of *(S)*-[^{11}C]CGP-12177 with a lower specific activity (~370 MBq *(S)*-[^{11}C]CGP-12177 containing 24.5 ± 3.8 μg unlabeled *(S)*-CGP-12177). Dynamic emission scanning comprising 55 frames started at the time of the first injection and continued for 75 min.

Images were analysed on Sun workstations (SUN Microsystems Inc., CA) by use of *Analyze* image analysis (12) and the Matlab (The MathWorks, Inc., Natick, MA) mathematical software package. Regions of interest (ROIs) for lung were drawn on the transmission images (7). In the 15 planes scanned, the most caudal plane was selected from the second plane above the diaphragm. ROIs for heart (left ventricular wall and septum) were drawn on summed dynamic images (Figure 1), which were obtained by adding the dynamic time frame images recorded between the first and second *(S)*-[^{11}C]CGP-12177 injections. Summing the dynamic time frames improves the signal-to-noise ratio and the visual appearance, making it easier to draw the ROIs. To generate lung and heart tracer time-activity curves, ROIs were projected onto the dynamic *(S)*-[^{11}C]CGP-12177 images. The mean tracer activity in serial lung and heart planes (craniocaudal) were calculated and plotted against time. The extravascular tissue tracer time-activity curves were obtained by subtracting the regional vascular *(S)*-[^{11}C]CGP-12177 time-activity curves

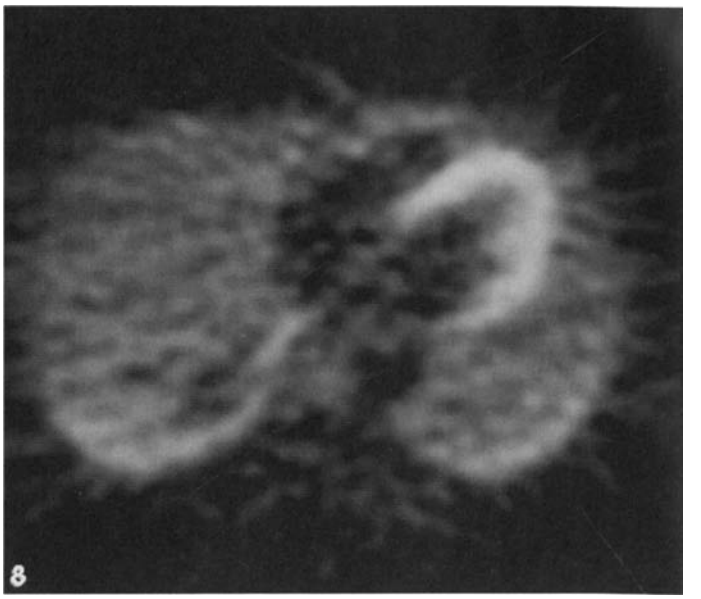

Figure 1. A representative PET image of β-adrenoceptor binding (pmol/ml thorax) obtained from an asthmatic subject by adding the dynamic time frame images recorded between 10 and 30 min following the first (*S*)-[^{11}C]CGP-12177 injection.

(calculated from the C^{15}O blood volume data and *(S)*-[^{11}C]CGP-12177 activity in the venous blood samples) from the regional *(S)*-[^{11}C]CGP-12177 time-activity curves.

Receptor density (Bmax) of β-adrenoceptors for ROIs was calculated through a graphical approach based on the method of Delforge and colleagues (11), which utilizes the relationship between Bmax and the uptake of ligand into the tissue in the ROI (7). Briefly, because the uptake of CGP-12177 is determined for two quite different molar concentrations of radioligand, the value of Bmax can be mathematically dissociated from that of the bimolecular association constant (k_{+1}). Conversion is made from the concentration of radioactivity (kBq/ml), measured regionally with the PET scanner, to molar concentration (pmol/ml), using the known radioactive and molar amounts of CGP-12177 injected, each obtained from quantitative assay. Furthermore, exponential extrapolation of the slow phase of the tissue time-activity curves accounts for the small loss of tracer from the tissue in the field of view by virtue of dissociation of the ligand from the receptor (dependent on the dissociation rate constant, k_{-1}). Therefore, the measurement is independent of the equilibrium dissociation constant ($K_D = k_{-1}/k_{+1}$). The original approach of Delforge and colleagues been modified as previously described (7), by taking into account the whole of the molar quantity of CGP-12177 injected, the introduction of the active *(S)* enantiomer, the use of a blood background subtraction, and expressing β-receptor density values as picomoles per gram of tissue by normalizing the measured receptor density (expressed as pmol/ml ROI) by extravascular density (grams of extravascular tissue per milliliter of ROI). The pulmonary Bmax values obtained *in vivo* with this method have been shown to correlate with those values determined with classic *in vitro* radioligand binding assays (13), and in a previous study we have shown that this technique has acceptable reproducibility (14).

Vascular density (grams of blood per milliliter of thorax) was obtained by multiplying blood volume (milliliters of blood per milliliter of thoracic volume) by 1.06 (whole-blood density in g/ml). Lung and heart density (blood and extravascular tissue) obtained from the normalized transmission scan were expressed as grams of tissue per milliliter of thoracic volume (g/ml). Extravascular tissue density (g/ml) was calculated by subtracting vascular density from lung and heart density scans. Bmax was expressed as picomoles per gram (pmol/g) of extravascular tissue.

Statistical Analysis

Data are presented as mean ± SD unless otherwise stated. Unpaired *t* testing was used for the comparisons between the normal and asth-

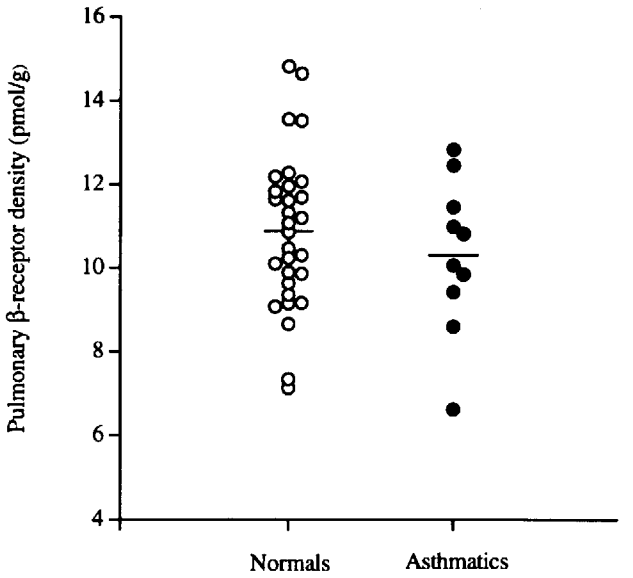

Figure 2. Comparison of pulmonary β-adrenergic receptor density between normal and asthmatic groups. The *horizontal bars* represent the means for each group.

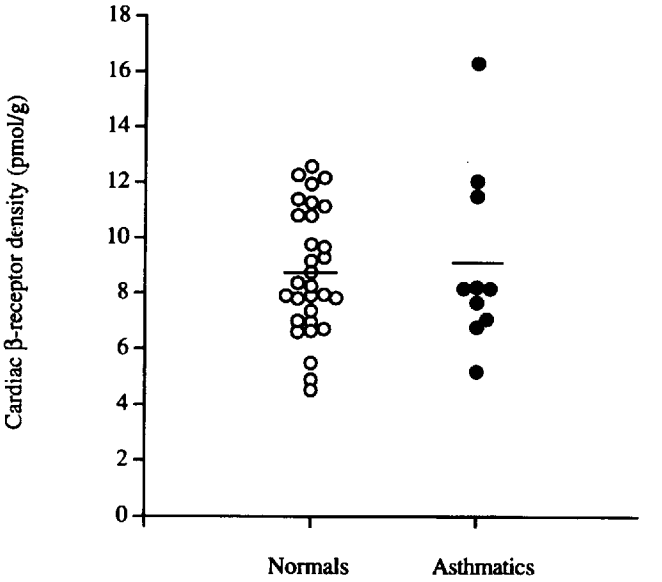

Figure 3. Comparison of cardiac β-adrenergic receptor density between normal and asthmatic groups. *Horizontal bars* represent the means for each group.

matic groups, and paired *t* testing was used for within-group comparisons of cardiac and pulmonary Bmax. All tests were two-tailed and significance was assigned to a value of $p < 0.05$.

RESULTS

Pulmonary Blood Volume

Pulmonary blood volume was 0.151 ± 0.016 ml/ml for the normal group and 0.156 ± 0.020 ml/ml for the asthma group. There was no significant difference between the two groups.

Pulmonary Extravascular Tissue Density

Pulmonary extravascular tissue density was 0.166 ± 0.027 g/ml for the normal group and 0.172 ± 0.028 g/ml for the asthma group. The small difference between the two groups was not significant.

β-Adrenoceptor Density

Pulmonary Bmax was 10.9 ± 1.9 pmol/g for the normal group and 10.3 ± 1.8 pmol/g for the asthma group. There were no significant differences between the two groups in pulmonary β-receptor densities (Figure 2). Cardiac Bmax was 8.8 ± 2.3 pmol/g for the normal group and 9.1 ± 3.3 pmol/g for the asthma group. There were no significant differences between the two groups in cardiac β-receptor densities (Figure 3).

Relationship Between Receptor Density and Lung Function

Pulmonary Bmax was plotted against FEV_1 % predicted in the asthmatic subjects. There was a significant inverse relationship ($r = -0.83$, $p < 0.005$, $n = 10$) between the two parameters (Figure 4). No relationship was found for the normals, whose FEV_1 values were closely grouped around 100% predicted.

Relationship Between Pulmonary and Cardiac β-receptor Density

β-receptor density in lung correlated with that in heart for normal subjects ($r = 0.46$, $p < 0.01$, $n = 30$), and also for asthmatic subjects ($r = 0.74$, $p < 0.05$, $n = 10$). The correlation remained significant if both normal and asthmatic subjects were plotted together ($r = 0.53$, $p < 0.001$) (Figure 5).

DISCUSSION

In this paper, we provide the first direct evidence that β-adrenoceptor numbers in lung and heart *in vivo* are not reduced in asthmatic subjects not taking β-agonist medication. This supports the notion that there is no major primary abnormality in β-receptor expression in asthma.

Comparison with Previous Estimates

Pulmonary β-adrenergic receptor density (Bmax) of 10.9 ± 1.9 pmol/g tissue obtained in the present study for 30 normal subjects compares well with our previous reported value (14) of 10.7 ± 1.9 ($n = 18$). Our *in vivo* value has been expressed as

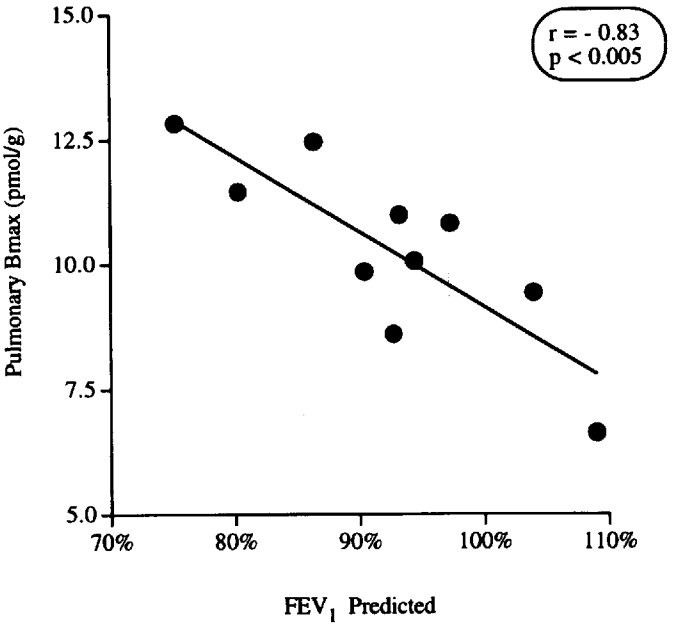

Figure 4. Inverse relationship between pulmonary β-adrenoceptor density and FEV_1 % predicted for asthmatic subjects.

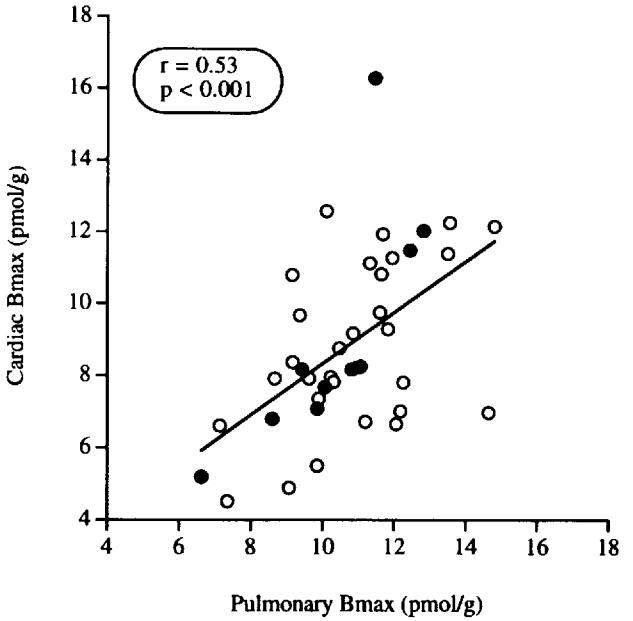

Figure 5. Relationship between cardiac and pulmonary β-receptor density. *Open circles* denote normal subjects and *closed circles* the β-agonist-free asthmatic subjects.

picomoles per gram of extravascular tissue, whereas literature values of Bmax obtained *in vitro* have been expressed as femtomoles per milligram of protein. An approximate conversion from one set of units to the other can be made assuming a tissue-to-protein ratio of 10:1 (11). Our pulmonary adrenoceptor Bmax of 10.9 ± 1.9 pmol/g would then be equivalent to 109 ± 19 fmol/mg protein. This value is of the same order as previous measurements in human lung tissue made *in vitro* with [^{125}I]cyanopindolol or [^{125}I]pindolol (mean ± SEM) of 126 ± 8.6 fmol/mg protein for tissue sections (15) and 83 ± 10 fmol/mg protein (16), 95 ± 5.5 fmol/mg protein (15), and 133 ± 6 fmol/mg protein (17) for membrane preparations, respectively. These values are all somewhat lower than those of 235 ± 26 fmol/mg protein for lung membranes previously published by Hauck and colleagues (4). The present study Bmax value of 10.8 pmol/g lung tissue is also in good agreement with our previous measurement, using (^{3}H)-CGP-12177, on resected lung tissue from patients with lung cancer, which gave a value of 99 fmol/mg protein (13).

Similarly, our cardiac Bmax value of 8.8 ± 2.3 pmol/g tissue would be equivalent to ~88 ± 23 fmol/mg protein. This value is of similar magnitude to those obtained from previous measurements made *in vitro* with [^{125}I]-cyanopindolol or [^{3}H]-CGP-12177 in nonfailing human left ventricular tissue obtained from would-be cardiac transplant donors of 79 ± 3 fmol/mg protein (n = 3) by Stiles and colleagues, 88 ± 7 (n = 12) by Bristow and colleagues and 93 ± 4 fmol/mg protein (n = 3) by Böhm and colleagues (mean ± SEM) (reviewed in Ref. 18). The present Bmax value of 8.8 ± 2.3 pmol/g tissue is somewhat lower than the value of 11.5 ± 2.2 pmol/g tissue obtained using PET in a smaller group of eight young (28 ± 7 yr of age) healthy men reported by Lefroy and associates (8).

Relationship Between β-Receptors in Lung and Heart

In majority of the subjects (26 of 30 normal and 9 of 10 in asthmatic subjects), β-receptor density was slightly higher in lung than in heart. For all normal and asthmatic subjects taken together, β-receptor density was 10.7 ± 1.9 pmol/g tissue in lung and 8.9 ± 2.5 pmol/g tissue in heart ($p = 0.0001$, paired t test). It is somewhat surprising to find a relationship between cardiac and pulmonary β-receptor density ($r = 0.53$, $p < 0.01$, $n = 40$), since the β_1 subtype dominates in the heart, whereas the β_2 subtype is more prevalent in lung.

β-Receptors in Asthmatic Subjects

The hypothesis that a reduced functioning of the β-adrenergic system might be a primary causal abnormality in asthma was first postulated by Szentivanyi in 1968 (2). Some early studies reported that the β-adrenoceptor density on circulating leukocytes, used as a surrogate for intrapulmonary β-receptor status, was reduced (3), but the results of these early studies are confounded by prior β-agonist therapy, and can be simulated in normal subjects given the same treatment (14).

In asthmatic patients, regular inhaled albuterol therapy leads to subsensitivity of systemic β-receptor responses in terms of chronotropic and hypokalemic effects (19). These studies suggest that the β-adrenoceptor dysfunction reported in asthmatic patients in early studies was likely to be due to downregulation as a result of prior chronic β-agonist therapy. Indeed, when β-agonist treatment was withdrawn, β-adrenergic responsiveness usually returned to normal (20, 21). The clinical effectiveness of β-agonists in the treatment of asthma also argues against an underlying major defect in β-receptors. A primary defect in asthma is unlikely, since blockade of β-adrenoceptors with propranolol in nonasthmatic individuals does not induce asthma or airway hyperresponsiveness (22, 23).

Studies of β-adrenoceptors utilizing postmortem asthmatic lung tissue have yielded conflicting results. Consistent with his hypothesis, Szentivanyi and colleagues (24) reported a decreased number of β-receptors in membranes of lung tissue from 12 patients with "reversible airway obstruction" (though clinical details of asthma were not included). However, using autoradiography, Spina and coworkers (5) observed a four-fold increase in β-receptor density in bronchial smooth muscle from a single severely asthmatic patient who died of myocardial infarction, compared with that in nonasthmatic bronchi obtained from victims of cardiovascular or traffic accidents. Nevertheless, the relaxant potencies of isoproterenol and fenoterol were 13- and 12-fold lower, respectively, in the isolated bronchial preparations from this asthmatic lung than in bronchi from nonasthmatic lung, as measured in functional organ bath experiments. Bai and colleagues (25) reported a three-fold increase in the number of β-receptors in asthmatic airway smooth muscle (n = 6), which was functionally hyporesponsive to isoproterenol *in vitro*. In another study, Sharma and Jeffery (17) measured β-receptor density in asthmatic lung tissue postmortem from four patients dying in status asthmaticus and compared this with the β-receptor density in control lung tissue obtained at thoracotomy from patients with bronchial carcinoma. They reported no significant change in either the total pulmonary receptor pool (lung tissue homogenate) or in airway smooth muscle (cryostat sections).

Thus, β-receptor-mediated relaxant abnormalities in airway smooth muscle, as demonstrated *in vitro* in fatal asthma, cannot be explained by a decrease in receptor number. A major limitation is that these results may apply to only a small subgroup of very severely asthmatic patients. Indeed, in peripheral lung resected from patients with mild asthma, there was no difference in either β-receptor density or affinity as compared with control lungs (26). Most of the asthmatic patients (all in Bai and colleagues' study and two of four in Sharma and Jeffery's study) were taking inhaled β-agonists and/or inhaled or oral steroids during the final attack. It is also possible that endogenous catecholamine and corticosteroid levels were increased during the fatal attack. All these premortem factors may have affected β-receptor

expression and may therefore hinder an accurate interpretation of the results. On the other hand, none of the 10 mildly asthmatic subjects in the present study had taken any antiasthma drugs for at least 4 wk prior to the measurements. Our results from asthmatic subjects not receiving β-agonist medication clearly indicate that pulmonary and myocardial β-adrenoceptor numbers in asthmatic subjects are perfectly normal, in accord with the typical response of subjects with well-controlled asthma to low doses of inhaled β-agonists (1).

Relationship Between Bmax and FEV_1

FEV_1 was plotted against Bmax for the asthmatic group (no correlation was found for the normal group). We were surprised to find an inverse relationship between FEV_1 % predicted and pulmonary β-receptor density (Figure 4) in the asthmatic subjects. Even though FEV_1 measurements were not always obtained on the same day as the PET scan (up to 5 d previously), these asthmatic subjects were not receiving β-agonist medication during this period, and did not develop symptoms, and we believe that their FEV_1 values were representative (*see* METHODS). The reason for such a relationship is unclear. The FEV_1 value is influenced by multiple factors besides β-adrenoceptor density and bronchial tone. Asthmatic subjects with a baseline FEV_1 of 70% predicted (Figure 4) probably have a greater degree of mucus plugging and airway inflammatory changes. This may lead to β-receptor uncoupling, and the increase in Bmax could be a compensatory mechanism to overcome this. In the extreme case of fatal asthma, β-adrenergic-receptor autoradiographic grain density was increased in tracheal and bronchial sections as compared with that in patients dying acutely from nonpulmonary causes, and smooth muscle relaxation responses to isoproterenol were impaired (25). Therefore, one of the reasons for the correlation of pulmonary β-receptor numbers with asthma severity might be as a response to inflammatory mediators or as compensation for the associated receptor uncoupling.

In summary, we quantified pulmonary and cardiac β-adrenoceptor expression in subjects with mild asthma *in vivo* using PET, and found no differences from that in normal controls. It would be interesting to study subjects with severe asthma; unfortunately, it would be very difficult to withdraw them from medication, which would be a confounding issue. These findings support the view that an intrinsic deficit in global β-receptor numbers in the lung is unlikely in asthma, but do not exclude heterogeneity in receptor density between different tissues (e.g., in bronchial smooth muscle versus alveolar tissue).

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