Decrease of sympathetic cardiovascular modulation after temporal lobe epilepsy surgery

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Summary
In temporal lobe epilepsy (TLE), there is evidence of ictal and interictal autonomic dysregulation, predominantly with sympathetic overactivity. The effects of TLE surgery on autonomic cardiovascular control and on baroreflex sensitivity (BRS) have not been studied. To evaluate such effects, we monitored heart rate (HR), systolic blood pressure (BP sys) and respiration in 18 TLE patients 3–4 months before and after TLE surgery. We used Blackman-Tukey spectral analysis to assess sympathetic and parasympathetic modulation as powers of HR and BP sys oscillations in the low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.5 Hz) bands. BRS was determined as the LF transfer function gain between BP and HR. After surgery, HR, BP sys, respiration and HF powers remained unchanged, while LF powers of HR (1.57 ± 1.54 bpm²) and BP sys (2.19 ± 1.34 mmHg²) and BRS (0.68 ± 0.31 bpm/mmHg) were smaller than pre-surgical LF powers of HR (3.87 ± 3.26 bpm²) and BP sys (4.80 ± 3.84 mmHg²) and BRS (1.12 ± 0.39 bpm/mmHg; P < 0.05). After TLE surgery, there is a reduction of sympathetic cardiovascular modulation and BRS that might result from decreased influences of interictal epileptogenic discharges on brain areas involved in cardiovascular autonomic control. TLE surgery seems to stabilize the cardiovascular control in epilepsy patients by reducing the risk of sympathetically mediated tachyarrhythmias and excessive bradycardiac counter-regulation, both of which might be relevant for the pathophysiology of sudden unexpected death in epilepsy patients (SUDEP). Thus, TLE surgery might contribute to reducing the risk of SUDEP.

Keywords: autonomic nervous system; baroreflex sensitivity; central autonomic network; epilepsy surgery; interictal sympathetic tone

Abbreviations: BP = blood pressure; bpm = beats per minute; BP sys = systolic BP; BRS = baroreflex sensitivity; HF = high frequency; HR = heart rate; LF = low frequency; MIBG = metaiodobenzylguanidine; SUDEP = sudden unexpected death in epilepsy patients; TLE = temporal lobe epilepsy

Introduction
Temporal lobe epilepsy (TLE) is associated with alterations of autonomic nervous system activity (Freeman and Schachter, 1995; Hilz et al., 1999a). Seizure-related autonomic hypo- and hyper-activity modifies the function of various systems such as the respiratory, gastrointestinal, urogenital and, most importantly, cardiovascular system (Freeman and Schachter, 1995; Benarroch, 1997b; Hilz et al., 1999a; Spyer, 1999). Heart rate (HR) and blood pressure (BP) increases frequently precede or accompany ictal discharges, while bradyarrhythmias and arterial hypotension are rather rare (Freeman and Schachter, 1995; Hilz et al., 1999a). Changes of interictal autonomic modulation that have been demonstrated are mostly described as enhanced sympathetic cardiovascular tone (Frysinger et al., 1993; Devinsky et al., 1994; Faustmann and Ganz, 1994). Some studies also report changes of parasympathetic HR modulation in TLE patients (Massetani et al., 1997; Tomson et al., 1998; Ansakorpi et al., 2000). Recently, our group found reduced uptake of the norepinephrine analogue [¹²³I]metaiodobenzylguanidine ([¹²³I]MIBG) into cardiac postganglionic sympathetic nerve fibres. From the analysis of HR variability, we concluded that the diminished cardiac MIBG uptake might result from a decrease as well as an increase of central sympathetic outflow (Druschky et al., 2001).

Imbalance of sympathetic and parasympathetic cardiovascular activity is a potential cause of sudden unexpected death in epilepsy (SUDEP) (Lown and Verrier, 1976; Myers et al., 2002).
Table 1  Clinical characterization of patients undergoing temporal lobe surgery for epilepsy refractory to drug treatment

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Handedness</th>
<th>Speech dominance</th>
<th>Seizure type</th>
<th>EEG focus</th>
<th>Antiepileptic medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>Female</td>
<td>Right</td>
<td>Left</td>
<td>CPS, GTC</td>
<td>Left frontotemporal</td>
<td>Cbz, Tpm</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>Female</td>
<td>Right</td>
<td>Left</td>
<td>CPS, GTC</td>
<td>Left frontotemporal</td>
<td>Cbz, Ltg</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>Female</td>
<td>Right</td>
<td>Left</td>
<td>SPS, CPS, GTC</td>
<td>Left frontotemporal</td>
<td>Phr, Ltg, Gbp</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>Male</td>
<td>Right</td>
<td>Left</td>
<td>SPS, CPS</td>
<td>Right frontotemporal</td>
<td>Cbz, Tpm</td>
</tr>
<tr>
<td>5</td>
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<td>Male</td>
<td>Right</td>
<td>Bilateral</td>
<td>CPS, GTC</td>
<td>Right frontotemporal</td>
<td>Cbz, Gbp, Tpm</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>Female</td>
<td>Right</td>
<td>Left</td>
<td>CPS, GTC</td>
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<td>Cbz, Gbp</td>
</tr>
<tr>
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</tr>
<tr>
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<tr>
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<td>Left</td>
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<td>Right mediotemporal</td>
<td>Phr, Gbp</td>
</tr>
<tr>
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<td>Left</td>
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<td>Right centromedial</td>
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<tr>
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<tr>
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<td>Cbz, Tpm</td>
</tr>
<tr>
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<td>Right</td>
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<tr>
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<td>Right frontotemporal</td>
<td>Cbz, Gbp, Tpm</td>
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<tr>
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<td>SPS, CPS, GTC</td>
<td>Left frontotemporal</td>
<td>Cbz, Ltg</td>
</tr>
<tr>
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<td>Male</td>
<td>Right</td>
<td>Left</td>
<td>SPS, CPS, GTC</td>
<td>Right frontotemporal</td>
<td>Cbz, Ltg</td>
</tr>
</tbody>
</table>

SPS = single partial seizures; CPS = complex partial seizures; GTC = generalized tonic-clonic seizures; Cbz = carbamazepine; Tpm = topiramate; Phr = phenytoin; Ltg = lamotrigine; Gbp = gabapentin; Ocbz = oxcarbazepine.

The incidence of SUDEP is not known exactly. In a recent follow-up study of 4578 epilepsy patients for 16,463 patient-years, Walczak et al. (2001) found that the incidence of SUDEP was 1.21 per 1000 patient-years and that SUDEP accounted for 18% of all deaths. In a review of SUDEP incidence, Annegers and Coan (1999) summarize that sudden unexpected death might occur 40 times more frequently among individuals with epilepsy than among those without epilepsy. Several risk factors for SUDEP have been identified or discussed, such as seizure severity (Annegers and Coan, 1999), occurrence of tonic-clonic seizures (Walczak et al., 2001), treatment with more than two anticonvulsant drugs (Walczak et al., 2001), young age (Terrence et al., 1975), a long history but infrequent seizures (Terrence et al., 1975) or subtherapeutic levels of anticonvulsants (Terrence et al., 1975). The exact mechanisms that induce SUDEP are not yet known (Natelson et al., 1998; Annegers and Coan, 1999; Nilsson et al., 1999; Walczak et al., 2001). Animal experiments suggest that there is a transmission of epileptogenic discharges onto the cardiovascular sympathetic modulation (Lathers et al., 1987). Reports of elevated troponin I levels in pediatric epilepsy patients without cardiac history (Greene-Chandos et al., 2001), and of ischaemic heart damage in epilepsy patients who died unexpectedly without a history or clinical signs of heart disease (Natelson et al., 1998), as well as scintigraphic evidence of myocardial ischaemia during seizures (Dam et al., 2001), support the assumption that surges of sympathetic outflow during seizures might contribute to the pathophysiology of SUDEP.

Ictal and interictal epileptogenic activity spreading from temporal lobe areas may interfere with the cardiovascular modulation in neighbouring structures of central autonomic control, such as the amygdala, the insular or orbitofrontal cortex, the cingular gyrus and their pathways (Pool and Ransohoff, 1949; Fringsger and Harper, 1989; Freeman and Schachter, 1995; Hilz et al., 1999a).

Surgical removal of temporal lobe seizure foci might alter epileptogenic influences on the autonomic cardiovascular control. In particular, the resection of the anterior amygdala and hippocampal areas should influence the autonomic modulation of BP and HR as well as the baroreflex (Benarroch, 1997a; Spyer, 1999; Hilz et al., 2000). The structures of the central autonomic network modify the sensitivity of the baroreflex loop that assures a beat-to-beat adjustment of BP and HR to each other (Benarroch, 1997a; Spyer, 1999; Hilz et al., 2000).

Several studies showed a hemispheric lateralization of sympathetic or parasympathetic cardiovascular control (Zamrini et al., 1990; Oppenheimer et al., 1992; Barron et al., 1994; Yoon et al., 1997; Al-Aweel et al., 1999; Critchley et al., 2000a). In epilepsy patients, central modulation of sympathetic cardiovascular activity is under greater influence of the right than the left hemisphere, while the left hemisphere contributes more to parasympathetic activity (Zamrini et al., 1990; Yoon et al., 1997; Hilz et al., 2001). Recently, we showed that there is also a hemisphere-specific modulation of the baroreflex sensitivity (BRS) (Hilz et al., 2001). Inactivation of the left hemisphere during the presurgical, intracarotid amobarbital procedure decreases BRS by nearly 30%. The BP increments needed to induce a given HR reduction must be significantly higher with only the right instead of both hemispheres active (Hilz et al., 2001).
cardiovascular modulation and the BRS change after temporal lobe surgery and whether such alterations depend on the laterality of the operation.

Patients and methods

Patients

We tested 10 women and eight men aged 28–52 years (mean age 37.3 years, SD 6.4 years) with epilepsy refractory to antiepileptic drug treatment. Sixteen patients were right-handed, two were left-handed, 16 presented with left-sided speech dominance, one with bilateral speech representation and one with right-sided speech dominance as determined by neuropsychological testing during the intracarotid amobarbital procedure (Table 1).

Four patients had single partial and complex partial seizures, seven had complex partial seizures with secondary generalization, seven had single partial, complex partial and generalized seizures. The duration of epilepsy ranged from 14 to 37 years (mean 22.1 years, SD 12.2 years). Pre-surgical epilepsy evaluation showed seizure onset in the left temporal lobe in nine patients and in the right temporal lobe in nine patients (Table 1). After approval of the study by the Institutional Review Board at New York University, informed consent was obtained according to the Declaration of Helsinki.

General physical and neurological examinations were unremarkable in all patients. None of the patients had clinical signs of autonomic dysfunction or diseases affecting autonomic function, such as high BP or diabetes mellitus. No study participant was being treated with drugs known to interfere with autonomic nervous function. On the days of autonomic testing, patients only took their regular antiepileptic medication. Medication was not changed between pre- and post-surgical evaluation (Table 1). All patients were free of seizures 48 h prior to the testing. Prior to the pre- and post-surgical autonomic evaluations, all patients had an EEG (electroencephalogram) using standard techniques.

As the comparison of the pre- and post-surgical evaluations might be biased by anxiety and stress prior to surgery and a more reassured and relaxed emotional state after surgery, patients underwent the pre-surgical testing before the indication for surgery was finalized. Patients who seemed to be particularly concerned because of possible surgery were not included in the study.

HR, BP and respiratory frequency

To minimize emotional influences on the cardiovascular responses due to an imminent intervention, we only tested patients 3–4 months before (and after) surgery. Between 9 and 12 a.m., patients were tested in relaxed, supine position in a quiet room with an ambient temperature of 22°C. After an adjustment period of at least 35 min, we monitored HR, BP and respiration.

HR was recorded as beats per minute (bpm) with a three-lead electrocardiogram using a Colin Pilot™ monitor (Colin Medical Instruments, San Antonio, Tex., USA). Skin electrodes were positioned at the areas under the right and left clavicle and the left iliac crest.

Systolic BP (BPsys) was recorded continuously from the left radial artery using non-invasive arterial tonometry (Colin Pilot™) (Kemmotsu et al., 1994). The tonometer consists of an array of 31 equally spaced piezoresistive pressure transducers, an automated positioning system, and signal conditioning and initial calibration by oscillometric cuff measurement of the brachial artery (Kemmotsu et al., 1994).

Respiratory frequency was monitored with a two-belt chest–abdomen inductance plethysmograph after calibration (Respiratr Calibrator™, Ambulatory Monitoring Inc., Ardsley, NY, USA).

BP, HR and respiratory signals were transferred via analogue output into a custom designed data acquisition and analysis system (HRview™, Boston Medical Technologies; Brington, Mass., USA) and a personal computer (PC). The analogue data were digitized by a 32-channel, 16-bit resolution analogue–digital converter (CIO-DAS64–02I/16, ComputerBoards Inc., Mansfield, Mass., USA). Each channel of data was sampled at 1 kHz and displayed on the PC.

During offline analysis, we determined the mean values and standard deviation of HR, BPsys and respiratory frequency during a 2-min interval.

To assess the contribution of the sympathetic and parasympathetic systems to HR and BP modulation, we evaluated HR and BP variability by means of power spectral analysis. HR and BP values show slow underlying fluctuations that are largely mediated by the undulating activity of the sympathetic and parasympathetic nervous systems (Saul et al., 1991; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Bernardi et al., 1997). Parasympathetic modulation of HR is most pronounced at the frequency of respiration, e.g. at 0.2 Hz with a breathing rate of 12 cycles per minute (cpm) (Saul et al., 1991; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Bernardi et al., 1997; Hilz et al., 1999b). Parasympathetic, respiratory influences are considered to account for HR modulation occurring in the so-called high frequency (HF) range between 0.15 and 0.5 Hz. Therefore, we used HR modulation in the HF range as an index of parasympathetic modulation (Saul et al., 1991; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Bernardi et al., 1997; Hilz et al., 1999b).

In contrast, fluctuations of the BP signal in the HF range are primarily a mechanical consequence of respiration-induced increases in venous return (Saul et al., 1991; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Bernardi et al., 1997; Hilz et al., 1999b).
Society of Pacing and Electrophysiology, 1996; Bernardi et al., 1997; Hilz et al., 1999b).

However, parasympathetic influences on HR still occur at frequencies below 0.15 Hz while fluctuations of the BP signal in the so-called low frequency (LF) range between 0.04 and 0.15 Hz are considered to be related to sympathetic outflow only (Saul et al., 1991; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Bernardi et al., 1997; Hilz et al., 1999b). Therefore, we determined the degree of sympathetic signal modulation primarily from the amount of LF BP modulation and not only from LF HR modulation (Saul et al., 1991; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Bernardi et al., 1997; Hilz et al., 1999b).

For spectral analysis, 120-s recordings of electrocardiogram RR intervals and BPmean values before and after surgery were cleaned of artefacts, resampled at 4 Hz and then taken for spectral processing using the Blackman-Tukey algorithm, as previously described in more detail (Hilz et al., 1999b).

Sympathetic and parasympathetic influences on BP and HR variability were assessed by quantifying the LF and HF components of both signals. The magnitude of these components was determined as the integral under the power spectral density curves of HR (bpm²/Hz) and BP (mmHg²/Hz) for the two frequency bands, and expressed as LF and HF power of HR (bpm²) and BP (mmHg²) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Hilz et al., 1999b).

Table 2 Mean values of HR, BPsys, respiration, HR and BPsys modulation in the LF and HF range and BRS before and after temporal lobe surgery

<table>
<thead>
<tr>
<th>TLE patients (n = 18)</th>
<th>Subgroup with left-sided focus (n = 9)</th>
<th>Subgroup with right-sided focus (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-surgical (mean ± SD)</td>
<td>Post-surgical (mean ± SD)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>70.8 ± 7.5</td>
<td>73.1 ± 11.7</td>
</tr>
<tr>
<td>BPsys (mmHg)</td>
<td>125.6 ± 13.8</td>
<td>122.2 ± 11.1</td>
</tr>
<tr>
<td>Respiration rate (cpm)</td>
<td>14.4 ± 2.7</td>
<td>14.0 ± 3.4</td>
</tr>
<tr>
<td>HR spectral power</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF (bpm²)</td>
<td>3.86 ± 3.26</td>
<td>1.57 ± 1.54</td>
</tr>
<tr>
<td>HF (bpm²)</td>
<td>1.85 ± 1.88</td>
<td>1.41 ± 1.17</td>
</tr>
<tr>
<td>BPsys spectral power</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LF (mmHg²)</td>
<td>4.80 ± 3.84</td>
<td>2.19 ± 1.34</td>
</tr>
<tr>
<td>HF (mmHg²)</td>
<td>1.28 ± 1.15</td>
<td>1.21 ± 1.34</td>
</tr>
<tr>
<td>BRS</td>
<td>1.12 ± 0.39</td>
<td>0.68 ± 0.31</td>
</tr>
</tbody>
</table>

Results are reported for all 18 patients, regardless of their seizure focus (left columns), and separately for patients with left hemispheric seizure focus (middle columns) or right hemispheric seizure focus (right columns). Temporal lobe surgery did not significantly alter mean values of HR, BPsys or respiration rate. Spectral powers of HR and BP modulation in the LF range decreased after surgery while HF HR and BP modulation remained stable. BRS, calculated as the gain of the HR–BPsys transfer function in the LF range, decreased after surgery. Results did not differ for patients with left or right hemispheric seizure focus. Bold numbers indicate significant differences between pre- and post-surgical values (P < 0.05).

Statistical analysis

To assess differences in cardiovascular regulation before and after surgery and to identify effects of the side of the surgery, we performed an ANOVA (analysis of variance) for repeated measures (general linear model, ANOVA; SYSTAT, Evanston, Ill., USA), with ‘hemisphere’ (left, right) and ‘surgery’ (before, after) as ‘within subject’ factors. The analysis was applied for the autonomic parameters HR, LF HR, HF HR, BPsys, LF BPsys, HF BPsys, respiration and BRS during a 120-s period before and after epilepsy surgery. In case of violation of the sphericity assumption, we applied the Greenhouse Geisser correction. The two-sided Wilcoxon test was used for single comparisons of the autonomic parameters before and after surgery if the interaction term (‘surgery × hemisphere’) was significant. The level of significance was set at P < 0.05.

that BRS can be determined without pharmacologically challenging the baroreflex. With this method, BRS is assessed by analysing the relationship between spontaneous sympathetically mediated fluctuations of the BP signal, reflecting the input activity of the baroreflex, and corresponding HR fluctuations, reflecting the reflex output activity (Robbe et al., 1987). The amplification between the input and output of the reflex is an index of BRS (Robbe et al., 1987). Mathematically, this amplification equals the gain of the transfer function between the oscillations of BP and HR in the LF range, provided there is sufficient coherence (>0.5), i.e. a stable relationship between both bio-signals (Robbe et al., 1987; Hilz et al., 1999b).
Results
Temporal lobe surgery did not significantly affect mean values of HR, BP, and respiratory frequency, and there were no differences between the pre- and post-surgical values of patients with left or right hemispheric seizure focus.

The pre-surgical EEG showed intermittent interictal epileptogenic activity over the right temporal leads in 9 of the 18 patients. In 2 of these 9 patients, there was occasional spreading to other areas of the right hemisphere. In the 9 other patients, there was focal intermittent epileptogenic activity over the left temporal leads. Intermittent spreading to other left hemispheric areas was seen in 3 of these 9 patients. Moreover, the EEG showed additional intermittent spreading of the epileptiform activity also to areas of the contralateral hemisphere in one patient of each subgroup, i.e. in 2 of the 18 patients. None of the patients developed clinical seizures. Post-surgical EEG recordings did not reveal epileptogenic activity in any of the 18 patients.

After surgery, mean values of HR (73.1 ± 11.7 bpm), BPsys (122.2 ± 11.1 mmHg) and respiratory frequency (14.0 ± 3.4 cpm) were quite similar to HR (70.8 ± 7.5 bpm), BPsys (125.6 ± 13.8 mmHg) and respiratory frequency (14.4 ± 2.7 cpm) before tailored resection (ANOVA, P < 0.05; Wilcoxon, P > 0.05) (Table 2; Fig. 1). There was no difference between BPsys and respiratory frequency before and after surgery within the subgroups who underwent right or left mesial temporal lobe resection (ANOVA, P > 0.05; Wilcoxon, P > 0.05; Table 2). Similarly, HR did not differ between the subgroups before and after surgery, although there was a minimal HR increase in patients after right-sided surgery (Table 2).

In contrast to the mean values of HR, BP, and respiratory frequency, the spectral analysis of LF and HF fluctuations of HR and BP showed that autonomic cardiovascular modulation after resection differed from the modulation before surgery. After temporal lobe surgery, the powers of the LF modulation of HR (1.57 ± 1.54 bpm²) and BPsys (2.19 ± 1.34 mmHg²) were smaller than the LF powers of HR (3.86 ± 3.26 bpm²) and BPsys (4.80 ± 3.84 mmHg²) before resection (ANOVA, P < 0.05; Wilcoxon, P < 0.05).

In contrast, the post-surgical HF modulation of HR (1.41 ± 1.17 bpm²) and BPsys (1.21 ± 1.34 mmHg²) was similar to the pre-surgical HF powers of HR (1.85 ± 1.88 bpm²) and BPsys (1.28 ± 1.15 mmHg²) (ANOVA, P > 0.05; Wilcoxon, P > 0.05; Table 2; Figs 1 and 2). These changes did not show any hemisphere-specific effects, but were similar in the subgroups of patients with left- or right-hemispheric intervention (Table 2).

BRS also differed before and after temporal lobectomy (Table 2; Fig. 3). Post-surgical BRS values (0.68 ± 0.31 bpm/mmHg) were significantly lower than the pre-surgical values (1.12 ± 0.39 bpm/mmHg) (ANOVA, P < 0.05; Wilcoxon, P < 0.05; Fig. 3). Similar to the changes in LF and HF powers, the reduction of BRS did not depend on the side of the operation (Table 2).

Discussion
To our knowledge, this is the first study showing changes of cardiovascular autonomic modulation after temporal lobe surgery in epilepsy patients. While the standard measures of cardiovascular function, HR, BP and respiration, remain stable, the autonomic modulation in the LF range shows an average reduction of 43% and the BRS is lowered by almost 40% after surgery.

The diminished LF power of HR modulation might reflect a decrease of both sympathetic and to some extent parasympathetic influences on HR (Saul et al., 1991; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Hilz et al., 2001). However, the constancy of the parasympathetic HR modulation in the HF range suggests that there were no major changes of parasympathetic cardiac tone after surgery (Saul et al., 1991; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Hilz et al., 2001). The decrease of the LF power of BP modulation supports the assumption that changes in autonomic modulation after surgery are primarily due to a reduction of sympathetic outflow, as the LF power of BP is an index of sympathetic modulation only (Malliani et al., 1991; Saul et al., 1991; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Hilz et al., 2001).

The finding is in agreement with several previous studies of epilepsy patients that demonstrated increased ictal as well as interictal sympathetic cardiovascular activity (Frysinger et al., 1993; Devinsky et al., 1994; Faustmann and Ganz, 1994). In patients with mesial temporal seizure foci, Faustmann and Ganz (1993) found interictally increased HR modulation in the frequency range of 0.07–0.156 Hz, reflecting augmented sympathetic activation. In complex partial seizure patients, Devinsky et al. (1994) observed enhanced BP and HR activation during sympathetic challenge such as orthostatic stress or cold pressor stimulation. Faustmann and Ganz (1994) analysed chaotic HR oscillations in patients with idiopathic generalized epilepsy during interictal states and found signs of reduced variability, which is likely to be due to a predominance of sympathetic modulation. In TLE patients, our group recently evaluated the function of cardiac sympathetic nerve fibres by means of [¹²³I][MIBG single photon emission tomography. The uptake of the norepinephrine analogue into post-ganglionic nerve vesicles was significantly reduced (Druschky et al., 2001), but it remained undetermined whether the functional alteration was due to a decrease of central sympathetic tone or to continuous sympathetic over-stimulation. The results of the present study support the conclusion that sympathetic tone is augmented in TLE patients.

During seizures, tachyarrhythmias, particularly sinus tachycardia, are far more frequent than bradyarrhythmias (Blumhardt et al., 1986; Devinsky et al., 1986; Keilson et al., 1987; Jacome and Seroppian, 1988; Freeman and Schachter,
There is evidence from animal experiments that interictal epileptogenic discharges enhance cardiovascular sympathetic tone more than parasympathetic outflow (Lathers et al., 1987). In pentyletetratrazole-treated cats, Lathers et al. (1987) observed intermittent 1:1 synchronization of interictal spikes with cardiac sympathetic discharges, while the transmission of epileptogenic activity onto cardiovagal fibres was far less common. We assume that the post-surgical decrease of sympathetic cardiovascular modulation was due to the diminished interictal stimulation of central sympathetic relay centres (Benarroch, 1997b; Spyer, 1999) from discharges arising from the seizure focus, as interictal epileptogenic activity was significantly reduced in all of our patients after surgery.

The structures removed during tailored resection of the anterior temporal lobe, amygdala and hippocampal structures are important centres of central cardiovascular control (Pool and Ransohoff, 1949; Frysinger and Harper, 1989; Freeman and Schachter, 1995; Benarroch, 1997b; Hilz et al., 1999a; Spyer, 1999). As mentioned above, the amygdala, hippocampus, fronto-orbital cortex, anterior cingulate gyrus, insular cortex, paraventricular and hypothalamic regions are all interconnected centres of cardiovascular autonomic modulation (Benarroch, 1997b; Spyer, 1999; Critchley et al., 2000a, 2001a, b). The reduction of nervous impulses onto these structures seems to lower sympathetic tone.

To some extent, the reduction of sympathetic activity after surgery might also be related to an altered emotional state of the patients after the tailored resection. Although we ensured that the pre-surgical autonomic evaluation was performed 3–4 months prior to surgery, before the patients learned about the final indication for surgery, and we excluded patients who seemed nervous or concerned about the surgery, we cannot rule out the possibility that patients were somewhat more reassured and relaxed after surgery than before. A difference between the emotional states before and after surgery might affect the cardiovascular responses. Moreover, the surgery itself might affect the emotional as well as autonomic responses of the patients (Critchley et al., 2000a, 2001a, b).

Several studies demonstrate an interaction and overlap of cerebral structures involved in autonomic modulation and in emotional states (Critchley et al., 2000a, b, 2001a, b; Damasio et al., 2000). Using positron emission tomography and functional magnetic resonance imaging, Critchley et al.
demonstrated activation of specific brain regions during different emotional states, such as relaxation or stress (Critchley et al., 2000a, b, 2001a, b), and even showed differences in regional activation during cognitive or physical stress (Critchley et al., 2000b, 2001a). During tasks generating different internal bodily states, the authors found activation of regions including somatosensory cortices, insula, the anterior and posterior cingulate cortices, as well as the caudate nucleus, left globus pallidus, left and right inferior parietal lobe, areas of the right medial temporal lobe adjacent to the amygdala, the dorsal pons or cerebellar vermis (Critchley et al., 2001a, b). Most of these brain regions are interconnected with the structures removed during TLE surgery (Benarroch, 1997a; Spyer, 1999). Critchley et al. (2001b) conclude from their data that ‘regions adjacent to the amygdala might serve directly in reducing the sympathetic bodily responses commonly associated with stress and anxiety’. Consequently, tailored resection of temporal lobe areas including the amygdala might yield an alteration of the emotional state, and by this contribute to a decrease of sympathetic cardiovascular modulation.

The post-surgical reduction of BRS occurring together with the diminished sympathetic outflow is somewhat unexpected. Normally, BRS decreases when sympathetic tone is enhanced, e.g. during exercise or the so-called defence reaction (Eckberg and Sleight, 1992; Spyer, 1999; Hilz et al., 2000). Therefore, we anticipated that lowered sympathetic outflow after removal of the seizure focus might result in an increase of BRS (Spyer, 1999). However, modification of BRS during acute changes of sympathetic tone seems to be secondary to the sympathetic influences on the amygdala and hypothalamic areas, which then modulate the descending output onto the nucleus tractus solitarius (Spyer, 1999). In TLE patients, the decrease of BRS and sympathetic tone might not be due to a sequential influence of interictal epileptogenic discharges, first on centres of sympathetic modulation and subsequently on baroreflex modulation. The concurrent change of sympathetic activity and BRS might

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**Fig. 1** The 120-s time series of HR (A) and BP$_{sys}$ (B) in a 36-year-old epilepsy patient showing no difference of HR and of BP$_{sys}$ values before and after temporal lobe surgery. Spectral analysis of HR and BP$_{sys}$ time series demonstrated a pronounced decrease of the powers of sympathetically mediated LF modulation (0.04–0.15 Hz; black arrows) but no change of parasympathetically mediated HF modulation (0.15–0.50 Hz) after surgery.
instead result from direct interference of seizure activity with various structures and levels of the central autonomic network. In pentylenetetrazole-treated rats, Kanter et al. (1995) evaluated seizure-induced neuron activation by testing for neuronal c-fos immunoreactivity. The authors demonstrated that central neurones involved in baroreflex modulation are activated directly by seizure discharges, and not in response to seizure associated hypertension (Kanter et al., 1995). These findings support our assumption that the decrease of BRS and sympathetic tone after surgery might be due to a diminished influence of interictal epileptogenic discharges on neurones involved in the modulation of both sympathetic activity and the baroreflex (Eckberg and Sleight, 1992; Benarroch, 1997b; Hilz et al., 1999a).

In previous studies, Zamrini et al. (1990) and Yoon et al. (1997), as well as our group (Hilz et al., 2001), have demonstrated a hemisphere-specific lateralization of central autonomic modulation with a more prominent up-regulation

Fig. 2 HR, BP<sub>sys</sub> and spectral powers of HR and BP<sub>sys</sub> modulation in the LF and HF range in 18 epilepsy patients before and after surgery. After surgery, the LF modulation of BP<sub>sys</sub> and HR was significantly lower than before surgery, indicating diminished sympathetic activity. The other parameters remained stable.

Fig. 3 BRS assessed as the LF transfer function gain between systolic BP and HR in 18 epilepsy patients before and after temporal lobe resection. After surgery, BRS was ~40% lower than before surgery (P < 0.05).
of sympathetic modulation in the right hemisphere and parasympathetic modulation in the left hemisphere. We also showed that BRS decreases during left hemispheric inactivation by means of the intracarotid amobarbital procedure, suggesting an up-regulation of BRS in the left hemisphere (Hilz et al., 2001).

Critchley et al. (2001a, b) recently showed in positron emission tomography studies of healthy subjects that there is a lateralization of regional brain activity and emotional states and autonomic responses. During relaxation, brain activity increased in the left anterior cingulate gyrus and globus pallidus, while sympathetic arousal was associated with augmented right cingulate and right inferior parietal activity (Critchley et al., 2000a, b, 2001a, b).

In the current study, we only found a minimal, insignificant increase of HR in the patients who had undergone right-sided TLE surgery. Otherwise, the pre- to post-surgical changes in HR, BP and respiration and in the powers of bio-signal modulation in the LF and HF range as well as BRS changes did not differ between patients with left- and right-sided surgery. The lack of hemisphere-specific changes might be due to the rather small number of patients in each subgroup in the presence of a fairly high inter-individual variability of the parameters analysed, as expressed by the rather high standard deviations of the data. A functional alteration of the resected brain areas before surgery might also contribute to the lack of hemisphere-specific differences. In all our patients, presurgical intracarotid amobarbital procedure testing showed a reduction of hemispheric memory function to various extents on the side of the seizure focus, i.e. the side of the consecutive TLE surgery.

However, we assume that the discrepancy between the lack of hemispheric differences after TLE surgery and the hemispheric lateralization during intracarotid amobarbital procedure modulation (Zamrini et al., 1990; Yoon et al., 1997; Hilz et al., 2001) or during selective insular cortex stimulation, as performed by Oppenheimer et al. (1992), results from different effects of TLE and of intracarotid amobarbital procedure or cortical stimulation on the central autonomic modulation.

While the intracarotid amobarbital procedure inactivates not only the brain areas of the seizure focus but also the entire left or right hemisphere (Jeffery et al., 1991), tailored resection only reduces impulses spreading from the suspected epileptogenic focus. Hemisphere-specific differences of sympathetic and parasympathetic outflow are not necessarily influenced by the surgery. After surgery, sympathetic modulation should still be higher in the right than the left hemisphere unless the removed structures were directly involved in the lateralization of sympathetic or parasympathetic activity. The surgery included removal of the amygdala, which contributes significantly to autonomic cardiovascular control (Benarroch, 1997a; Spyer, 1999; Critchley et al., 2000a, 2001a, b). However, Epstein et al. (1992) demonstrated that seizure activity limited to the amygdala does not induce hemisphere-specific changes of HR. Similarly, our data do not support a direct or dominant influence of the removed structures on the hemispheric lateralization of sympathetic or parasympathetic tone. It seems more likely that neurones in adjacent areas such as the insular, cingulate or even parietal cortex, account for the effects of hemispheric lateralization (Benarroch, 1997b; Spyer, 1999; Critchley et al., 2000a, 2001a, b). In presurgical epilepsy patients, Oppenheimer et al. (1992) demonstrated that right insular cortex stimulation furthers sympathetic activation, while left insular stimulation predominantly results in depressor effects on HR and BP.

To conclude, our findings suggest that temporal lobe surgery contributes to a stabilization of the cardiovascular system in epilepsy patients. Before surgery, higher sympathetic outflow may predispose towards tachyarrhythmic and hypertensive events. As pre-surgical BRS is also augmented, baroreflex counter-regulation to sympathetic bouts might result in excessive cardioinhibitory or vasodepressor responses. Increased BRS with excessive bradycardia or asystole and arterial hypotension is a common finding in patients with cardiot sinus hypersensitivity (Eckberg and Sleight, 1992; Somers and Abboud, 1994). The defect of this syndrome is unclear, but there is evidence of central up-regulation of the reflex sensitivity that might be similar to the augmentation of BRS in our epilepsy patients before surgery (Eckberg and Sleight, 1992; Somers and Abboud, 1994). We hypothesize that elevated sympathetic tone and concomitant increase of BRS might contribute to cardiovascular emergencies and even to SUDEP. Several reports of myocardial alterations in epilepsy patients without a history of cardiac disease lend support to our assumption. Dam et al. (2001) were able to demonstrate a reduction of myocardial perfusion in a small number of epilepsy patients during seizures. Ictal perfusion scintigraphy showed decreased blood flow, particularly in the anterior and anterior-septal heart regions, although the baseline scintigraphy, as well as the echocardiography and coronary artery angiography, had been normal. In paediatric patients admitted with seizures, Greene-Chandos et al. (2001) found elevated troponin I levels in the absence of cardiac disease. The authors concluded that the troponin I increase may result from diffuse myofibrillary necrosis secondary to catecholamine surges during seizure (Greene-Chandos et al., 2001). Natelson et al. (1998) found perivascular and interstitial fibrosis as well as myocyte vacuolization in five of seven hearts from epilepsy patients who had died suddenly without a history or clinical evidence of heart disease. Since these findings occurred in the absence of coronary pathology, the authors concluded that the cardiac damage results from chronically recurring ischaemia. They hypothesize that recurring seizures induce coronary vasospasm and myocardial damage that sensitizes the heart to further seizures with concomitant autonomic storm (Natelson et al., 1998).

If these observations are due to an increased sympathetic outflow in epilepsy patients, our findings of a decreased cardiovascular sympathetic modulation and a reduced BRS...
after TLE surgery might suggest that TLE surgery has positive influences on the mechanisms of SUDEP. In conclusion, lower sympathetic outflow and BRS after surgery should be accompanied by a reduced risk of cardiovascular emergencies in epilepsy patients.

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**References**


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