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High Thoracic Epidural Anesthesia Does Not Alter Airway Resistance and Attenuates the Response to an Inhalational Provocation Test in Patients with Bronchial Hyperreactivity

Harald Groeben, M.D., Andreas Schwalen, M.D.,† Stefan Irsfeld,‡ Jörg Tarnow, M.D., F.R.C.A.,§ Peter Lipfert, M.D.,‖ Hans-Bernd Hopf, M.D.‖*

Background: **The functional relevance of an intact pulmonary sympathetic innervation for airway resistance is unknown. We therefore evaluated whether or not pulmonary sympathetic denervation by thoracic epidural anesthesia decreases the threshold of an inhalational provocation with acetylcholine in 20 patients with documented bronchial hyperreactivity scheduled for elective upper abdominal or thoracic surgery.**

Methods: **Baseline inhalational provocation with acetylcholine was performed 2–4 days before surgery. The acetylcholine threshold concentration for a hyperreactivity response (*i.e.*, for a 20% decrease in forced expiratory volume in 1 s and a 100% increase in total respiratory resistance by oscillometry) was determined. On the day of surgery a second inhalative provocation with acetylcholine was performed 45 min after the patients had received 6–8 ml epidural bupivacaine 0.75% (n = 10), intravenous bupivacaine (1.2 mg · min^{-1}, n = 6), or 6–8 ml epidural saline (n = 4). The acetylcholine threshold concentration for a hyperreactive response was again determined. We also measured vital capacity, forced expiratory volume in 1 s as a percentage of vital capacity, spread of sensory blockade (pin prick), skin temperature on hand and foot (telethermography).**

Results: **During thoracic epidural anesthesia, C4–T8 skin temperature increased significantly on hand and foot indicating widespread sympathetic blockade including the lungs. Compared to values obtained immediately before pulmonary sympathetic blockade, forced expiratory volume in 1 s as a percentage of vital capacity, and total respiratory resistance by oscillometry remained unchanged, while vital capacity decreased. Compared to baseline the acetylcholine threshold concentration for the hyperreactive response increased threefold after epidural as well as after intravenous bupivacaine. Epidural saline evoked no directional changes in the acetylcholine threshold concentration.**

Conclusions: **We conclude that in patients with bronchial hyperreactivity 1. blockade of pulmonary sympathetic innervation seems to be of no relevance for airway resistance and 2. both epidural and intravenous bupivacaine substantially attenuate the response to an inhalational provocation with acetylcholine. (Key words: Anesthetics, regional: bupivacaine. Anesthetic techniques: epidural. Sympathetic nervous system. Lung(s): airway resistance; bronchospasm.)**

WHETHER sympathetic innervation of the human bronchial system is of functional and clinical importance remains controversial.[1–5] In patients with chronic obstructive pulmonary disease or bronchial hyperreactivity (asthma) β-adrenoceptor blockade results in a increased airway resistance.[6,7] However, the effects of a preganglionic sympathetic blockade in these patients are unknown. Because direct stimulation of sympathetic nerves in isolated tissue from human trachea and peripheral lung tissue relaxes airway smooth muscle, some bronchodilating capacity of an intact sympathetic innervation on the human bronchial system has been assumed.[4,8]

If sympathetic innervation indeed has an influence on bronchial smooth muscle tone, preganglionic sympathetic blockade induced by thoracic epidural anesthesia should increase both airways resistance and susceptibility to bronchoconstriction preferentially in patients with bronchial hyperreactivity. In fact, the development of severe bronchoconstriction during high thoracic epidural or spinal anesthesia has been reported in these patients.[9–11]

* Staff Anesthesiologist, Institut für Anaesthesiologie.

† Resident, Klinik für Kardiologie, Pulmonologie und Angiologie.

‡ Resident, Institut für Anaesthesiologie.

‖ Assistant Professor of Anesthesiology, Institut für Anaesthesiologie.

§ Professor of Anesthesiology and Chair, Institut für Anaesthesiologie.

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Address reprint requests to Dr. Groeben: Anesthesiology and Critical Care Medicine, The Johns Hopkins Hospital, 600 North Wolfe Street, Meyer 295, Baltimore, Maryland 21287-7294.

Accordingly, we evaluated lung function both before and in the presence of pulmonary sympatholysis induced by high thoracic epidural anesthesia in patients with known bronchial hyperreactivity. Because the importance of an intact bronchial sympathetic innervation might be evident only during a bronchoconstrictive challenge, we performed an inhalational provocation test with acetylcholine before and during thoracic epidural anesthesia.

Materials and Methods

Patients

After institutional approval and the patients' informed written consent, 20 nonpremedicated patients (ASA physical status 2–3) of either sex (age 50 ± 7 yr, mean ± SD), scheduled for elective upper abdominal surgery, were consecutively enrolled in the study.

All patients had a history of acute dyspneic attacks relieved by inhalation of a bronchodilating aerosol. During the last years all patients had been successfully treated with β-mimetic aerosols, but none used the aerosol 24 h before the investigation. None of the patients received corticosteroids within the last six weeks. In the first part of the study ten patients received epidural bupivacaine and four epidural saline. In the second part, six patients received bupivacaine intravenously and saline epidurally. These three groups did not differ with respect to age, body weight, height, or smoking habits (table 1).

Table 1. Demographic Data of Patients

	Age (yr)	Weight (kg)	Height (cm)	Smoking History (py)
Thoracic epidural anesthesia	51 ± 8	72 ± 10	175 ± 6	29 ± 16
Bupivacaine intravenously	49 ± 7	71 ± 11	176 ± 5	26 ± 12
Saline epidurally	50 ± 4	67 ± 15	181 ± 7	30 ± 9

Values are mean ± SD.

py = pack years, *i.e.*, packs of cigarettes a day per year.

Methods

The same room with an average ambient temperature of 24.3 ± 0.6°C was used throughout the study. All measurements were done with the patient lying supine. Two to 4 days before surgery bronchial hyperreactivity was verified by an inhalational provocation with acetylcholine.[12,13] Acetylcholine inhalation was performed with an air compressing nebulizer (Pari Inhalierboy, Pari Werk, Germany). Each inhalation period lasted 2 min with stepwise increase in the concentrations of acetylcholine (0.5%, 1%, and 3%) diluted in 0.9% saline solution until a hyperreactive response was obtained. The response was defined as hyperreactive when forced expiratory volume in 1 s (FEV_1) had decreased by at least 20%.[12,13] Before the interventions all patients had a hyperreactive response to acetylcholine-concentrations less than 3%.

The FEV_1 and the vital capacity (VC) were obtained using a pneumotachograph (Siregnost FD1, Siemens, Germany). FEV_1 and VC were measured three times with the most normal result chosen for further analysis.

To control the FEV_1 measurement by a method independent of the patient's effort and cooperation, we simultaneously measured total respiratory resistance and calculated the threshold for a 100% increase. Total respiratory resistance was measured oscillometrically (Siregnost FD5, Siemens, Erlangen, Germany), as described previously.[14] This method has been validated in terms of reproducibility and sensitivity by body plethysmography[15] and has the advantage of being useful in supine subjects. In brief, the patient breathes through a tube as a reference resistance, with an oscillating flow interposed between mouth and tube. The tube has a diameter of 12 mm and a length of 1 m, representing a resistance of 10 $mbar \cdot l^{-1} \cdot s$ for a oscillating frequency of 10 Hz and a oscillating volume of 0.7 ml. The alternating pressure is picked up by a microphone membrane. Because flow and reference resistance are known, the change in pressure reflects changes in respiratory resistance expressed in $mbar \cdot l^{-1} \cdot s$.

FEV_1, VC, and total respiratory resistance were evaluated after the inhalation of each acetylcholine concentration. The acetylcholine threshold concentrations necessary for the 20% decrease in FEV_1 and the 100% increase in total respiratory resistance were calculated for each patient.[12] In case that the patient did not respond with a 20% decrease in FEV_1 until the inhalation of 3% acetylcholine, the threshold has to be calculated by extrapolation.[12] This was only the case after epidural or intravenous administration of bupivacaine.

On the morning of surgery, after administration of regional anesthesia, a radial artery was cannulated percutaneously for arterial blood pressure measurement and blood sampling. Also during regional anesthesia, a central venous catheter was placed intrathoracically

via the basilic or the right internal jugular vein; the correct position was judged from the pressure tracing. Arterial and central venous pressures were measured electromanometrically (B. Braun, Melsungen, Germany) with the midthorax level as zero reference. Heart rate was derived from the electrocardiogram (lead II). Arterial pressure, central venous blood pressure, and heart rate were recorded continuously on a multichannel recorder.

Epidural catheterization was performed between the T4–T6 interspace with the patient in the lateral decubitus by the loss-of-resistance technique with air and the catheter advanced 5–10 cm into the epidural space.

After 30 min of rest baseline values were evaluated, including FEV_1, VC, total respiratory resistance by oscillometry, and functional residual capacity, measured by the helium dilution technique[16] (Siregnost FD5, Siemens).

Thereafter ten patients received epidural bupivacaine 0.75%, the dose adjusted to each patient's height (mean dose 7.9 ± 0.7 ml). Sensory block was assessed 15, 30, and 45 min after epidural injection by pin prick and loss of cold sensation (alcohol spray). Borders were defined as the most cranial and caudal dermatome unresponsive to the respective stimulus.

As an indicator of sympathetic blockade, skin temperatures were measured at the thumb and fifth toe before and 5, 15, 30, and 45 min after epidural injection by infrared telethermometry (Bio-Therm C-600M, Linear Laboratories, Los Altos, CA).

Forty-five minutes after epidural injection (*i.e.*, after complete spread of epidural anesthesia) lung function tests were repeated, followed by a second inhalational provocation with acetylcholine as described previously.

To account for any time-dependent effects, four additional patients received epidural saline (7.5 ml).

Finally, to evaluate possible systemic effects of bupivacaine on airway resistance or the response to the inhalational challenge six patients received saline epidurally but 1.2 $mg \cdot min^{-1}$ bupivacaine intravenously for 45 min after an otherwise identical protocol. The dose of intravenous bupivacaine was appropriate to achieve plasma bupivacaine concentrations in the range of or greater than those observed after epidural injection.[17]

Arterial blood samples for measurements of bupivacaine plasma concentrations and blood gas analyses were withdrawn before and 45 min after epidural injection or intravenous bupivacaine infusion. Arterial blood gases were determined by an automatic blood gas analyzer (ABL3, Radiometer, Denmark). Arterial bupivacaine plasma concentration were attained by capillary gas chromatography (Sichromat 3, nitrogen detector, Siemens), as described previously,[18] using mepivacaine as internal standard.

Data Analysis

Data are presented as means ± SD. Measurements before epidural injection were defined as baseline. Two *a priori* null hypotheses were tested: (1) there is no difference in variables before and 45 min after epidural injection of bupivacaine; and (2) acetylcholine concentration threshold for a hyperreactive response remains unchanged after epidural or intravenous bupivacaine. Values before and after epidural or intravenous injection of bupivacaine were compared by Wilcoxon's rank test. Null hypotheses were rejected and significance assumed with $P < 0.05$.

Results

Baseline acetylcholine provocation 2–4 days before surgery revealed the following acetylcholine threshold concentrations for the 20% decrease in FEV_1 (means ± SD): 0.9% ± 0.5% acetylcholine for patients scheduled for epidural bupivacaine, 1.3% ± 0.9% acetylcholine for patients scheduled for epidural saline, and 1.1% ± 0.7% acetylcholine for those scheduled for intravenous bupivacaine. These thresholds did not differ among the groups. Thus all patients were comparably hyperreactive.

The time course of sensory blockade after the epidural administration of bupivacaine along with skin temperatures is shown in figure 1. Forty-five minutes after the epidural injection of bupivacaine, the spread of the sensory blockade was 12.7 ± 1.7 segments (pin prick), with a cranial border of C4 ± 1.1 and a caudal border of T8 ± 2.3 (at least T6). The cranial border of loss of cold sensation was identical, the caudal border exceeded pin prick blockade by one segment. Thus, pulmonary sympathetic fibers, emerging from the spinal cord between T2–T7, were blocked.

As an indicator of sympathetic blockade skin temperatures significantly increased on the thumb (spinal segment C6) from 31.4 ± 2.9°C to 34.0 ± 1.6°C and fifth toe (S1) from 28.1 ± 3.0°C to 32.5 ± 2.6°C. In addition, mean arterial pressure and heart rate decreased significantly, by 10 ± 12 mmHg and 10 ± 8 $beats \cdot min^{-1}$, respectively, also indicating sympathetic blockade, while central venous pressure and arterial

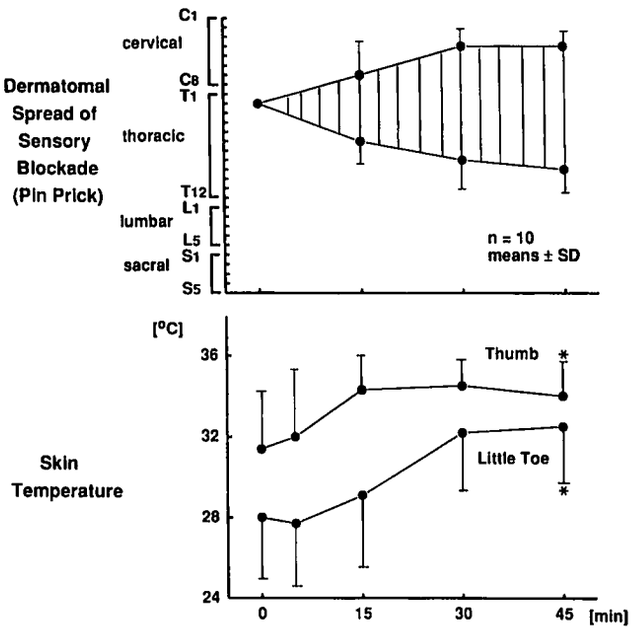

Fig. 1. Time course of dermatomal spread of sensory blockade (measured by the response to pin prick stimulation) along the spinal axis (*top*) and skin temperature on thumb and fifth toe (*bottom*) before and during high thoracic epidural anesthesia. Data represents means ± SD for ten patients. Epidural injection of a mean dose of 7.9 ml bupivacaine 0.75% resulted in a sensory blockade from C4 to T8. As an indicator of widespread sympathetic blockade, skin temperature increased significantly on both the thumb and fifth toe. *$P < 0.05$.

blood gas values remained unchanged (table 2). After intravenous bupivacaine or epidural saline, skin temperatures, mean arterial pressure and heart rate did not change. Mean arterial pressure and heart rate are shown in table 2.

In the presence of pulmonary sympathetic denervation before the provocation test, total respiratory resistance (by oscillometry), FEV_1 in percentage of VC, and functional residual capacity essentially did not increase, while VC decreased (table 2). Thus, blockade of neural sympathetic outflow to the lung seems to be of no relevance for airway resistance at rest.

The effects of thoracic epidural anesthesia, intravenous bupivacaine or epidural saline on the acetylcholine threshold concentrations are shown in figure 2. Regardless of whether bupivacaine was administered epidurally or intravenously, the acetylcholine threshold for a 20% decrease in FEV_1 (fig. 2) increased substantially, by three to four times, after epidural bupivacaine (from 0.9% to 2.9% acetylcholine) and after intravenous bupivacaine (from 1.1% to 4.0% acetylcholine). The acetylcholine threshold for a 100% increase in total respiratory resistance by oscillometry increased after epidural (from 1.5% ± 1.0% to 4.3% ± 3.9% acetylcholine) and intravenous bupivacaine (from 1.7% ± 0.8% to 4.7% ± 2.0% acetylcholine).

Thus, both epidural and intravenous bupivacaine, substantially and significantly ($P < 0.05$) attenuated the response to an inhalational challenge with acetylcholine, whereas no directional changes were observed after epidural saline.

Forty-five minutes after epidural injection of bupivacaine, mean bupivacaine plasma concentration was 0.91 ± 0.49 $\mu g \cdot ml^{-1}$, while intravenous bupivacaine infusion led to a plasma concentration of 1.75 ± 0.71 $\mu g \cdot ml^{-1}$ (table 2).

Discussion

This study has yielded two main findings. First, in patients with bronchial hyperreactivity, blockade of pulmonary sympathetic efferents does not increase airway resistance at rest; second, epidural as well as intravenous bupivacaine substantially attenuates the airway response to an inhalational challenge with acetylcholine. These conclusions were drawn under the following premises: (1) other variables possibly influencing airway resistance were controlled or excluded; (2) bronchi were sympathetically denervated; and (3) patients with bronchial hyperreactivity are the most susceptible subjects to study even small changes in airway resistance.

Other variables influencing airway resistance in humans, such as drugs, blood volume expansion,[19] or ambient temperature,[20] either were kept constant or excluded. All patients were free of any drug treatment affecting our measurements and CVP remained constant, indicating no relevant shift in central blood volume. Ambient temperature was constant during our study, excluding any temperature effect on airway resistance.

Time dependent effects on airway resistance can also be excluded, because epidural saline had no directional effects on measured variables. Thus, it can be excluded that environmental and study design factors have influenced our results.

Because sensory blockade extended from C4 to T8 and pulmonary sympathetic efferents emerge from the spinal cord between T2 and T7,[21] pulmonary sympatholysis can be assumed. Moreover, temperature increased on the thumb (C6) as well as on the fifth toe

(S1), indicating widespread sympathetic blockade including the lungs.[22] In addition, mean arterial blood pressure and heart rate decreased significantly during epidural anesthesia also indicating sympathetic blockade. Finally, in anesthetized dogs epidural blockade from C7 to T6 abolished cardiac sympathetic nerve activity during rest and its increase provoked by coronary artery constriction.[23] Because efferent pulmonary sympathetic fibers (T2–T7) nearly match cardiac sympathetic fibers (T1–T4)[21] it can be assumed, that pulmonary sympathetic denervation was complete in our patients with a sensory blockade extending from C4 to T8.

Because patients or volunteers free from obstructive lung disease are neither susceptible to inhaled parasympathomimetics nor to intravenously administered β-adrenoceptor antagonists, changes in airway resistance induced by pulmonary sympathetic blockade might not be detected in healthy subjects, even if present at all.[1] Accordingly, we studied patients with bronchial hyperreactivity. Because such patients are highly susceptible to β-adrenoceptor blocking agents[6,7] and, by definition, to inhalational provocation tests,[24] they are supposed to be the most susceptible to changes in airway resistance induced by sympatholysis.

Thus, even small changes in airway resistance at rest and during inhalational provocation with acetylcholine before and during pulmonary sympathetic denervation by thoracic epidural anesthesia should be detected.

β-Adrenoceptor blocking drugs (even those with a supposed β_1 selectivity) are known to cause severe

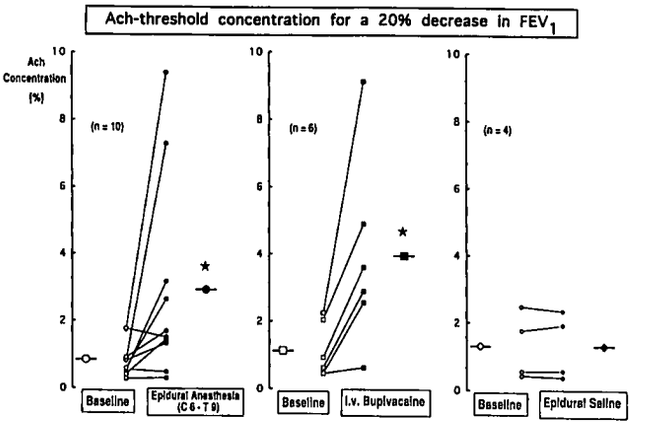

Fig. 2. Concentration of inhaled acetylcholine (Ach) necessary for a 20% decrease of FEV_1. Each pair of symbols = one patient subjected to an inhalational challenge before (open symbols) and after (filled symbols) epidural anesthesia, intravenous bupivacaine, or epidural saline. Mean values are shown beside individual values. Baseline thresholds refer to the provocation 2–4 days before surgery. On the day of surgery a second provocation was performed 45 min after epidural injection of 6–8 ml bupivacaine 0.75%, intravenous infusion of bupivacaine (1.2 mg · ml^{-1} for 45 min), or epidural saline. *$P < 0.05$.

bronchoconstriction in patients with chronic obstructive pulmonary disease and asthma.[6,7] However, despite its widespread clinical use the consequences of neural sympathetic blockade by thoracic epidural anesthesia for human airway resistance are unknown. *In vitro*, a bronchodilating effect has been shown by direct electrical stimulation of sympathetic ganglia (tracheal ganglia, stellate ganglion) and isolated bronchial and tra-

Table 2. Respiratory and Hemodynamic Variables (mean ± SD) and Bupivacaine Plasma Concentrations before and during Pulmonary Sympathetic Denervation by Thoracic Epidural Anesthesia (n = 10), before and after Intravenous Bupivacaine (n = 6), and Epidural Saline (n = 4), Respectively

	Baseline	Epidural Bupivacaine	*P* Value	Baseline	Intravenous Bupivacaine	*P* Value	Baseline	Epidural Saline
Ros (mbar · L^{-1} · s)	3.9 ± 1.3	3.8 ± 1.3	0,234	3.3 ± 0.7	3.3 ± 0.6	0,529	3.1 ± 0.7	3.1 ± 0.7
VC (L)	3.24 ± 0.78	2.91 ± 0.64	0,033	3.89 ± 1.04	3.80 ± 1.07	0,208	3.96 ± 0.66	4.10 ± 0.76
FEV1 (L)	2.61 ± 0.90	2.31 ± 0.81	0,014	3.22 ± 0.94	3.13 ± 0.91	0,208	3.37 ± 0.92	3.41 ± 0.88
FEV1 (%)	79.8 ± 11.6	79.3 ± 14.3	0,726	85.2 ± 9.8	87.8 ± 6.1	0,295	83.5 ± 9.1	82.5 ± 7.6
FRC (L)	3.85 ± 0.93	3.68 ± 1.02	0,234	3.98 ± 0.33	3.96 ± 0.53	0,834	3.93 ± 0.22	3.94 ± 0.29
Pa_{O_2} (mmHg)	88 ± 11	89 ± 10	0,767	92 ± 6	92 ± 5	0,855	93 ± 5	92 ± 4
Pa_{CO_2} (mmHg)	38 ± 3	39 ± 3	0,735	39 ± 1	39 ± 1	0,899	37 ± 1	37 ± 1
MAP (mmHg)	97 ± 13	87 ± 18	0,044	104 ± 14	105 ± 10	0,893	88 ± 8	90 ± 9
HR (min)	75 ± 8	66 ± 8	0,006	82 ± 22	83 ± 19	0,753	73 ± 9	73 ± 6
CVP (mmHg)	5 ± 3	5 ± 3	0,499	5 ± 2	5 ± 2	0,371	4 ± 3	4 ± 2
Bupivacaine (μmol · L^{-1})	0.05 ± 0.03	0.91 ± 0.49	0,004	0.02 ± 0.02	1.75 ± 0.71	0,031	0.03 ± 0.03	0.02 ± 0.01

R_{os} = oscillometrically measured airway resistance; VC = vital capacity; FEV1 = forced expiratory volume in 1 s; FRC = functional residual capacity; PA_{O_2} and Pa_{CO_2} = arterial partial pressure of oxygen and carbon dioxide, respectively; MAP = mean arterial pressure; HR = heart rate; CVP = central venous pressure.

cheal tissue.[1,4,8] This suggests but does not prove some importance of neural sympathetic outflow in the regulation of human airway resistance. The clinical relevance of our study is underlined by three case reports of severe acute bronchospasm in patients with chronic obstructive pulmonary disease or asthma developing during high thoracic epidural or spinal anesthesia.[9-11]

In contrast, our results in patients with bronchial hyperreactivity do not support this view. That blockade of neural sympathetic outflow to the lungs does not seem to be of any relevance for airway resistance even in patients with bronchial hyperreactivity neither at rest nor in response to a bronchoconstrictive challenge might have several explanations.

First, pulmonary β_2 adrenoceptors outnumber β_1 adrenoceptors by far (three- to fourfold).[25,26] In contrast to β_1 adrenoceptors, β_2 adrenoceptors are not innervated sympathetically and are stimulated preferentially by circulating catecholamines.[5,6,25] Because epidural anesthesia does not depress circulating catecholamines[27] β_2 adrenoceptors remain unaffected from pulmonary sympathetic blockade.

Second, an uneven anatomic distribution of β-adrenoceptors in addition to the unequal ratio of β adrenoceptor subtypes might be responsible for the unchanged airway resistance in our patients. On the one hand, Carstairs and coworkers[26] have shown by autoradiography in human lungs, that about 90% of β_1 and β_2 adrenoceptors are located in alveolar walls, with only 10% located in airway smooth muscle, glands, and epithelium. However, these authors were unable to detect β_1 adrenoceptors in airway smooth muscle, possibly due to limitations of the technique. On the other hand, electron microscopic studies have shown a direct β_1 adrenoceptor–mediated sympathetic innervation of bronchial smooth muscle in humans.[2-4] Thus, the number of β_1 adrenoceptors in human bronchial smooth muscle might be too small and, based on our data, it can be assumed that the blockade of these receptors is of no clinical relevance for airway resistance.

Most important, the acetylcholine threshold for a bronchoconstrictive challenge even increased three- to fourfold in our patients with bronchial hyperreactivity during epidural anesthesia. Because intravenous and epidural bupivacaine led to the same attenuation of bronchial hyperreactivity bupivacaine absorption into the blood is the most likely explanation for the increase in the acetylcholine threshold after epidural anesthesia. This conclusion is supported by experiments in anesthetized dogs undergoing inhalational challenge with and without previous intravenous administration of lidocaine.[28] Intravenous lidocaine leading to blood concentrations of 1.5–2.5 $\mu g \cdot ml^{-1}$ abolished reflex bronchospasm in response to nonspecific (citric acid) and significantly reduced bronchial hyperreactivity induced by specific (ascaris antigen) inhalational challenge.

In summary, our results show that, in patients with bronchial hyperreactivity, blockade of sympathetic efferent drive of the lungs does not increase airway resistance. Moreover, both epidurally and intravenously administered bupivacaine substantially increased the threshold for a bronchoconstrictive response, and the patients were less susceptible to the challenge. Finally our data suggest that the reported cases of severe bronchospasm during epidural anesthesia are unrelated to sympathetic blockade and may be caused by mechanisms other than pulmonary sympathetic denervation.

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