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Cerebral autoregulation improves in epilepsy patients after temporal lobe surgery

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Abstract Patients with temporal lobe epilepsy (TLE) often show increased cardiovascular sympathetic modulation during the interictal period, that decreases after epilepsy surgery. In this study, we evaluated whether temporal lobectomy changes autonomic modulation of cerebral blood flow velocity (CBFV) and cerebral autoregulation. We studied 16 TLE patients 3–4 months before and after surgery. We monitored heart rate (HR), blood pressure (BP), respiration, transcutaneous oxygen saturation (sat-O_2), end-expiratory carbon dioxide partial pressure (pCO_2) and middle cerebral artery CBFV. Spectral analysis was used to determine sympathetic and parasympathetic modulation of HR, BP and CBFV as powers of signal oscillations in the low frequency (LF) ranges from 0.04–0.15Hz (LF-power) and in the high frequency ranges from (HF) 0.15–0.5Hz (HF-power). LF-transfer function gain and phase shift between BP and CBFV were calculated as parameters of cerebral autoregulation. After surgery, HR, BP_{mean}, $CBFV_{mean}$, respiration, sat-O_2, pCO_2 and HF powers remained unchanged. LF-powers of HR, BP, CBFV and LF-transfer function gain had decreased while the phase angle had increased ($p < 0.05$). The reduction of LF powers and LF-gain and the higher phase angle showed reduced sympathetic modulation and improved cerebral autoregulation. The enhanced cerebrovascular stability after surgery may improve autonomic balance in epilepsy patients.

Key words epilepsy surgery · autonomic nervous system · cerebral autoregulation · interictal sympathetic tone · cerebral blood flow velocity

Introduction

Temporal lobe epilepsy is associated with alterations of autonomic nervous system activity [3, 33]. During seizures, autonomic hypo- or hyperactivity can alter the function of respiratory, gastrointestinal, urogenital, cardio- or cerebrovascular systems [3, 33]. In addition, interictal autonomic function may be altered in patients with temporal lobe epilepsy (TLE) [13, 18]. Most studies found increased sympathetic cardiovascular modulation in interictal TLE patients [13, 18] while only a few studies have reported interictal changes of parasympathetic heart rate modulation [28, 35]. Interictally, Diehl et al. demonstrated significantly increased sympathetic modulation of cerebral blood flow velocity using transcranial Doppler sonography of the middle cerebral artery [14].

In previous studies conducted on different groups of interictal TLE patients, we not only found hemispheric differences between sympathetic and parasympathetic cardiovascular modulation [23] and altered cardiac au-

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tonomic modulation [17, 21, 23, 24] but we also showed compromised post-ganglionic cardiac sympathetic innervation with reduced uptake of the norepinephrine analogue [^{123}I]-metaiodobenzylguanidine (MIBG) into myocardial sympathetic nerve terminals [17]. After epilepsy surgery, we moreover observed changes in cardiac sympathetic innervation that differed between patients who became seizure free and patients with seizure-persistence after surgery [24]. We also saw a decrease of sympathetic cardiovascular modulation after successful TLE surgery with post-surgical cessation of seizures [21]. We assumed that the post-surgical decrease of cardiovascular sympathetic activity [21] was due to a decrease or cessation of interictal epileptogenic activity spreading from the seizure focus and stimulating central sympathetic relay areas, such as the amygdala [4, 33].

Based on our previous observations of a decreased sympathetic cardiovascular modulation after successful TLE surgery [21] and on the finding of Diehl et al. [14] that there is also increased sympathetic modulation of cerebral blood flow velocity in non-operated epilepsy patients [14], we hypothesize that tailored epilepsy surgery not only influences cardiovascular autonomic modulation, but also affects cerebral blood flow and cerebral autoregulation. Cerebral autoregulation depends on sympathetic modulation of the cerebral vessels [7, 20]. The finding of altered sympathetic outflow [14, 21] suggests that cerebral autoregulation might be compromised in TLE patients. So far, cerebral autoregulation and effects of TLE surgery on this reflex loop have not been evaluated in epilepsy patients.

In the current study, we analysed the modulation of cerebral blood flow velocities (CBFV) in comparison with heart rate and blood pressure signals and determined the effects of TLE surgery on autonomic modulation of cerebral blood flow and cerebral autoregulation in a group of TLE patients in whom we had recently observed a reduction of autonomic modulation of heart rate and blood pressure after epilepsy surgery [21].

Methods

We re-evaluated nine women and seven men aged 28 to 52 years (mean 36.2, SD 6.9) with epilepsy refractory to antiepileptic drug treatment [21]. Fourteen patients were right-handed, two were left-handed, 14 patients had left-sided speech dominance, one patient had bilateral speech dominance and one patient had right-sided speech dominance as determined by neuropsychological testing during intracarotid amobarbital injection (Table 1) [21].

Four patients had single partial and complex partial seizures, seven patients had complex partial seizures with secondary generalization, five patients had single partial, complex partial and generalized seizures. The duration of epilepsy ranged from 14 to 37 years (mean 22.9 years, SD 12.8). Presurgical epilepsy evaluation showed seizure onset in the left temporal lobe in eight patients and in the right temporal lobe in eight patients (Table 1). The study protocol was approved by the Institutional Review Board of New York University School of Medicine and all subjects gave informed written consent 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 blood pressure or diabetes mellitus. No study participant was being treated with drugs known to interfere with autonomic nervous function. All participants were asked not to consume nicotine, caf-

Table 1 Clinical characterization (age, gender, handedness, speech dominance, seizure types, seizure focus, antiepileptic medication) of 16 patients undergoing temporal lobe surgery for epilepsy refractory to drug treatment (*SPS* single partial seizures; *CPS* complex partial seizures; *GTC* generalized tonic-clonic seizures; *Cbz* Carbamazepine; *Tpm* Topiramate; *Pht* Phenytoin; *Ltg* Lamotrigine; *Gbp* Gabapentin; *Ocbz* Oxcarbazepine)

Patient	Age (years)	Gender	Handedness	Speech	Seizure type	EEG focus	Operation	Medication
1	29	female	right	left	CPS, GTC	left frontotemporal	temporal lobectomy; hippocampectomy	Cbz, Tpm
2	37	female	right	left	CPS, GTC	left frontotemporal	temporal lobectomy; hippocampectomy	Cbz, Ltg
3	36	female	right	left	SPS, CPS, GTC	left frontotemporal	temporal lobectomy; hippocampectomy	Pht, Ltg, Gbp
4	31	male	right	left	SPS, CPS	right frontotemporal	temporal lobectomy; hippocampectomy	Cbz, Tpm
5	28	male	right	bilateral	SPS, CPS, GTC	right frontotemporal	temporal lobectomy; hippocampectomy	Cbz, Gbp, Tpm
6	40	female	right	left	CPS, GTC	left frontotemporal	temporal lobectomy; hippocampectomy	Ocbz, Tpm
7	39	male	left	left	SPS, CPS, GTC	right frontotemporal	temporal lobectomy; hippocampectomy	Cbz, Gbp
8	34	male	right	left	CPS, GTC	left frontotemporal	temporal lobectomy; hippocampectomy	Pht, Gbp
9	52	male	right	left	SPS, CPS	right mediotemporal	temporal lobectomy; hippocampectomy	Pht, Gbp
10	39	male	right	left	CPS, GTC	left frontotemporal	temporal lobectomy; hippocampectomy	Cbz, Gbp, Tpm
11	41	female	right	left	CPS, GTC	right centrotemporal	temporal lobectomy; hippocampectomy	Pht, Ltg, Gbp
12	49	female	right	left	SPS, CPS, GTC	left frontotemporal	temporal lobectomy; hippocampectomy	Cbz, Ltg,
13	43	female	right	left	SPS, CPS, GTC	right frontotemporal	temporal lobectomy; hippocampectomy	Cbz, Gbp,Tpm
14	31	female	right	left	SPS, CPS	left frontotemporal	temporal lobectomy; hippocampectomy	Cbz, Tpm
15	33	male	left	right	SPS, CPS	right frontotemporal	temporal lobectomy; hippocampectomy	Pht, Gbp
16	39	female	right	left	CPS, GTC	right frontotemporal	temporal lobectomy; hippocampectomy	Cbz, Gbp,Tpm

feine or alcohol 18 hours before testing. On the days of autonomic testing, patients only took their regular antiepileptic medication. Antiepileptic medication was not changed between the pre- and postsurgical evaluation (Table 1). All patients were free of seizures 48 hours prior to the testing. Prior to the pre- and postsurgical autonomic evaluations, all patients underwent recording of the electroencephalogram (EEG) using standard techniques.

As the comparison of the pre- and postsurgical evaluations might be biased by anxiety and stress prior to surgery and a more reassured and relaxed emotional state after surgery, patients underwent the presurgical 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. To minimize emotional influences on the cardiovascular responses due to an imminent intervention, we only tested patients three to four months before (and after) surgery.

Patients were tested between 9 and 12 am in a 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 heart rate (HR), blood pressure and respiration during a 10 minutes resting period.

Heart rate was recorded as beats per minute (bpm) with a three-lead electrocardiogram using a Colin Pilot™ monitor (Colin Medical Instruments, San Antonio, TX). Mean blood pressure (BP_{mean}) was continuously recorded from the left radial artery using non-invasive arterial tonometry (Colin Pilot™, Colin Medical Instruments Corp., San Antonio, TX, USA) [27]. Respiratory frequency was monitored with a two-belt chest-abdomen inductance plethysmograph after calibration (Respitrace Calibrator™, Ambulatory Monitoring, Inc., Ardsley, NY, USA). Mean cerebral blood flow velocities ($CBFV_{mean}$) at the left and right proximal middle cerebral artery (MCA) were studied using transcranial Doppler sonography (Multidop XL™, DWL, Sipplingen, Germany).

Transcutaneous oxygen saturation (sat-O_2) was measured by means of infrared plethysmography at the right index finger (Nellcor®, Pleasanton, CA). End-expiratory carbon dioxide partial pressure (pCO_2) was monitored via nasal cannulas and analysed by the Colin Pilot™ monitor.

Blood pressure, heart rate, CBFV and respiratory signals were transferred via analogue output into a custom designed data acquisition and analysis system (HRView™, Boston Medical Technologies; Brighton, MA, USA). Each channel of data was sampled at 1 kHz and displayed on the PC.

Calculation of mean values, standard deviation and cerebrovascular resistance

From the 120-second epochs monitored before and after TLE surgery at rest, we calculated mean values and standard deviation of all biosignals. We compared mean cerebral blood flow velocities between the left and right MCA and intended to further analyse CBFV values of the MCA opposite to the seizure focus only, provided there was no difference between values of the left and right sides (Wilcoxon, $p > 0.05$).

Cerebrovascular resistance (CVR) was calculated according to Ohm's law as the ratio between the driving force of cerebral blood flow, i. e. the arterial blood pressure at brain level (BP_{mean_brain}) and cerebral blood flow expressed as $CBFV_{mean}$ ($CVR = BP_{mean\_brain}/CBFV_{mean}$) [26, 32]. As patients were lying in the supine position, we estimated BP_{mean_brain} as the BP_{mean} at heart level.

Spectral analysis, coherence, transfer function gain and phase shift between BP and CBFV

Autonomic cardio- and cerebrovascular regulation is often investigated by measuring mean responses of HR, BP or CBFV to external stimuli e. g. tilting. However, the calculated net changes of e. g. blood pressure or heart rate often disregard information on the instantaneous dynamics of autonomic modulation [22, 31, 34]. Analysis of spontaneously occurring fluctuations in autonomic tone by means of spectral analysis might offer a more subtle insight into the physiological mechanisms of autonomic cardio- and cerebrovascular control [22, 31, 34]. Spectral analysis allows the splitting of the overall variance of a signal into its various underlying frequency components, as most biosignals that vary around a mean value can be reconstructed as a sum of sines and cosines at different frequencies [6, 26, 35, 38]. Differences in the results of spectral analysis can be attributed to differences in the neural influences responsible for cardio- and cerebrovascular regulation.

Slow fluctuations of HR, BP and CBFV are largely mediated by the undulating activity of the sympathetic and parasympathetic nervous systems [22, 31, 34]. Parasympathetic modulation of HR is most pronounced at the frequency of respiration, e. g. at 0.2 Hz if breathing rate is 12 cycles per minute (cpm) [22, 31, 34]. Parasympathetic, respiratory influences are considered to account for heart rate modulation occurring in a frequency range from 0.15–0.5 Hz, the so-called high frequency or HF range. Therefore, heart rate modulation in the HF range can be considered an index of parasympathetic activity [22, 31, 34]. In contrast, fluctuations of vascular signals, such as BP and CBFV, in the HF range are primarily a mechanical consequence of respiration-induced increases in venous return [22, 31, 34]. However, parasympathetic influences on heart rate can still occur at frequencies below 0.15 Hz. Therefore, modulation of heart rate in the range from 0.04–0.15 Hz, the so-called low frequency or LF range, is considered to result not only from sympathetic activity, but may also contain parasympathetic influences. In contrast, fluctuations of the BP and CBFV signal in the LF range can be related to sympathetic outflow only [22, 31, 34]. Consequently, we determined the degree of sympathetic signal modulation primarily from the amount of LF modulation of BP and CBFV and not from LF heart rate modulation only [22, 31, 34].

For spectral analysis, 120 second recordings of electrocardiogram RR-intervals, BP_{mean} and $CBFV_{mean}$ values recorded before and after surgery, were cleaned of artifacts, resampled at 4 Hz, and then taken for spectral processing using the Blackman-Tukey algorithm, as previously described in more detail [22].

Sympathetic and parasympathetic influences on CBFV, BP and HR variability were assessed by quantifying the LF and HF components of the three signals. The magnitude of these components was determined as the integral under the power spectral density curves of HR (bpm^2/Hz), BP ($mmHg^2/Hz$) and CBFV [$(cm/sec)^2/Hz$] for the two frequency bands and expressed as LF and HF power of HR (bpm^2), BP ($mmHg^2$) and CBFV [$(cm/sec)^2$] [22, 34].

Cerebral autoregulation maintains constancy of cerebral blood flow in the face of changing BP by buffering spontaneous blood pressure changes through a corresponding increase or decrease in cerebrovascular resistance, i. e. cerebral autoregulation attempts to minimize the effects of BP on CBFV by adjusting the diameter of cerebral arteriole vessels [11, 22, 32]. The spectral method of transfer function calculation can evaluate the dynamic cerebral autoregulatory capacity by analysing the cerebral blood flow adjustment (output signal) to continuously changing blood pressure values (input signal) [7, 16]. The mechanisms of cerebral autoregulation can be considered to reflect a high-pass filter that dampens and shifts slow fluctuations of BP but allows for passing through of rapid oscillations, such as the pulsatile signals of the BP waves [7, 16]. The degree of dampening of dynamic BP changes, i. e. the extent or 'gain' to which BP oscillations are transferred onto the CBFV, and the degree of shifting between the BP and the CBFV signal, i. e. the phase angle between both signals, are two spectral indices of cerebral autoregulation [7, 16]. The gain indicates the magnitude of change in CBFV that is caused by a change in BP. A smaller gain means more effective cerebral autoregulation [7, 16]. The phase describes the shift in degrees at a specific frequency necessary to align the input signal BP with the output signal CBFV. The higher the phase shift between the input signal BP and the output signal CBFV, the better the effect of cerebral autoregulation [7, 16]. We calculated the transfer function gain and phase shift between BP and CBFV in the LF band as parameters reflecting the quality of

dynamic cerebral autoregulation, provided there was significant coherence between BP and CBFV [16, 31, 32, 37].

The coherence between BP and CBFV signal oscillations [5, 6] might span from 0 (i. e. no association) to 1 (i. e. maximal association) [5, 6]. If there was a coherence above 0.5, the two signals were considered to have a stable phase relation for a given frequency of oscillation and the signals were thought to be synchronized with each other. In this case, we calculated the LF gain and phase shift between CBFV and BP oscillations [16, 31, 32, 37].

To normalize the cerebral autoregulation gain, we divided the LF transfer function gain between BP and CBVF by the mean values of the input signal BP and the output signal CBFV of cerebral autoregulation, i. e. by the cerebrovascular conductance (CBFV/BP) of each patient [7, 32].

Statistical analysis

To assess differences in cardio- and cerebrovascular regulation before and after surgery and to identify effects of the side of the surgery, we performed an analysis of variance for repeated measures (general linear model, ANOVA), with "hemisphere" (left, right) and "surgery" (before, after) as "within subject" factors. The analysis was applied for all above mentioned autonomic parameters recorded during the 120 s recording 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 x hemisphere") was significant. The level of significance was set at $p \leq 0.05$.

A commercially available statistical program (SPSS-V10; SPSS, Chicago, Il) was used for data analysis.

Results

Time domain analysis

The presurgical electroencephalogram (EEG) showed interictal epileptogenic activity over the right temporal leads in 8 of the 16 patients. In 2 of these 8 patients, the field extended to other right hemisphere areas. In the 8 other patients, there was interictal epileptogenic activity over the left temporal leads. In 2 of these 8 patients, the field extended to other right hemisphere areas. The EEG also showed occasional spread, but not independently, of the epileptiform activity to areas of the contralateral hemisphere in one patient of each subgroup, i. e. in 2 of the 16 patients. None of the patients developed simple partial, complex partial or tonic-clonic seizures after surgery. Postsurgical EEG recordings did not reveal epileptogenic activity in any of the 16 patients [21].

Temporal lobe surgery did not affect mean values of HR, BP_{mean}, respiratory frequency $CBFV_{mean}$, transcutaneous oxygen saturation (sat-O_2) and pCO_2 significantly. Moreover, there was no difference between CBVF values of the left and right middle cerebral artery (Table 2).

After surgery, mean values of HR, BP_{mean}, $CBFV_{mean}$, respiratory frequency, sat-O_2 and pCO_2 were quite similar to the respective presurgical values (ANOVA: $p < 0.05$; Wilcoxon: $p > 0.05$; Table 2). Similarly, CVR values after surgery (1.37 ± 0.38 mmHg^{-1} cm/sec^{-1}) did not differ significantly from the CVR values before surgery (1.43 ± 0.48 mmHg^{-1} cm/sec^{-1}) (ANOVA: $p < 0.05$; Wilcoxon: $p > 0.05$; Table 2).

There was no difference of the time domain parameters before and after surgery within the subgroups who underwent right or left mesial temporal lobe resection and between the pre- and postsurgical values of patients with left or right hemispheric seizure focus (ANOVA: $p > 0.05$; Wilcoxon: $p > 0.05$; Table 2).

Frequency domain analysis

Spectral analysis of biosignal fluctuations showed a change of cardiovascular as well as cerebrovascular au-

Table 2 Mean values of heart rate (HR), mean blood pressure (BP_{mean}), mean cerebral blood flow velocity ($CBFV_{mean}$), respiration (RESP), transcutaneous oxygen saturation (sat-O_2), endexpiratory carbon dioxide partial pressure (pCO_2) and cerebrovascular resistance (CVR). Temporal lobe surgery did not alter mean values of HR, BP_{mean}, $CBFV_{mean}$, RESP, sat-O_2, pCO_2 or CVR significantly

	Temporal lobe epilepsy patients (n = 16)		Subgroup with left-sided focus (n = 8)		Subgroup with right-sided focus (n = 8)	
	Presurgical (mean ± SD)	Postsurgical (mean ± SD)	Presurgical (mean ± SD)	Postsurgical (mean ± SD)	Presurgical (mean ± SD)	Postsurgical (mean ± SD)
Cardio- and cerebrovascular parameters						
HR (bpm)	69.2 ± 6.9	71.4 ± 10.7	68.1 ± 9.1	69.4 ± 15.5	70.3 ± 4.9	73.1 ± 5.2
BP_{mean} (mmHg)	90.9 ± 15.6	85.1 ± 10.4	87.2 ± 6.3	83.6 ± 10.5	94.7 ± 10.5	86.6 ± 11.2
$CBFV_{mean}$ (cm/sec)	68.4 ± 11.4	62.8 ± 12.9	68.0 ± 12.3	62.7 ± 17.0	68.9 ± 11.8	62.9 ± 8.3
Respiratory parameters						
RESP (cpm)	14.6 ± 3.5	14.4 ± 3.2	14.8 ± 2.3	15.1 ± 5.0	14.9 ± 3.1	14.0 ± 2.7
sat-O_2 (%)	98.0 ± 2.0	96.0 ± 3.0	97.0 ± 2.0	98.0 ± 2.0	96.0 ± 2.0	96.0 ± 3.0
pCO_2 (mmHg)	42.0 ± 3.0	42.0 ± 4.0	40.0 ± 2.0	41.0 ± 5.0	38.0 ± 4.0	43.0 ± 4.0
Cerebrovascular resistance						
CVR (mmHg^{-1} cm/sec^{-1})	1.43 ± 0.48	1.37 ± 0.38	1.30 ± 0.17	1.57 ± 0.70	1.44 ± 0.51	1.29 ± 0.15

tonomic modulation after temporal lobe surgery. After surgery, the powers of the LF-modulation of HR (1.47 ± 1.31 bpm^2) and BP_{mean} (2.02 ± 1.59 mmHg^2) were smaller than the LF-powers of HR (3.63 ± 3.02 bpm^2) and BP_{mean} (3.29 ± 2.23 mmHg^2) before tailored resection [21]. In addition, the postsurgical LF powers of CBFV (3.96 ± 2.49 [cm/sec]^2) were lower than the presurgical LF powers (6.04 ± 4.14 [cm/s]^2) (ANOVA: $p < 0.05$; Wilcoxon: $p < 0.05$; Table 3).

In contrast, the postsurgical HF modulation of HR (1.61 ± 1.23 bpm^2), BP_{mean} (0.88 ± 1.56 mmHg^2) and $CBFV_{mean}$ (1.85 ± 2.35 [cm/s]^2) was similar to the presurgical HF-powers of HR (1.88 ± 1.72 bpm^2), BP_{mean} (0.61 ± 0.41 mmHg^2) and $CBFV_{mean}$ (1.91 ± 1.39 [cm/s]^2) (ANOVA: $p > 0.05$; Wilcoxon: $p > 0.05$; Table 3).

Again, these changes did not show any hemisphere-specific effects, but were similar in the subgroups of patients with left- or with right-hemispheric intervention (ANOVA: $p > 0.05$; Wilcoxon: $p > 0.05$; Table 3).

After TLE surgery, the LF transfer function gain between BP and CBFV was significantly lower (0.83 ± 0.33 cm/s/mmHg) than before surgery (1.32 ± 0.68 cm/s/mmHg) (ANOVA: $p < 0.05$; Wilcoxon: $p < 0.05$; Table 3). After normalization of the gain by the mean BP and CBFV values of each patient, the gain was also lower after surgery (1.24 ± 0.79) than before surgery (1.81 ± 1.10) (ANOVA: $p < 0.05$; Wilcoxon: $p < 0.05$; Table 3).

In addition, the phase angle between BP_{mean} and $CBFV_{mean}$ – calculated as second parameter of cerebral autoregulation – was significantly higher after surgery (43.6 ± 10.1 deg) than before surgery (29.8 ± 9.9 deg) (ANOVA: $p < 0.05$; Wilcoxon: $p < 0.05$; Table 3).

Like the changes of LF and HF powers, the reduction of the cerebral autoregulation gain and phase did not depend on the side of surgery (ANOVA: $p > 0.05$; Wilcoxon: $p > 0.05$; Table 3).

Discussion

This study shows significantly reduced sympathetic influences on CBFV and improved cerebral autoregulation after TLE surgery. The results confirm our previous findings of decreased sympathetic cardiovascular modulation after TLE surgery, reflected in decreased LF power of HR modulation by 59 % and of BP by 39 % [21]. The postoperative reduction of LF power of CBFV by 34 % also shows an attenuation of sympathetic influences on CBFV.

However, we cannot decide whether the epilepsy patients returned to a state of sympathetic normality after temporal lobe surgery or remain blunted in their responses as we did not introduce a control group.

The observed changes of CBFV may reflect changes of vessel diameter at the site of Doppler insonation or a

Table 3 Mean values of HR, BP_{mean} and $CBFV_{mean}$ modulation in the low frequency (LF) and high frequency (HF) range and indices of cerebral autoregulation, transfer function gain and phase angle between BP_{mean} and $CBFV_{mean}$ oscillations in the LF range, before and after temporal lobe surgery.

Results are reported for all 16 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).

Spectral powers of HR, BP and CBFV modulation in the LF range decreased after surgery while HF powers of HR, BP and CBFV modulation remained stable. The gain between BP and CBFV oscillations in the LF range, i. e. the impact of BP fluctuations on CBFV fluctuations, decreased after surgery. In contrast, the phase angle between BP and CBFV oscillations in the LF range increased after surgery confirming improved filtering of BP oscillations by mechanisms of cerebral autoregulation. Results did not differ for patients with left or right hemispheric seizure focus.

Bold numbers indicate significant differences between pre- and postsurgical values ($p < 0.05$)

	Temporal lobe epilepsy patients (n = 16)		Subgroup with left-sided focus (n = 8)		Subgroup with right-sided focus (n = 8)	
	Presurgical (mean ± SD)	Postsurgical (mean ± SD)	Presurgical (mean ± SD)	Postsurgical (mean ± SD)	Presurgical (mean ± SD)	Postsurgical (mean ± SD)
HR spectral power						
LF (bpm^2)	3.63 ± 3.02	**1.47 ± 1.31**	4.21 ± 3.99	**1.78 ± 1.93**	3.03 ± 1.92	**1.09 ± 0.92**
HF (bpm^2)	1.88 ± 1.72	1.61 ± 1.23	2.22 ± 2.01	2.29 ± 1.88	1.25 ± 1.01	1.12 ± 0.33
BP_{mean} spectral power						
LF (mmHg^2)	3.29 ± 2.23	**2.02 ± 1.59**	3.25 ± 2.18	**2.31 ± 1.94**	3.32 ± 2.44	**1.74 ± 1.23**
HF (mmHg^2)	0.61 ± 0.41	0.88 ± 1.56	0.57 ± 0.36	0.99 ± 1.19	0.64 ± 0.47	0.46 ± 0.27
$CBFV_{mean}$ spectral power						
LF (cm/s)^2	6.04 ± 4.14	**3.96 ± 2.49**	5.34 ± 3.78	**3.21 ± 1.79**	6.75 ± 4.60	**4.71 ± 2.97**
HF (cm/s)^2	1.91 ± 1.39	1.85 ± 2.35	1.79 ± 1.12	1.92 ± 0.99	1.95 ± 1.53	1.78 ± 1.61
Autoregulatory indices						
Gain (cm/s/mmHg)	1.32 ± 0.68	**0.83 ± 0.33**	1.32 ± 0.81	**0.82 ± 0.39**	1.32 ± 0.59	**0.80 ± 0.29**
Normalized gain	1.81 ± 1.10	**1.24 ± 0.79**	1.81 ± 1.36	**1.38 ± 1.05**	1.81 ± 0.86	**1.02 ± 0.41**
Phase angle (deg)	29.8 ± 9.9	**43.6 ± 10.1**	29.2 ± 6.7	**42.3 ± 11.4**	30.4 ± 12.8	**43.4 ± 8.6**

change of vessel resistance downstream from insonation [1, 14, 20]. Neither case influences the interpretation of our results, since only the LF power of CBFV modulation decreased after surgery, while CBFV remained unchanged. The spectral powers are quantified independently from changes in vessel diameter [19].

The changes of CBFV modulation in the LF range cannot be explained by altered influences of respiration on autonomic control or cerebral blood flow, as respiratory frequency, sat-O_2 and pCO_2 remained unchanged before and after surgery. Instead, we suggest that the reduced sympathetic cardiovascular modulation [21], decreased sympathetic CBFV modulation and improved cerebral autoregulation that we observed result from reduced interference of interictal epileptogenic activity with autonomic pathways [21]. These relevant interictal influences on autonomic function may extend beyond epileptiform activity, affecting neurotransmitter, neuroendocrine, receptor, and modulation of neural networks. After surgery, seizure frequency and severity and interictal epileptiform activity significantly improved in all of our patients. Therefore, the influence of seizure discharges spreading into centers that modulate sympathetic tone was significantly attenuated after surgery [21]. Diehl and co-workers observed increased CBFV in response to generalized spike-wave discharges before the clinical seizure onset [15]. They concluded that epileptogenic discharges activated autonomic neurons innervating cerebral blood vessels and thereby elevated CBFV [15].

During the interictal period, Diehl and coworkers [14] recorded increased sympathetic modulation of CBFV and concluded that there was a dysfunction of cerebral autonomic relay areas [14]. We suggest that in addition to reduced epileptogenic activity, removal of autonomic relay areas contributed to the postsurgical decrease of sympathetic CBFV modulation. The tailored resection includes the removal of the amygdala, that strongly modulates autonomic activity [3, 18, 33].

Since emotional states have a direct influence on autonomic modulation [8–10, 12], decreased sympathetic modulation after surgery may partly result from improved emotional well-being (e. g., being more relaxed) after surgery. Critchley et al. showed an interaction between tasks inducing different internal bodily states and the activation of central autonomic relay areas (e. g. insula, cingulate cortex, the right medial temporal lobe adjacent to the amygdala) as well as inferior parietal areas, and subcortical areas [8, 10, 12]. TLE surgery affects the interaction between these brain regions, as the operation includes the resection of structures that are interconnected with many autonomic relay regions [3, 33]. Consequently, a modified interaction between regions subserving emotional and autonomic function may partly reduce sympathetic cardio- and cerebrovascular activity [21].

The reduced sympathetic CBFV modulation is accompanied by an improved cerebral autoregulation. The ~35 % reduction of the LF transfer function gain between BP and CBFV oscillations suggests that surgery reduces the effects of BP fluctuations on CBFV oscillations. The increase of the phase angle between BP and CBFV oscillations from 29.8 degree before to 43.6 degree after surgery supports that the postsurgical decrease of gain is not a mathematical artifact but indicates improved dampening of BP fluctuations [30, 31]. As a result of enhanced high pass filtering, suggested by lower gain values, the phase shift between BP and CBFV oscillations is higher after than before surgery [31, 32, 37]. Thus, the combined finding of lower gain and higher phase angle documents improved cerebral autoregulation after surgery, with higher stability of the output signal CBVF against fluctuations of the input signal BP [16].

Decreased sympathetic cerebrovascular modulation is probably the major factor in improving cerebral autoregulation after surgery. Sympathetic, and to a lesser extent parasympathetic, innervation of cerebral vessels is essential for sufficient cerebral autoregulation [20, 32]. The reduced sympathetic modulation after surgery allows for a more efficient interaction of the different mechanisms of autoregulation, such as the myogenic Bayliss effect or neurohumeral and endothelial factors [20, 32]. Also, improved autoregulation might result from a reduced influence of seizure activity on cerebral perfusion. Hexamethylpropylene amine oxime-SPECT studies show that seizure activity alters cerebral blood flow regulation with hyperperfusion during or shortly after a seizure [25].

By reducing the excessive interictal sympathetic CBFV modulation, temporal lobectomy can improve cerebral autoregulation and may stabilize cardio- and cerebrovascular control in epilepsy patients. Compromised cerebral autoregulation might contribute to the pathophysiology of sudden unexplained death in epilepsy patients (SUDEP), a poorly understood but significant cause of mortality in seizure disorders [2, 36]. In sudden infant death syndrome (SIDS), impaired cerebral autoregulation may contribute to cerebral hypoperfusion and other factors leading to death [29]. Similarly, dysfunction of cerebral blood flow modulation and of cerebral autoregulation might increase the risk of SUDEP [2, 36]. The normalization of baroreflex function and sympathetic heart rate and blood pressure modulation after TLE surgery may reduce the risk of autonomic dysfunction in epilepsy patients, and possibly reduce the risk of SUDEP [21]. Similarly, the positive effects of TLE surgery on cerebral blood flow modulation and autoregulation observed in this study might contribute to a lower risk of cardiovascular dysregulation in epilepsy patients.

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