Seizure 22 (2013) 713–718

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Heart rate variability remains reduced and sympathetic tone elevated after temporal lobe epilepsy surgery

Nese Dericioglu [a,c,*], Mehmet Demirci [a], Oguz Cataltepe [b], Nejat Akalan [b], Serap Saygi [a]

[a] Department of Neurology Faculty of Medicine, Hacettepe University, Ankara, Turkey
[b] Department of Neurosurgery Faculty of Medicine, Hacettepe University, Ankara, Turkey
[c] Institute of Neurological Sciences and Psychiatry, Hacettepe University, Ankara, Turkey

ARTICLE INFO

Article history:
Received 11 February 2013
Received in revised form 13 May 2013
Accepted 14 May 2013

Keywords:
Epilepsy surgery
Temporal lobe epilepsy
Heart rate variability
Autonomic nervous system

ABSTRACT

Purpose: There is evidence of autonomic dysregulation in temporal lobe epilepsy. The structures removed during temporal lobectomy are important centers of central cardiovascular control; therefore surgery may conceivably alter the cardiovascular autonomic function. The effects of temporal lobectomy on autonomic cardiac control are controversial. We investigated the effects of temporal lobectomy on heart rate variability (HRV) in the early and late postoperative periods.

Methods: We used 1-h ECG recordings to assess heart rate variability by spectral analysis in 24 consecutive patients who underwent temporal lobectomy due to intractable temporal lobe epilepsy. ECG recordings were performed before and twice (early and late) after surgery. The results were compared with age and sex matched controls.

Results: When compared with controls, all the time and frequency domain indices (SDRR, RMSSD, TP, LF and HF) were significantly lower in the patient group before surgery. Findings were similar in the early and late post-operative periods except that the LF/HF ratio increased in the patient group after the late post-operative period. Within the patient group, compared to pre-operative results, normalized HF was increased in the early post-operative period; however in the late post-operative period, LF/HF ratio was increased.

Conclusions: These findings show that in patients with intractable temporal lobe epilepsy, HRV is decreased globally in both sympathetic and parasympathetic domains. While the total HRV remains reduced throughout the postoperative periods, the LF/HF ratio, i.e., sympathovagal balance is altered, in favor of parasympathetic side early after surgery, but towards the sympathetic side after the first postoperative month.

1. Introduction

There is increasing evidence for neurally mediated cardiac damage in patients with epilepsy. Previous clinical studies have indicated that cardiac autonomic functions may be altered interictally in patients with either generalized[1] or partial epilepsy,[1–3] mainly of temporal lobe origin. Cardiac autonomic control can be assessed clinically by spectral analysis of heart rate variability (HRV), which allows assessment of the sympathetic and parasympathetic components separately from each other. The literature of HRV investigations in epileptic adults is contradictory, indicating inhibition of both sympathetic and parasympathetic tones;[1,2,4,5] sympathetic dominance[6,7] or parasympathetic dominance.[1,8] These alterations are commonly attributed to spread of seizure discharges to autonomic centers in the cortex and various limbic structures, or the effect of antiepileptic drugs (AED).[9]

Reduced HRV has been associated with increased mortality in various clinical disorders and sudden unexpected death in epilepsy patients (SUDEP).[10] Several studies have reported that the mortality ratio decreases after epilepsy surgery,[11–14] which is in part attributed to decrease in the number or complete cessation of seizures. Given that some of the suprabulbar centers that are removed during temporal lobe epilepsy (TLE) surgery are also involved in autonomic cardiovascular (CV) control, any possible changes in interictal cardiac autonomic function postoperatively may also contribute to this finding. Very few studies have investigated the effects of TLE surgery on autonomic control of CV function[15–18] and the results are conflicting. Besides, the time

* Corresponding author at: Faculty of Medicine, Department of Neurology, Hacettepe University, Sihhiye 06100, Ankara, Turkey. Tel.: +90 312 305 1806; fax: +90 312 309 3451.
E-mail addresses: nesedericioglu@yahoo.com, nesedr@hacettepe.edu.tr (N. Dericioglu), mdemirci@hacettepe.edu.tr (M. Demirci), oguz.cataltepe@umassmemorial.org (O. Cataltepe), nakalan@hacettepe.edu.tr (N. Akalan), ssaygi@hacettepe.edu.tr (S. Saygi).

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http://dx.doi.org/10.1016/j.seizure.2013.05.007

course of post-operative alterations is not known; and it is not clear if the changes reflect a functional loss secondary to removal of the relevant anatomical structures, or if they are due to a malfunction secondary to late plastic changes. Therefore we designed a prospective study to evaluate the characteristics of HRV in TLE patients who underwent temporal lobectomy with amygdalo-hippocampectomy and we investigated HRV within the first postoperative week and after the first month of surgery.

2. Patients and methods

2.1. Patients

Twenty-four consecutive patients (11M, 13F; age: 15–48 (median 27.5 years)) who underwent temporal lobectomy due to intractable epilepsy in our center were included in this prospective study (Table 1). Patients with clinical or laboratory evidence of coexisting heart failure, coronary artery disease, relevant rhythm disturbances such as marked sinus arrhythmia, atrial fibrillation or flutter, frequent ectopic beats or conduction blocks, diabetes mellitus, uremia or any other disease that might affect autonomic function were excluded from the study. None of them had a clinical history or complaints regarding the ANS. General physical and neurological examinations of the patients were not remarkable. Duration of epilepsy ranged from 2 to 43 (median: 16) years. Preoperatively the patients were investigated with interictal/ictal scalp video-EEG recordings, high resolution cranial MR imaging (1.5–3 T), and interictal/ictal SPECT and PET when needed. All of them were right handed. Clinical and laboratory findings were discussed by an epilepsy surgery team before a final consensus was reached. The patients underwent standard anterior temporal lobectomy with amygdalo-hippocampectomy (13R, 11L), after which they were followed up for at least a year.

Propofol, fentanyl, nitrous oxide or desflurane were used during general anesthesia. All the patients gave informed consent. During testing in the preoperative and postoperative periods, no study participant received any additional drugs, which are known to interfere with autonomic function. Neither the antiepileptic drugs nor their dosages were changed during the evaluation period.

Twenty-three age- and sex-matched healthy volunteers (13F, 10M; age: 15–50 (median 27 years)) served as a control group.

2.2. HRV

The preoperative evaluation was performed 1–21 (median 2.5) days before the surgery, while postoperative evaluations were carried out twice: (a) 3–8 (median 5) days after surgery (early postoperative period) and (b) 35–188 (median 59.5) days after surgery (late postoperative period). Although we aimed to perform the late postoperative tests at 6 weeks to 3 months after surgery, some of the patients admitted before or after the proposed time-window for postoperative control, leading to the large variation in timing of the late postoperative period. Heart rate variability recordings were performed between 9 AM and 4 PM. Patients were tested in relaxed, supine position in a room with ambient temperature of about 20 °C and were awake during the procedure. Approximately 1-h of recordings were made for each session. All but one (who had a complex partial seizure 16 h before the test) were free of seizures for at least 24 h prior to the testing. None of them reported auras or had seizures during the test.

The ECG signals were recorded with the negative electrode 5 cm right of the suprasternal notch, the positive electrode at the left anterior-axillary line in the sixth intercostal space, and the indifferent electrode on the right mid-axillary line. The analog output of the ECG amplifier (model PM4; Graseby Medical, UK) was connected to a custom-made triggering device, which generated a TTL pulse (a standard +5 V pulse for "Transistor–Transistor Logic") for each incoming R wave of ECG. The pulses were fed to the serial port of a PC. Subsequent stages of recording, editing, and analyses were performed using software developed in our laboratory. The software continuously scanned the computer's serial port and detected the time intervals between incoming pulses at a

Table 1
Clinical charateristics of the study group.

Patient no.	Age (years)	Gender	Seizure type	AED and daily dose (mg)	MRI findings/pathology	Side of surgery	Outcome (Engel class)
1	15	M	SPS, CPS, GTCS	DPH (300)	Left TL tumor (ganglioglioma)	L	I
2	15	F	SPS, CPS	CBZ (800), GBP (900)	HS	R	I
3	25	M	SPS, CPS, GTCS	OXCBZ (1800)	HS	L	I
4	17	F	SPS, CPS, GTCS	OXCBZ (1200)	HS	L	I
5	22	M	SPS, CPS	CBZ (1200), PHB (100)	Right amygdalar hyperintensity	R	I
6	23	F	SPS, CPS	VGB (2000), GBP (1600)	HS	L	I
7	24	M	CPS, GTCS	DPH (100), CBZ (400), GBP (800)	HS	R	I
8	27	F	CPS, GTCS	CBZ (800), GBP (600)	HS	R	II
9	37	M	SPS, CPS	GBP (1600), PHB (150)	HS	R	I
10	28	F	SPS, CPS	OXCBZ (1200)	Left hippocampal hyperintensity without atrophy	L	III
11	41	F	CPS, GTCS	VGB (2000)	Left TL cavernoma	L	I
12	33	M	SPS, CPS, GTCS	CBZ (800)	HS	R	I
13	31	F	SPS	CBZ (800), LTG (300), PHB (200)	Right TL cortical dysplasia	R	II
14	28	F	SPS, CPS	CBZ (2000), PRM (1000), LTG (125)	HS	R	I
15	44	F	SPS, CPS, GTCS	CBZ (1200), GBP (900)	HS	R	II
16	21	F	SPS, CPS, GTCS	OXCBZ (900), PRM (500)	HS	R	II
17	48	M	SPS, CPS, GTCS	CBZ (1200), VGB (2000); PHB (125)	HS	L	I
18	36	F	SPS CPS GTCS	CBZ (800), TPM (100)	HS	L	I
19	23	F	SPS CPS	CBZ (800), PHB (200), GBP (2000)	HS	L	I
20	34	M	SPS, CPS, GTCS	PRM (500), CBZ (800)	HS	L	II
21	43	M	SPS, GTCS	TPM (150), CBZ (400)	HS	R	I
22	18	F	SPS, CPS, GTCS	CBZ (600)	Ganglioglioma, HS	R	I
23	28	M	SPS, CPS, GTCS	CBZ (1200), LEV (1500)	HS	R	I
24	43	M	CPS, GTCS	TPM (200), OXCBZ 1800	Ganglioglioma	L	I

AED, antiepileptic drug; SPS, simple partial seizure; CPS, complex partial seizure; GTCS, generalized tonic clonic seizure; R, right; L, left; TL, temporal lobe; HS, hippocampal sclerosis; DPH, phenytoin; CBZ, carbamazepine; GBP, gabapentin; OXCBZ, oxcarbazepine; PHB, phenobarbital; VGB, vigabatrin; LTG, lamotrigine; PRM, primidone; TPM, topiramate; LEV, levetiracetam.

resolution of 1 ms. The obtained R–R interval series were recorded and stored for off-line processing. Erroneous R–R intervals due to missing or extra triggers were detected by inspecting the R–R series. Extra triggers splitting a normal interval into two pieces, such as T-wave triggers, were summed to reconstruct the original interval. Double intervals that resulted from missing R-wave triggers were split into two equal intervals. Split intervals of ectopic heart beats were removed and replaced by an interpolated interval. Erroneous intervals that resulted from other artifacts were deleted. R–R series that contained more than 5% erroneous intervals were discarded. Mean R–R interval was calculated for each recording. To obtain time series of evenly spaced samples, the R–R series were resampled at 4 Hz by cubic spline interpolation. The resampled signal was split into 50% overlapping epochs of 1024 data points that corresponded to 4.27 min of recording. Linear trends were removed and a Hanning window was applied to each epoch. The power spectrums of all epochs were computed using the FFT (Fast Fourier Transform) technique, and the ensemble averaged. Power was computed as area under the averaged spectrum at the corresponding frequency band. The high-frequency band (HF, 0.15–0.4 Hz) in the power spectrum of HRV represents the parasympathetic influences on the heart rate. The power in the low-frequency band (LF, 0.04–0.15 Hz) however, reflects modulations for predominantly sympathetic and to a lesser extent parasympathetic activities controlling the heart rate. Total power (TP, 0.0033–0.4 Hz) and normalized values of HF (nHF = HF/TP) and LF (nLF = LF/TP) were also computed. The ratio of LF to HF (LF/HF) has been considered as an index of sympathovagal balance.[20]

2.3. Statistical analysis

Since spectral power was not normally distributed, a logarithmic transformation was applied to TP, LF, and HF. Control and patient groups were compared using analysis of variance (STATISTICA 8.0, Statsoft Inc.) for SDRR, RMSSD, LogTP, LogLF, LogHF and LF/HF ratio. Within the patients' group, preoperative and two subsequent measurements were compared using ANOVA for repeated measures. Results were considered significant if $p < 0.05$. A significant main effect was followed by contrast analysis.

3. Results

Preoperatively, compared to the controls, all time- and frequency domain measures were significantly lower in the patients' group (SDRR, $p < 0.001$; RMSSD, $p = 0.002$; TP, $p < 0.001$; HF, $p = 0.001$; LF, $p < 0.001$) except nHF ($p = 0.96$), nLF ($p = 0.93$), and the LF/HF ratio ($p = 0.63$) (Table 2). Similar results were obtained in the early period. However, in the late period, while the other measures remained similar, the LF/HF ratio increased ($p = 0.015$).

Within the patient group, compared to pre-operative results, nHF was increased in the early period ($p = 0.048$). In the late period, there was a significant increase in nLF ($p = 0.039$) with a trend of a decrease in nHF ($p = 0.12$). Accordingly; LF/HF ratio was increased in this period ($p = 0.012$) (Fig. 1).

4. Discussion

This study shows that (a) in patients with intractable TLE, time and spectral domain indices of HRV are reduced, but sympathovagal ratio is preserved; (b) the decrease in HRV measures persists after TLE surgery; (c) several parameters indicate alteration of the sympathovagal balance towards parasympathetic side early after the surgery; (d) but towards the sympathetic side in the late period.

Many studies have investigated HRV alterations in patients with epilepsy. They have been performed in different patient populations such as newly diagnosed epilepsy patients who were free from AEDs[18,21,22]; chronic patients on different AEDs[22,23] and patients with well controlled vs drug resistant seizures.[5,23–25] Results have been inconsistent making it hard to draw strict conclusions such that, some have reported findings within normal limits[26] and others have reported increase/decrease in sympathetic activity, parasympathetic activity or both.[1–3] A recent meta-analysis of HRV in epilepsy indicated that HF decreases significantly, whereas LF is not altered in epilepsy patients vs controls.[27] Lotufo et al. also concluded that (1) time-domain analyses showed lower HRV and lower vagal activity in patients with epilepsy; (2) patients receiving AEDs tended to have higher LF values; (3) there were no differences between well controlled and refractory patients; and (4) age and gender did not influence the results.

Interictal autonomic dysfunction seems to be particularly evident in patients with TLE[2,3] in whom the degree of abnormality may be related to the severity of TLE.[3] It has been suggested that epileptogenic changes in the limbic system might be reflected in alteration or removal of the influence normally exerted on cardiac control mechanisms, potentially leading to unusual cardiac interval patterns. Some of the anatomical structures involved in TLE (i.e. amygdala, hippocampus, temporal pole) are also part of

Table 2
Time and frequency domain indices of HRV in controls and patients in the pre-operative, early post-operative and late post-operative periods.

	Age and sex matched controls	Patients					
	Mean (SD)	Pre-operative period		Early post-operative period Postop1		Late post-operative period Postop2	
		Mean (SD)	p^*	Mean (SD)	p^*	Mean (SD)	p^*
MeanRR	852.68 (101.8)	793.64 (111.48)	n.s.	823.33 (111.08)	n.s.	748.42 (94.79)	0.0007
SDRR	75.59 (29.35)	43.75 (16.08)	0.0001	43.12 (18.55)	0.0001	46.11 (19.20)	0.0004
RMSSD	50.52 (26.0)	26.83 (16.04)	0.0004	30.62 (18.68)	0.0041	24.19 (18.18)	0.0002
TP	3522.02 (2587.57)	1182.69 (1092.78)	–	1276.89 (1251.25)	–	1309.80 (1496.87)	–
LF	1777.11 (1218.57)	583.26 (416.25)	–	510.07 (414.08)	–	701.30 (560.05)	–
HF	1544.49 (1465.29)	498.87 (549.35)	–	677.59 (695.69)	–	548.35 (947.04)	–
LF/HF	1.69 (0.86)	1.85 (1.26)	0.0003	1.49 (1.37)	0.0006	3.25 (2.83) ($p = 0.012$)[b]	0.0005
Log TP	3.38 (0.43)	2.92 (0.36)	0.0001	2.94 (0.39)	0.0001	2.93 (0.38)	0.0005
Log LF	3.12 (0.38)	2.65 (0.33)	0.0018	2.59 (0.32)	0.0212	2.73 (0.32)	0.0007
Log HF	2.95 (0.53)	2.47 (0.43)	n.s.	2.57 (0.55)	n.s.	2.36 (0.55)	0.0152
nLF	55.46 (12.0)	55.79 (14.78)	n.s.	48.24 (17.28)	n.s.	64.55 (18.44) ($p = 0.039$)[c]	n.s.
nHF	38.25 (12.43)	38.06 (13.29)	n.s.	46.24 (17.42) ($p = 0.048$)[a]	n.s.	31.30 (17.38)	n.s.

[a,b,c] Comparisons with pre-operative period (similar comparisons for other parameters were not significant).
n.s, not significant.
[*] Comparison between controls and patients in the pre-operative, early post-operative and late post-operative periods.

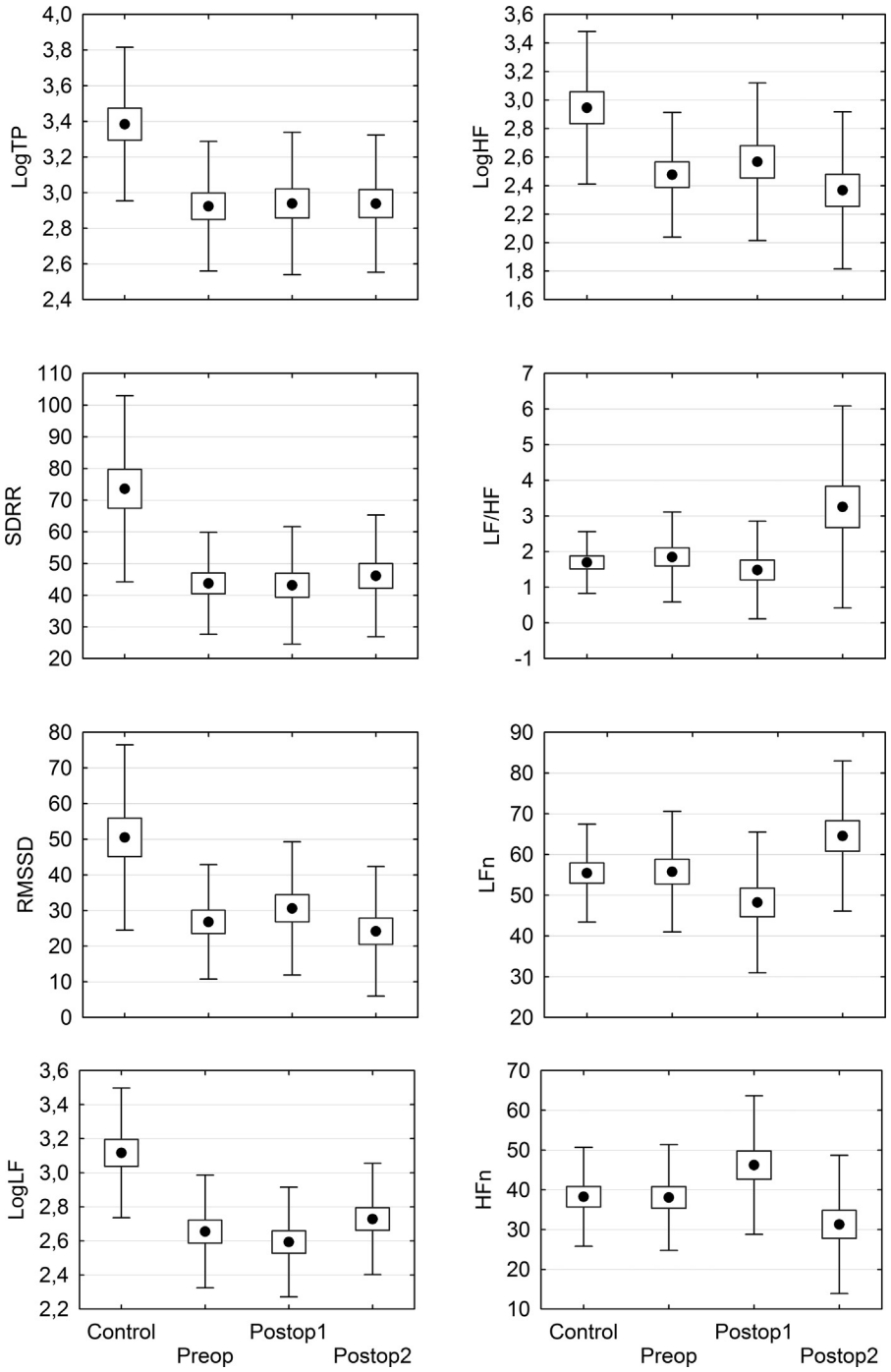

Fig. 1. Mean, SE (boxes), and SD (bars) values of time- (SDRR, RMSSD) and frequency-domain (logarithmic transformations of: LogTP: total power; LogLF: low-frequency power; LogHF: high-frequency power; LF/HF ratio; nLF: normalized LF power; nHF: normalized HF power) indices of HRV in the control and patient groups (PreOp: preoperative; Postop1: early postoperative period; Postop2: late postoperative period).

the higher autonomic CV control centers; therefore interictal alterations of HRV in this group of patients are not surprising. It is also reasonable to expect that their removal might lead to further alterations in the heart rhythm. Little information exists in the literature regarding the effect of TLE surgery on postoperative cardiac autonomic functions,[15–18] which have been investigated at least 3 months after surgery. Given that previous studies in patients with stroke and those who underwent intracarotid amobarbital procedure (IAP) demonstrated changes in HRV in the acute period,[28,29] we hypothesized that HRV parameters could possibly be altered immediately after surgery. Therefore we studied HRV at the earliest convenient time (i.e. when patients were taking only their regular anticonvulsants, had no complaints related to surgery and were ready for discharge from hospital). Indeed, we found that there was an increase in parasympathetic modulation, without a significant alteration in sympathetic activity while HRV remained decreased. It may be argued that the very early test results may have been influenced by various factors such as alterations in the perioperative brain tissue, concomitant drugs that were introduced and then withdrawn after surgery (like pain killers), the effect of general anesthesia, emotional state of the patients, etc. among others. In fact, general

anesthetics have been shown to affect HRV during anesthesia.[30] Since studies in the literature have been performed up to 3 h of recovery, it is not known when their effect on HRV disappears. However because of the short half-life of these medications, it is unlikely that they could have influenced the early HRV findings in our patients prior to discharge from hospital. It has been argued that differences between the emotional states before and after surgery may affect the CV responses. Several studies have demonstrated an interaction and overlap of cerebral structures involved in autonomic modulation and in emotional states.[31] Therefore it is hard to tell whether postoperative alterations in HRV measurements are due to emotional changes, or alternatively alterations in both emotions and HRV findings are the result of surgery itself. Although it is possible that the early post-operative results were influenced by some other factors, they still provide important information about acute HRV changes after TLE surgery. In order to better understand and interpret these results, similar studies must be performed in epileptic patients who had surgical resections in areas other than the temporal lobe and mesial temporal structures.

Late postoperative test results in our study were significantly altered and indicated a shift in sympathovagal balance in favor of the sympathetic system, compared to both the pre-operative and early post-operative periods. Studies where the effect of temporal lobectomy on CV autonomic function was addressed revealed different results. One group of investigators suggested that there was a decrease in sympathetic CV modulation after TLE surgery.[15] It was also reported that sympathetic cardiac modulation was altered differentially in patients with good or poor outcome.[16] Both LF-power and LF/HF ratio slightly decreased postoperatively in patients with good outcome, but increased significantly in patients with poor outcome. Nevertheless, several recent studies by another group reported that TLE surgery had no apparent effect on HRV, regardless of outcome.[17,18] Contrary to the previous studies, our findings reveal sympathetic over activity after the first postoperative month, similar to the findings in patients with poor prognosis in the above study.[16] However our results were not correlated with outcome as 75% of our patients were seizure-free. There are several methodological issues that might account for the contradictory results between these studies. First of all, heart rate recording durations varied in a wide range (2 min to 24 h). Some studies were carried out prospectively[17] whereas in others[16] patients were enrolled after the surgical outcome was known. The definition of good versus poor outcome and duration of postoperative follow-up were also different. Besides, the HRV measures were obtained at various time points in the preoperative (at least 1 day to 4 months) and postoperative (5 weeks to 10 months) periods. Apart from the aforementioned methodological issues, these results may also indicate that HRV measures are influenced by many variables, some of which are unknown or cannot be controlled.

It is not known exactly how different neural networks are affected by epileptic foci, how they are influenced by the surgical removal of the offending lesion and what the time course of this alteration is. In epilepsy patients, ictal and interictal epileptiform activity spreading from temporal lobe areas may interfere with the CV modulation in neighboring structures of central autonomic control, such as the amygdala, the insular or orbitofrontal cortex, the cingulate gyrus, and their pathways.[33,34] Thus surgical removal of temporal lobe seizure foci may alter epileptogenic influences on the autonomic CV control. Indeed, FDG-PET studies in TLE patients undergoing resective surgery indicate increased cerebral glucose metabolism in remote areas after 6 months.[35] Some of these areas are known to represent the propagation pathways of interictal and ictal epileptic discharges in mesial TLE and are also involved in the neural network representing the ANS. The findings in our study suggest that significant alterations are already evident after the first month.

The effects of epilepsy on CV autonomic regulatory functions are important because of the increased risk of SUDEP, where reduced HRV has been considered as a potential cause.[10] Therefore it is important to know if TLE surgery somehow influences the sympathetic/parasympathetic balance (either due to loss of part of the higher autonomic control centers or elimination of the effect of interictal discharges upon neighboring and/or distant areas). Clinical observations indicate that successful surgery may reduce the risk of SUDEP.[11,12] It has been claimed that temporal lobectomy contributes to a "stabilization" of the CV system in epilepsy patients due to decreased LF and thus decreased sympathetic autonomic CV control.[15] However reduced LF[36] or LF/HF ratio[37] were also correlated with mortality or worse outcome in different patient populations. Two recent studies in patients with epilepsy did not reveal a clear-cut ECG predictor for SUDEP,[38,39] whereas one reported that RMSSD was inversely correlated with the SUDEP score.[10] Because of these conflicting results, it is hard to make assumptions at that point about the prognostic value of HRV parameters in SUDEP.

The current study is subject to certain limitations. Some conventional AEDs, especially CBZ, are known to affect the heart rhythm.[9] Therefore AEDs may have influenced our HRV measurements, contributing to the difference between patients and controls. But since the AEDs and their dosages were not changed after surgery, alterations in HRV findings due to AEDs are unlikely in the post-operative period. The wide range in timing of the late postoperative test is another limitation, since some factors such as social adjustment during that time period could presumably confound the results.

In summary, HRV and both sympathetic and parasympathetic cardiac modulations are significantly reduced in TLE patients compared to controls. Cardiovascular autonomic functions are altered in favor of the parasympathetic system early after TLE surgery, but the sympathetic system predominates after the first post-operative month while HRV remains reduced. These findings suggest that resection of the temporal lobe, amygdala and hippocampus may have acute effects on CV autonomic control. Further alterations however indicate that mechanisms other than removal of the aforementioned anatomical structures are also active. Given the contradictory results in the literature, it is not clear at this point whether decreased mortality after epilepsy surgery is correlated with alterations in HRV findings.

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