The Effect of Esmolol on Cerebral Blood Flow, Cerebral Vasoreactivity, and Cognitive Performance: A Functional Magnetic Resonance Imaging Study

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Background: Esmolol is often applied perioperatively to maintain stable hemodynamic conditions in neurosurgical patients. Little is known, however, about its effects on cerebral circulation. The authors employed functional magnetic resonance imaging based on blood oxygenation level-dependent contrast to explore the effect of esmolol on the human brain. The purpose of the study was to investigate the effect of esmolol on cerebral blood flow, cerebral vasoreactivity, and cognitive performance.

Methods: Ten healthy volunteers were investigated in two separate experimental sessions using functional magnetic resonance imaging. During the first experimental session, a hyperventilation task and a cognitive task, subjects had to perform both tasks twice, once after administration of an esmolol bolus of 1 mg/kg followed by a continuous infusion of 150 μg · kg⁻¹ · min⁻¹ and once without β-blockade, in a random order. During the second experimental session subjects were scanned at resting state after administration of esmolol. Furthermore, the effect of the esmolol dose on hemodynamic changes caused by β-adrenergic stimulation with orciprenaline was investigated.

Results: Esmolol decreased heart rate and blood pressure during the various experimental conditions and blunted the increase in heart rate and blood pressure caused by orciprenaline. Infusion of esmolol affects neither the blood oxygenation level-dependent contrast during the functional challenges nor the reaction times during the cognitive task. However, the esmolol bolus caused a brief blood oxygenation level-dependent contrast increase.

Conclusion: The results indicate that effective β-blockade with esmolol does not affect cerebral blood flow, cerebrovascular reactivity, or cognitive performance.

CEREBRAL blood vessels constrict in response to increases in blood pressure or dilate as blood pressure decreases to ensure a constant cerebral blood flow (CBF). This modulatory phenomenon is known as the principle of cerebral autoregulation.¹ There are several situations (e.g., brain trauma, brain surgery, carotid endarterectomy) in which cerebral autoregulation is impaired. In these situations, marked increases of systemic blood pressure should be treated promptly to avoid cerebral hyperperfusion, preferably using drugs that do not affect cerebral circulation or cerebral vasoreactivity.

The β₁-antagonist esmolol, with its unique pharmacokinetic features (rapid onset of activity after intravenous injection and full recovery from β-blockade within 20 min),² is often used to control heart rate and blood pressure perioperatively. The hydrophilic properties of esmolol suggest that the drug does not cross the blood-brain barrier and thus does not alter cerebral circulation. However, this assumption has never been tested in humans. Moreover, indirect effects of esmolol on cerebral vasomotor tone might be expected because the drug decreases heart rate, blood pressure, and cardiac output.³ Within the autoregulatory range these global hemodynamic changes cause a brief decrease in CBF in patients with intact cerebral autoregulation⁴,⁵ and even a permanent CBF decrease when blood pressure decreases to less than the lower limit of autoregulation.

Moreover, recent studies demonstrated that esmolol reduces anesthetic requirements during surgery and depresses electrocortical activity during anesthesia.⁶–⁸ Although several theories have been put forward to try to explain the cortical suppression under esmolol (e.g., regional effects of esmolol on CBF or, alternatively, central drug action)⁶–⁸ the precise mechanism underlying this phenomenon remains to be elucidated.

Functional magnetic resonance imaging (fMRI) based on blood oxygenation level-dependent (BOLD) contrast offers the possibility of investigating central nervous system drug effects noninvasively.⁹ This technique uses deoxyhemoglobin as a natural contrast agent that distorts the local magnetic field as a result of its paramagnetic properties. Because changes in CBF are accompanied by changes in the deoxyhemoglobin concentration, any alteration in regional or global CBF (e.g., resulting from neural activation, pharmacological interventions, or hypocapnia) can be visualized by BOLD-based fMRI.¹⁰ Using this technique, BOLD signal increases have been reported for cerebral vasodilators,¹¹ whereas cerebral vasoconstrictors have been shown to produce BOLD signal decreases.¹²–¹⁴

We employed fMRI to investigate the effects of esmolol on CBF, cerebral vasoreactivity, and cognitive function in human volunteers. The BOLD signal was thus measured at rest, during a hyperventilation challenge, and during a cognitive task in the presence and absence of β-blockade. Because of the hydrophilic properties of esmolol, no direct effects on cerebral circulation or any effects on the parameters of cognitive performance were expected. However, esmolol might have been expected...
to indirectly affect the BOLD signal as a result of changes in the cerebral vasomotor tonus or a CBF decrease induced by global hemodynamic changes. A CBF decrease would increase the deoxyhemoglobin concentration (via reduced deoxyhemoglobin washout) and would cause a decrease in the BOLD signal.

Materials and Methods

Subjects

Ten healthy young volunteers (four females, six males, all right-handed) between the ages of 22 and 29 yr participated in the study. None of the subjects had a history of cardiac or neurologic disease. All subjects had normal or corrected-to-normal vision and normal color vision and were native German speakers. This study was approved by the local Ethics Committee of the Medical School, University of Leipzig, Leipzig, Germany. Written informed consent was obtained from each participant after detailed information about the experiment had been given and before the study itself. Subjects were instructed to refrain from consuming alcohol, nicotine, and caffeine or using any medication before the experiment. All subjects were again instructed on the task immediately before the actual experimental session.

Each subject underwent two different MRI sessions. One session was aimed at monitoring immediate drug effects on the BOLD response at rest, whereas the other session was aimed at investigating the effect of esmolol on the BOLD response to hyperventilation and to a cognitive task. In addition, another experiment was performed to demonstrate the efficacy of esmolol to produce a β-blockade. With this objective in mind, eight of the 10 subjects were investigated again in a double-blinded, placebo-controlled trial.

Experimental Procedure of the fMRI Experiments

The subjects were positioned supine on the gantry of the scanner. Foam padding was used to limit head movements. For the application of esmolol, an intravenous catheter was inserted in the right forearm. Heart rate, noninvasive blood pressure, end-tidal carbon dioxide partial pressure, and arterial oxygen saturation were monitored and recorded during the entire experimental session using an magnetic resonance-compatible monitoring system (MagLife C plus, Schiller Medizintechnik AG, Baar, Switzerland).

MRI monitoring of the drug effect on BOLD signal at rest was based on a 20-min protocol. An esmolol bolus (Brevibloc® 100 mg/10 ml, Baxter Deutschland GmbH, Unterschleißheim, Germany) of 1 mg/kg body weight was slowly administered (over 2 min) 1 min after the onset of scanning by one investigator (W.H.). Subjects were not informed exactly when during the experiment esmolol administration was scheduled (i.e., they were unaware of the exact moment of intravenous injection). The drug bolus was followed by a constant infusion rate of 150 μg·kg⁻¹·min⁻¹ of esmolol (Brevibloc® 2.5 mg/10 ml, Baxter Deutschland GmbH, administered in a diluted solution as recommended by the manufacturer) for 2 min. Then, esmolol infusion was stopped. Subjects were scanned for 15 min longer to evaluate possible recovery effects from β-blockade.

The experimental session performed to assess the effects of esmolol on cognitive function and cerebral vasoractivity comprised two identical subsessions, each consisting of two tasks (fig. 1). Each session started with the Stroop task as cognitive challenge. The Stroop task has been chosen for this purpose because its usefulness to assess drug effects on the brain has been repeatedly demonstrated. Moreover, the task has been recently adapted for fMRI experiments. The Stroop task was followed by a hyperventilation task. Subjects had to perform one experimental session under β-blockade (esmolol experiment); the other session served as a control experiment. In random order, one half of the subjects performed the esmolol experiment first and the other half started with the control experiment. Subjects were not informed whether they would be starting with the esmolol or the control experiment. Between the two experimental blocks at least 20 min of rest period was set. This break allowed subjects who performed the esmolol experiment first to recover from β-blockade and was used to acquire individual anatomical images.

At the beginning of the esmolol experiment, an esmolol bolus of 1 mg/kg body weight was slowly injected (over 2 min) by one investigator. Then, esmolol infusion
was initiated with a constant rate of 150 μg·kg⁻¹·min⁻¹ using a magnetic resonance-compatible infusion system. The actual experiment was started after a 2-min delay to allow for full β-blockade. Esmolol infusion was stopped after subjects had finished both tasks.

**Color-Word Matching Stroop Task**

The Color-Word Matching Stroop task was presented in a blocked design. During the task subjects were offered two rows of letters on a screen. Subjects were asked to give a yes/no button-press answer indicating whether the color of the letters on the top row corresponded to the color name printed in black on the bottom row. Two different conditions of the Stroop task were used: an easier neutral condition (the letters in the top row were "XXXX" printed in red, green, blue, or yellow, and the bottom row consisted of the color words "RED," "GREEN," "BLUE," and "YELLOW" printed in black) and a more difficult incongruent condition (the letters of the top row consisted of the color words "RED," "GREEN," "BLUE," and "YELLOW" printed in an incongruent color, e.g., "green" printed in red) (fig. 1). In half of the trials in both conditions the color in the top row corresponded to the color name of the bottom row. "Matches" and "mismatches" were presented randomly. One block consisted of 12 trials, each lasting approximately 1.5 s (resulting in a block time of approximately 20 s). The first block was preceded and the other blocks were followed by a 10 s fixation on a small dot (baseline condition). Twenty blocks (10 "neutral" and 10 "incongruent" blocks) were presented in pseudorandom order during one experimental run. This procedure resulted in 120 trials of each type and a scan time of 10 min and 10 s.

**Hyperventilation Task**

Subjects were asked to perform voluntary hyperventilation for 2 min on request by one investigator. End-tidal carbon dioxide partial pressure was monitored via a nasal cannula using the Maglifc capnometer (Maglifc C plus, Schiller Medizintechnik AG, Baar, Switzerland). The hyperventilation task design was as follows: periods of hyperventilation (activation condition, three periods of 2 min) were alternated with 2 min of normal ventilation. The first hyperventilation period was preceded and the third hyperventilation period was followed by 1 min investigation of normal ventilation, resulting in a scan time of 12 min during the hyperventilation run (fig. 1).

In addition to the fMRI experiments, eight subjects (all of whom took part in the actual fMRI experiments) were investigated again in a placebo-controlled, double-blind trial to demonstrate the efficacy of the esmolol dose studied to produce β-blockade (orciprenaline experiment). This experiment was performed outside the magnetic resonance scanner. At the beginning of the orciprenaline experiment, half of the subjects randomly received an esmolol bolus (1 mg/kg) followed by an esmolol infusion (150 μg·kg⁻¹·min⁻¹). The other half of the subjects started this experiment with a placebo bolus (NaCl 0.9%) followed by a placebo infusion. Three minutes after the esmolol infusion (or the placebo infusion) had been initiated, a single dose (2 μg/kg) of the β-agonist orciprenaline (Alupent®, Boehringer Ingelheim, Germany) was intravenously administered to all participants. The orciprenaline bolus was followed by an orciprenaline infusion of 0.3 μg·kg⁻¹·min⁻¹ for 5 min. Then, the administration of esmolol (or NaCl 0.9%, respectively) and orciprenaline was discontinued. After a break of 20 min to allow those subjects who had received esmolol first to recover from β-blockade, the experiment was continued. This time the other half of the subjects started the experiment with esmolol instead of placebo. The esmolol and placebo syringes used for this experiment were prepared by a physician who was not involved in the actual investigation. Heart rate and blood pressure were recorded every minute during this experiment.

**MRI Scanning Procedure**

The experiment was performed using a 3 Tesla whole-body scanner (Bruker Medical, Ettlingen, Germany). Twenty axial slices (19.2 cm field of view, 64 × 64 matrix, 4 mm thickness, 1 mm spacing), parallel to the anterior and posterior commissures plane and covering the whole brain were acquired using a single shot, gradient-recalled echo-planar imaging sequence (recovery time 2000 ms, echo time 30 ms; 90° flip angle). For the Stroop task 305 scans were acquired and for the hyperventilation task 360 scans were acquired.

Between the two experimental blocks (esmolol experiment, control experiment), 20 anatomical T1-weighted modified driven equilibrium Fourier transform images (256 × 256 matrix, recovery time 1300 ms, echo time 10 ms) and 20 T1-weighted echo-planar images with identical geometrical parameters as the functional data were recorded.

For the monitoring of the drug effect on BOLD signal at rest, the T1-weighted modified driven equilibrium Fourier transform images were acquired at the beginning, followed by 600 scans of gradient-recalled echo-planar images (20 axial slices, recovery time 2000 ms, echo time 30 ms; 90° flip angle).

**fMRI Data Analysis**

The fMRI data were processed with the software LIPSIA (Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany). This software package contains tools for preprocessing, registration, statistical evaluation, and presentation of fMRI data. Functional data were corrected for motion using a matching metric based on linear correlation. To correct for the temporal offset between the slices acquired in one scan, a cubic spline interpolation was applied. A spatial Gaussian...
Sinian filter with sigma = 0.8 was applied and the signal was normalized to 10,000. For the “at rest” experimental data, the signal was in addition filtered with a high-pass filter of 1/400 Hz to remove slow signal drifts.

To align the individual functional data slices onto the corresponding three-dimensional stereotactic coordinate reference system, a rigid linear registration with six degrees of freedom (three rotational, three translational) was performed. The rotational and translational parameters were acquired on the basis of the modified driven equilibrium Fourier transform and echo-planar imaging-T1 slices to achieve an optimal match between these slices and the individual three-dimensional reference data set. This three-dimensional reference data set was acquired for each subject during a previous scanning session. The modified driven equilibrium Fourier transform volume data set with 160 slices and 1 mm slice thickness was standardized to the Talairach stereotactic space.21 The rotational and translational parameters were then used to transform the functional slices using trilinear interpolation, so that the resulting functional slices were aligned with the stereotactic coordinate system.

For the Stroop task, the activated voxels were determined for each subject individually. The statistical evaluation was based on a least-squares estimation using the general linear model for serially autocorrelated observations.22–25 The design matrix was generated utilizing a box-car function, convolved with a hemodynamic response function. The model equation, including the observation data, the design matrix, and the error term, was convolved with a Gaussian kernel with a dispersion of 4 s full width at half maximum. Contrast maps (i.e., estimates of the raw-score differences between specified conditions) were then generated for each session and subject. For multi-session analysis, the random-effects analysis can be effected as a one-sample Student t test on the resulting contrast images across subjects and sessions.26,27

### Results

#### Effect of Esmolol on Cardiovascular Parameters during the fMRI Experiments

All subjects tolerated the esmolol application without any major adverse effects. No subject reported any pain during the injection of the drug. However, three subjects reported a short period of dizziness associated with the injection of esmolol.

Tables 1 and 2 show heart rate, systolic, diastolic and mean arterial blood pressures, end-tidal carbon dioxide partial pressure values, and breathing rate averaged over all subjects for the different experimental conditions. Analyses of variance were conducted to reveal differences.

<table>
<thead>
<tr>
<th>HR (bpm)</th>
<th>Sys BP (mmHg)</th>
<th>Dia BP (mmHg)</th>
<th>MABP (mmHg)</th>
<th>ETCO₂ (mmHg)</th>
<th>BR (breaths/min)</th>
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<tr>
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<td>69 ± 12*</td>
<td>127 ± 15</td>
<td>123 ± 12</td>
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</tbody>
</table>

Values are mean ± SD.

BR = breathing rate; C = control; Dia BP = diastolic blood pressure; E = esmolol; ETCO₂ = end-tidal carbon dioxide partial pressure; HR = heart rate; HV = hyperventilation; MABP = mean arterial blood pressure; NV = normoventilation; ST = Stroop task; Sys BP = systolic blood pressure.

Significant decreases (P < 0.05) in physiological variables under esmolol compared with the control experiment are marked by an asterisk.

### Table 1. Physiological Parameters during the Functional Session

<table>
<thead>
<tr>
<th>Condition</th>
<th>HR (bpm)</th>
<th>Sys BP (mmHg)</th>
<th>Dia BP (mmHg)</th>
<th>MABP (mmHg)</th>
<th>ETCO₂ (mmHg)</th>
<th>BR (breaths/min)</th>
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<td>87±9</td>
</tr>
</tbody>
</table>

HR = heart rate; Sys BP = systolic blood pressure; Dia BP = diastolic blood pressure; MABP = mean arterial blood pressure; ETCO₂ = end-tidal carbon dioxide partial pressure; BR = breathing rate; NV = normoventilation; HV = hyperventilation; ST = Stroop task.
in the physiologic variables. Heart rate was significantly decreased after bolus injection of esmolol at rest (P = 0.044), during the hyperventilation task (P < 0.001), and during the Color-Word Matching Stroop task (P = 0.01). The observed decreases in blood pressure caused by esmolol infusion during the functional challenges failed to reach statistical significance. During the “at rest” session esmolol injection decreased diastolic (P = 0.012) and mean arterial (P = 0.045) blood pressures.

Effect of Esmolol on Cardiovascular Parameters during the Orciprenaline Experiment

Figures 2 and 3 show the results of the orciprenaline experiment. Heart rate (P = 0.002), systolic blood pressure (P = 0.027), and diastolic blood pressure (P = 0.02) were significantly decreased as a result of esmolol administration. β-adrenergic stimulation with orciprenaline caused an increase in systolic blood pressure in the placebo group (P = 0.019). In contrast, no significant increase in systolic blood pressure was observed in the esmolol group (fig. 2). Heart rate increased significantly in both groups after the injection of orciprenaline (placebo group, P = 0.001; esmolol group, P = 0.014) (fig. 3). However, the increase in heart rate was less pronounced in the esmolol group (9.1 ± 7 beats/min) than the placebo group (24.4 ± 11 beats/min; P < 0.001), confirming the effect of the investigated esmolol dose on β-adrenergic receptors.

Fig. 2. Comparison of systolic and diastolic blood pressure (mean ± SD) between the esmolol group and the placebo group before the administration of esmolol (baseline), 2 min after the administration of esmolol, and 1, 3, and 5 min after the administration of orciprenaline. Significant differences (*P < 0.05; †P < 0.01) between the two groups are marked by asterisks. Esmolol caused a significant decrease in blood pressure compared with placebo and eliminated the increase in systolic blood pressure caused by β-adrenergic stimulation with orciprenaline. orcipr. = orciprenaline.

Fig. 3. Comparison of heart rate (mean ± SD) between the esmolol group and the placebo group before the administration of esmolol (baseline), 2 min after the administration of esmolol as well as 1, 3, and 5 min after the administration of orciprenaline. Significant differences (*P < 0.05, †P < 0.01) between the two groups are marked by asterisks. Esmolol caused a significant decrease in heart rate compared with placebo and blunted the increase in heart rate caused by β-adrenergic stimulation with orciprenaline. orcipr. = orciprenaline.

Effects of Esmolol on BOLD Signal at Rest

Figure 4 depicts mean BOLD MRI signal intensity time courses in six selected ROIs averaged across all subjects before, during, and after administration of esmolol during the “at rest” session. Esmolol caused immediate signal increases within the 2-min administration period in selected frontal areas, in the cerebellum and in the white matter (P < 0.01), and in the parietal and temporal lobes (P < 0.05). The observed BOLD signal increase in the occipital lobe (P > 0.2) failed to reach statistical significance. However, the BOLD signal decreased toward baseline immediately after the bolus injection was completed.

Hyperventilation Task

All subjects performed hyperventilation well, without any adverse side reactions. Mean end-tidal carbon dioxide partial pressure values during normoventilation and hyperventilation did not differ between the control experiment and the esmolol experiment (table 1). Hyperventilation resulted in a decrease in mean end-tidal carbon dioxide partial pressure values during the control experiment (P < 0.001) and during the esmolol experiment (P < 0.001).

As displayed in figure 5, hyperventilation was associated with a significant decrease (P < 0.001; one-sample
Student *t* test) in BOLD signal in all investigated brain areas (frontal cortex, parietal cortex, occipital cortex, temporal cortex, and cerebellum). The observed signal changes are larger in well vascularized gray matter than in cerebral white matter (*P* < 0.001), confirming results of previous studies. The hyperventilation-induced magnetic resonance signal changes showed no differences between the esmolol experiment and the control...
experiment in any of the investigated regions \( (P > 0.33; \text{paired Student } t \text{ test}) \).

**Color-Word Matching Stroop Task**

For the Color-Word Matching Stroop task reaction times and error rates from both conditions (neutral, incongruent) and both experiments (control, esmolol) were analyzed (fig. 6). Shorter reaction times were found in the neutral condition than in the incongruent condition during both experiments, reflecting the cognitive interference (i.e., processing of a specific stimulus attribute is impeded by simultaneous processing of a second stimulus attribute). The interference effect between incongruent and neutral conditions was 56 ms during the
control experiment and 75 ms during the esmolol experiment. β-blockade did not change the reaction time for either condition (Student t test, $P > 0.3$), nor did it change the interference effect (Student t test, $P = 0.31$).

Figure 7 shows the mean BOLD signal intensity time courses averaged across all subjects during the different conditions (neutral condition, incongruent condition) of the Color-Word Matching Stroop task in the presence and absence of esmolol. All investigated ROIs showed a significant signal increase in the neutral and incongruent conditions ($P < 0.05$, one-sample Student t test). A two-factorial analysis of variance (neutral versus incongruent and esmolol versus control) with repeated measures showed a significant effect for the condition ($P < 0.001$) and no significant effect for esmolol or control ($P > 0.4$) for all ROIs.

**Discussion**

Intravenous bolus injection of esmolol caused a brief BOLD signal increase in most investigated brain areas. However, despite a continuous infusion of the drug after the initial esmolol bolus, the BOLD signal decreased towards baseline immediately after the bolus was administered. Furthermore, the study demonstrates that esmo-
Esmolol neither affects the BOLD signal increases or the reaction times while subjects perform a cognitive task nor affects the global BOLD signal decrease in response to hyperventilation. These findings indicate that moderate esmolol doses do not affect cognitive performance and exhibit no direct effects on CBF and that cerebral vasoreactivity remains intact under esmolol.

As expected, our study clearly demonstrates that moderate doses of esmolol do not impair cognitive performance. This is indicated by similar reaction times with and without β-blockade during both conditions (neutral, incongruent) of the Stroop task and confirms the view that esmolol does not act centrally. Thus, possible anesthetic properties of esmolol during adequate anesthesia6–8 (as indexed by a decrease in the bispectral index and an increase in the burst suppression ratio by esmolol during anesthesia) are probably not mediated by central or sedative actions of the drug. However, the results of this study do not rule out the possibility of central effects of esmolol in other clinical conditions, as we investigated our subjects at rest. Other authors demonstrated for example that esmolol did not change the baseline depth of anesthesia but blunted the increase in the bispectral index as a result of laryngoscopy.30

Drugs changing the cerebral vasomotor tone and the CBF have been shown to affect BOLD signal in response to cognitive processing.11 We found no alterations of BOLD signal at rest or during the Stroop task in the presence of esmolol; this excludes regional or global effects of esmolol on CBF (note that the BOLD signal had returned to baseline immediately after the esmolol bolus despite a subsequent esmolol infusion.). Furthermore, the unaffected BOLD signal time course during the Stroop task under esmolol suggests that the drug does not impair the hemodynamic response to cognitive stimuli and thus does not affect vasodilatory properties of cerebral blood vessels. In addition to the unaffected regional vasodilatation, we observed an unchanged BOLD signal decrease (indicating an unaffected cerebral vasoconstriction in response to hypocapnia) during the hyperventilation challenge. These findings clearly indicate that cerebral vasoreactivity remains intact under esmolol.

Although esmolol produced only small changes in the hemodynamic variables during the different experiments (probably as a result of the fact that our subjects were at rest), it blunted the increase in heart rate and eliminated the increase in systolic blood pressure caused by the β-agonist orciprenaline (figs. 2 and 3). This indicates that our subjects were indeed β-blocked during the fMRI experiments and suggests that not only esmolol but also β-blockade using predominantly hydrophilic agents does not influence cerebral circulation. Thus, the results of the current study (no effect of esmolol on CBF and cerebral vasoreactivity) suggest that moderate doses of esmolol can be administered safely to control heart rate and blood pressure in patients with an impaired intracranial compliance. The finding of an unchanged cerebrovascular carbon dioxide reactivity under esmolol is probably of further clinical relevance for the assessment of cerebral vasoreactivity in patients with cerebrovascular diseases, as these patients are frequently under chronic therapy with β-blocking agents.

Several possibilities need to be considered to explain the brief BOLD signal increase during the bolus injection of esmolol. For example, direct effects of esmolol on the cerebral circulation might be assumed because the involvement of β-receptors in the regulation of CBF has been suggested.31–33 However, the observed BOLD signal increases are very unlikely to be related to direct effects of esmolol on the cerebral vasculature because esmolol is believed not to cross the blood-brain barrier and because one would expect a reduced CBF as a result of a reduction of the β-mediated vasodilator tonus by β-adrenergic blockade. Indeed, β-blockers have been repeatedly reported to reduce CBF.34–36

Furthermore, indirect actions of the esmolol injection on cerebral circulation could have resulted in a BOLD signal increase (e.g., as a result of a painful injection or awareness of the injection). However, these possibilities seem unlikely because none of our subjects reported any pain associated with the drug bolus and both stimuli (pain and stress) have been reported to produce regional increases in CBF37,38 rather than a global cerebral activation as observed in our study. Moreover, potential vasodilatory effects of the preservatives (namely sodium acetate and acetic acid) of Brevibloc® 100 mg/10 ml (Baxter Deutschland GmbH) on cerebral blood vessels should be discussed as well in relation to the effect observed. Besides these possibilities, changes in the global hemodynamic could have caused the BOLD signal increase. Rapid bolus injection of esmolol causes a sudden drop in cerebral perfusion pressure because of a reduction in heart rate, cardiac output, and blood pressure.39 According to the principle of cerebral autoregulation,1 these changes in global hemodynamics induce a general vasodilatation of cerebral blood vessels to maintain a constant CBF with a subsequent increase in the BOLD signal in most of the brain regions investigated. The short duration of the BOLD signal increase could be explained by a parallel increase in the systemic vascular resistance to compensate for the reduced cardiac output.40 To complete this discussion, further investigations are necessary to confirm the finding of global cerebral vasodilatation induced by an esmolol bolus and to make the above suggestions more specific.

The failure of this study to produce marked effects of esmolol on cerebral circulation could be a result of the moderate drug dose used. Whether higher esmolol doses causing a greater reduction of cardiovascular variables affect the fMRI BOLD signal needs to be clarified in future investigations.
In summary, the results of this study confirm our initial hypothesis that esmolol exhibits no direct effect on the cerebral circulation of healthy volunteers at rest. Esmolol does not affect the BOLD signal time course during regional or global hemodynamic challenges, indicating that CBF and cerebral vasoreactivity remain unchanged during moderate β-blockade. Moreover, our results show that β-adrenergic blockade induced by esmolol does not interfere with cognitive processing in awake human volunteers. Thus, the observed esmolol-induced cortical depression during anesthesia is probably not mediated by sedative or central actions of esmolol. However, whether these findings can be applied to other clinical conditions will have to be determined in further studies.

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