Brief Communication

Insular resection may lead to autonomic function changes

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ABSTRACT

Objective: The aim of this study was to determine if insular damage is associated with markers of autonomic dysfunction.

Methods: We studied patients who underwent temporal lobe and/or insular resections for epilepsy surgery between April 2010 and June 2015 at University Hospitals Cleveland Medical Center (UHCMC). Presurgical T1-weighted MPRAGE, standard T1, T2 and FLAIR sequences were compared with postsurgical MRI by a neuro-radiologist and classified as type 0 (no involvement of insula), type 1 (minimal involvement of insular margin), type 2 (insular involvement <25%), and type 3 (insular involvement ≥25%).

Analysis of heart rate variability (HRV) was carried out in pre- and postoperative video-electroencephalography (vEEG) recording. Time-domain parameters were calculated: (mean of the RR intervals (MNN), root mean square difference of successive RR intervals (RMSSD), standard deviation of the RR intervals (SDNN), and coefficient of variation (CV)). In addition, frequency-domain parameters were calculated: low frequency (LF), high frequency (HF), and low frequency/high frequency (LF/HF).

Results: Twenty-one patients (14 females) with mean age of 36.2 ± 14.4 years (30; 22–75) were studied. Insular involvement was classified as type 0 (4 patients [19%]), type 1 (9 [43%]), type 2 (7 [33%]), and type 3 (1 [5%]). Significant decrease in RMSSD ($p = 0.025$) and CV ($p = 0.008$) was seen in insular damage types 2 and 3 compared with no or minimal insular involvement (types 0 and 1). Right-sided resections were associated with increase in LF power ($p = 0.010$) and the LF/HF ratio ($p = 0.017$).

Conclusions: This study indicates that insular resection may lead to autonomic function changes.

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1. Introduction

The insula, by virtue of its role in autonomic and cardiovascular control, has been linked to stroke-related mortality [1,2] and more recently, to sudden unexpected death in epilepsy (SUDEP) [3–5]. Right or left lesional insular epilepsy may result in ictal bradycardia and asystole [6,7] and may also be related to postictal cardiac dysrhythmia [5]. It is, therefore, possible that the SUDEP may result from a predisposition toward fatal cardiac rhythms due to an insular epileptogenic zone [4,5] or damage to insular structures [3] that alters autonomic tone. Insular damage may arise from several different mechanisms in epilepsy including direct insular resections during epilepsy surgery to generalized convulsive seizures that induce damage to the insula [8,9]. Cortical thinning [8] and increased insular connectivity [9] are known to occur in high-risk patients, although their association with periictal

cardiovascular dysfunction remains to be proven [10]. Heart rate variability (HRV) (a measure of the autonomic function) is known to be significantly reduced in epilepsy, and decreased HRV is associated with increased risk of sudden cardiac death [10]. We set out to determine the presence and extension of insular involvement in different types of temporal lobe and/or insular epilepsy and the effect of such resection on changes in baseline HRV measures before and after surgical resection.

2. Methods

We retrospectively analyzed the epilepsy surgery database at University Hospitals Cleveland Medical Center (UHCMC) for all patients who underwent temporal lobe and/or insula resections between April 2010 and June 2015. Exclusion criteria for analysis were patients with insular damage prior to epilepsy surgery, unavailable postoperative brain MRI and/or postoperative video-electroencephalography (vEEG) recordings for HRV analysis.

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2.1. Neuroimaging and surgical details

Presurgical thin-cut (1 mm) T1-weighted MPRAGE, standard T1, T2, T2-weighted FLAIR precontrast and/or postcontrast sequences were compared with postsurgical MRI by two neuroradiologists and classified according to the presence and severity of insular involvement or resection as type 0 (no involvement of insula), type 1 (minimal involvement of insular margin), type 2 (insular involvement <25%), and type 3 (insular involvement ≥25%) (Fig. 1).

2.2. Autonomic function analysis

Analysis of HRV metrics was carried out in a subset of patients who underwent postoperative long-term epilepsy monitoring, usually as a result of continuing seizures, in whom pre- and postoperative HRV comparisons were possible. Video-electroencephalography records were analyzed to exclude movement, activity, and electroclinical seizures, so as to ensure similar pre- and postoperative interictal records using a MATLAB program.

In this study, we used linear analytical methods to study differences in HRV patterns between patients with and without radiological insular resection (type 2–3 vs type 0–1). Several time-domain parameters were calculated including mean of the RR intervals (MNN), root mean square difference of successive RR intervals (RMSSD), standard deviation of the RR intervals (SDNN), and coefficient of variation (CV). In addition, frequency-domain parameters were calculated including normalized low frequency (LF) power (0.04–0.15 Hz), normalized high frequency (HF) power (0.15–0.4 Hz), and low frequency/high frequency (LF/HF) power ratio. These were calculated over 5-minute periods during 30 min of identical interictal awake states in two successive vEEG evaluations in each patient.

2.3. Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) IBM, Corp. version 24. Summary statistics were reported as mean ± standard deviation (median, range). Chi-square test was used to assess the association between the dichotomous variable radiological insular resection (yes/no) with nominal variables. Paired sample t-test between 5-minute periods averaged in the preoperative vEEG with 5-minute periods averaged in the postoperative vEEG was carried out with each patient. Kruskal–Wallis one-way analysis of variance was used to assess the relationship between insular resection extent with HRV changes and Mann–Whitney U test to compare HRV in between both hemispheres. Spearman's correlation coefficient was used to assess the relationship between epilepsy surgery outcome and HRV changes. Significance was set at $p < 0.05$ using two-sided tests. The study was reviewed and approved by the local Institutional Review Board.

3. Results

Seventy-two patients underwent temporal lobe and/or insular resection during the period April 2010–June 2015. Two SUDEP cases previously reported were not included in this study [3]. Forty-nine patients were excluded because of the presence of insular damage prior to epilepsy surgery, unavailable postoperative brain MRI or postoperative vEEG recordings for HRV analysis, or because of the absence of artifact-free EKG recordings.

Thus, 21 patients were analyzed (14 females) with a mean age of 36.2 years ± 14.4 (30; 22–75) were included in the study (Table 1). The mean time between pre- and postsurgical vEEG recordings was 40.7 ± 31 months (35; 9–168). Mean time between surgery and
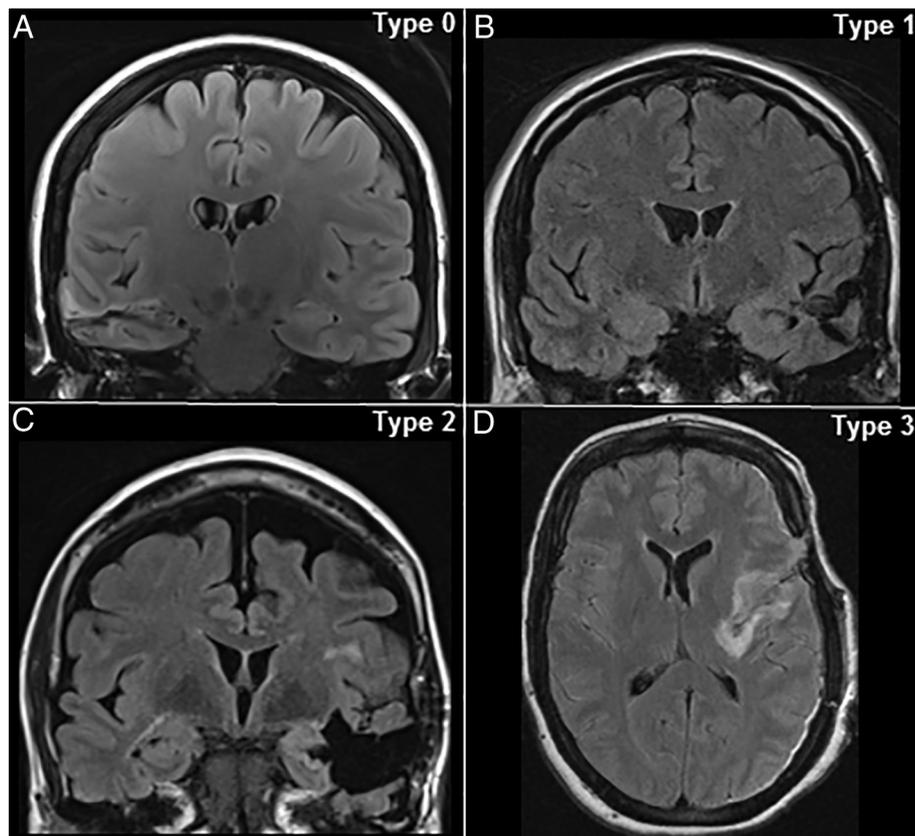
Fig. 1. Types of insular radiological involvement. Legend: FLAIR MRI brain sequences showing: A) no involvement of insula (type 0) after right-sided selective surgery, B) minimal involvement of posterior insular border (type 1) after left-selective extensive surgery, C) <25% of insular involvement (type 2) after left-sided extensive surgery, and D) ≥25% (type 3) after left-sided extensive surgery.

Table 1
Epilepsy surgery characteristics, radiological insular involvement, outcome.

Case	Age	Operation	Side		Preoperative brain MRI	Insular involvement on postoperative MRI	Outcome (ILAE)[*]
1	25	Selective temporal lobectomy + hippocampal transections	L	Negative	2		2
2	30	Selective temporal lobectomy	R	Negative	2		1
3	60	Hippocampal transections	L	Negative	0		3
4	75	Selective temporal lobectomy + hippocampal transections	L	Negative	1		1
5	30	Selective temporal lobectomy + hippocampal transections	L	Negative	1		4
6	44	Selective temporal lobectomy + hippocampal transections	L	Negative	1		3
7	22	Selective temporal lobectomy + hippocampectomy	L	Negative	2		1
8	23	Selective temporal lobectomy + hippocampal transections	L	Negative	2		1
9	48	Selective temporal lobectomy	R	Negative	0		4
10	39	Temporooccipital lesionectomy	R	Positive	0		4
11	43	Anterior temporal lobectomy	L	Negative	1		1
12	22	Temporoinsular lobectomy	L	Negative	3		5
13	23	Anterior temporal lobectomy	L	Positive	1		3
14	24	Hippocampal transections	L	Negative	1		1
15	26	Hippocampectomy	R	Negative	1		5
16	24	Selective temporal lobectomy + hippocampal transections	R	Negative	1		1
17	40	Selective temporal lobectomy + hippocampal transections	L	Negative	2		1
18	26	Selective temporal lobectomy + hippocampal transections	L	Negative	0		1
19	44	Selective temporal lobectomy + hippocampal transections	R	Positive	2		4
20	34	Anterior temporal lobectomy	R	Negative	1		1
21	58	Anterior temporal lobectomy	L	Negative	2		1

Legend: Selective temporal lobectomy = resection of amygdala, temporal pole and/or hippocampus; anterior temporal lobectomy = resection of temporal neocortex and mesial temporal structures, R: right, L: left.

presurgical vEEG recoding was 14.04 ± 13.6 months (7; 1–46), surgery to postsurgical vEEG recording was 20.5 ± 17.04 months (20; 1–70).

Insular radiological involvement was classified as type 0 (4 patients [19%]), type 1 (9 [43%]), type 2 (7 [33%]), and type 3 (1 [5%]) [Table 1].

We analyzed autonomic function changes (pre- and postsurgery) comparing the extent of radiological insular involvement (type 2–3 vs type 0–1). Significant differences were found on RMSSD ($p = 0.025$) and CV ($p = 0.008$) between patients with no or minimal insular involvement (types 0 and 1) and patient with more extent insular involvement (types 2 and 3), such that the latter had comparatively decreased RMSSD and CV indices (Table 2). No significant differences were found on frequency-domain parameters of HF, LF, and LF/HF ratio and the extent of insular resection (Table 2). Right-sided resections were significantly correlated with an increase in LF power ($p = 0.010$) and the LF/HF ratio ($p = 0.017$) [Fig. 2]. There was no association between epilepsy surgery outcome and pre- and postoperative HRV changes ($p > 0.05$).

4. Discussion

We found autonomic changes, characterized by marked differences in HRV patterns, in patients with radiological evidence of insular involvement after epilepsy surgery. We previously reported two such patients, who subsequently succumbed to SUDEP [3]. Two important

questions arose from their analysis and led to the current study: first, the incidence and extent of insular involvement in temporal lobe epilepsy surgery and second, the presence and extent of autonomic dysfunction in insular damage. Analysis of HRV metrics in postsurgical insular involvement suggests significant HRV changes based on the extent of resection and the hemisphere. This may reflect tendency to specific types of autonomic dysfunction [11] in these patients.

Heart rate variability noninvasively reflects sympathetic and parasympathetic balance as a measure of cardiac autonomic tone using EKG recordings [11]. It reflects oscillations in the interval between consecutive heartbeats defined as adjacent QRS complexes of a continuous artifact-free EKG and includes measures based on time and frequency domain analysis. A close relationship is known to exist between increased sympathetic activity and/or decreased parasympathetic activity with a consequent tendency toward development of fatal arrhythmia [11]. Heart rate variability is known to be significantly reduced in epilepsy, and decreased HRV is associated with increased risk of sudden cardiac death [10]. We found that patients with minimal or no insular involvement had increased HRV, suggesting predominance of vagal tone whereas those with more marked insular damage had significantly larger decreases in HRV, implying decreased parasympathetic tone or overall increased sympathetic tone. The implications of such changes in patients with intractable generalized convulsive seizures in particular may include tendency to cardiac rhythm changes seen in near-SUDEP

Table 2
Autonomic function changes (pre- and postsurgery) comparing extent of radiological insular involvement.

	Pre vs post Q (p-value)	Estimated mean		Pre vs post with severity interaction	Estimated mean	
		Pre-Q	Post-Q		Type 0–1	Type 2–3
MNN (ms)	0.973	0.810	0.811	0.583	0.806	0.814
SDNN (ms)	0.649	0.056	0.054	0.086	0.056	0.055
RMSSD (ms)	0.654	0.044	0.044	**0.025**[*]	0.044	0.042
CV (%)	0.210	0.070	0.065	**0.008**[*]	0.069	0.066
LFP (%)	0.102	5.469	6.386	0.203	6.471	5.384
HFP (ms^2)	0.639	1.926	2.038	0.459	2.023	1.941
LF/HF (ms^2)	0.531	5.115	5.613	0.486	5.183	5.545

Legend: MNN (mean of the RR intervals), SDNN (standard deviation of the RR intervals), RMSSD (root mean square difference of successive RR intervals), CV (coefficient of variation), LF (low frequency), HF (high frequency), ms (milliseconds).
 * Statistically significant.
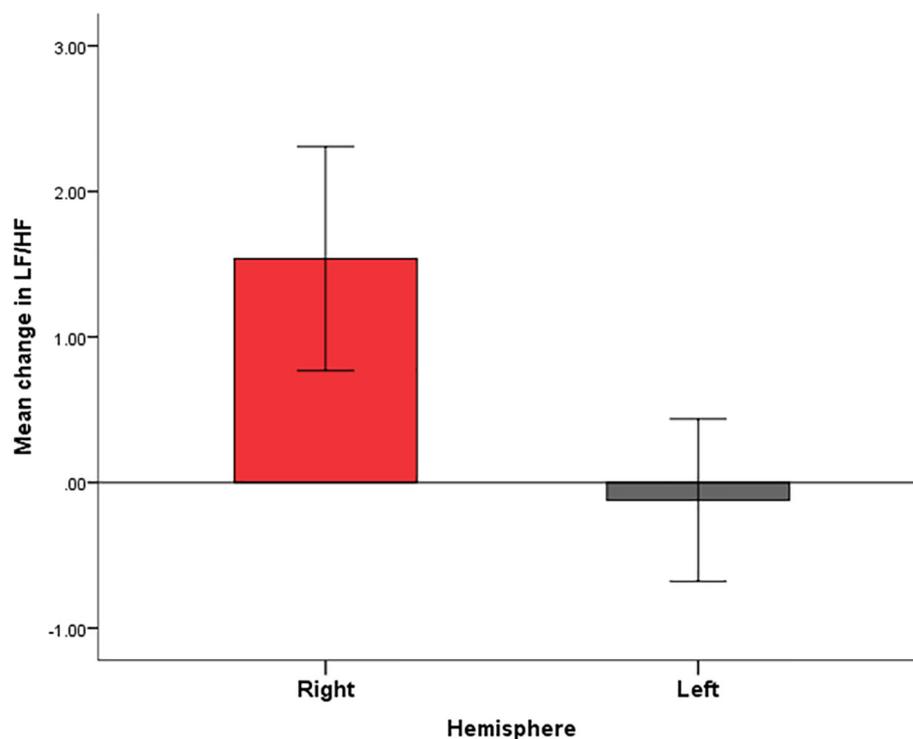
Fig. 2. Autonomic function changes (pre- and postsurgery) comparing laterality (right and left hemisphere) of radiological insular involvement. Legend: The y axis represents mean change in LF/HF ratio comparing pre- with postsurgery, and the x axis denotes the hemisphere of epilepsy surgery. Right-sided surgery was associated with increased LF/HF ratio ($p = 0.017$). HF: high frequency, LF: low frequency.

and SUDEP phenomena. A progressive, serial increase in interictal and preictal HRV was reported in one case of SUDEP over a seven-month period, followed by a monitored death characterized by shortened QTc interval (335–358 ms) and postictal tachycardia followed by bradycardia/asystole, atrial fibrillation, and ventricular fibrillation [12]. Based on these observations, increased parasympathetic tone was posited as a potential causative mechanism. The converse scenario of decreased HRV and autonomic instability is also thought to contribute to SUDEP [13]. Root mean square differences of successive RR intervals, a measure of HRV, is inversely correlated with the SUDEP-7 risk inventory since subjects with epilepsy with low RMSSD have higher inventory scores and greater risk [13]. The RMSSD has been suggested as a biomarker for SUDEP risk. Such decreased HRV metrics have been associated with ventricular tachyarrhythmias and increased risk of mortality [11–14].

The bidirectional change in HRV observed in cardiac risk is consistent with the variable pattern of cardiac autonomic and respiratory dysfunction observed in the phenomenological heterogeneity of monitored SUDEP cases [5,15]. The role of autonomic cortical control structures in SUDEP is intriguingly unknown since several such structures (insula, amygdala, hippocampus, orbitofrontal cortex) are either primary epileptogenic zones or part of putative seizure networks. The insula has been directly or indirectly implicated in both cardiac autonomic control and mortality in patients with stroke. Prolonged direct electrical stimulation of the rat insular cortex produces lethal cardiac arrhythmia and sudden death [16]. Electrical stimulation of the human insula produced cardiac chronotropic and blood pressure responses in five patients with insular epilepsy [17]. Left-sided insular dominance for parasympathetic cardiovascular effects was noted [17]. Insular damage in patients with cerebral infarction is associated with increased sympathetic activity, cardiac arrhythmias, conduction blocks, and risk of mortality including due to sudden death [14,18].

The LF HRV domain is thought to represent both sympathetic and parasympathetic activity whereas the HF domain predominantly reflects parasympathetic activity. Consistent with autonomic changes

and mortality noted in earlier studies of patients with stroke, we observed that right-sided insular resection is associated with increased LF domain and LF/HF ratio and, therefore, a significant increase in overall sympathetic tone [11]. Although the number of cases was small in each group and more severe damage cases were predominant in the left-sided group, our results may indicate that even minor insular involvement in the right-sided group was enough to produce autonomic changes. Sudden unexpected death in epilepsy mortality may not be exclusive to right-sided insular resection; both right and left insular epilepsy have been implicated in SUDEP [6,7].

Radiological evidence of insular damage as detected by MRI may be a more prominent manifestation of the subtle changes reported by imaging studies of SUDEP and high-risk patients. Prominent cortical thinning may be seen in several structures related to autonomic and breathing control such as the orbitofrontal, anterior cingulate, and insular cortices [8]. Autonomic indices and HRV metrics have yet to be reported in these imaging cohorts. However, in the population with postsurgical insular involvement, findings of HRV change appear to be robust. Whether insular involvement in epilepsy surgery translates to increased mortality is uncertain. Postoperative seizure freedom entails no greater mortality risk than the seizure-free population who have not had epilepsy surgery [19]. Failed epilepsy surgery patients understandably continue to be at high risk (10.4/1000 vs 5.2/1000 person years) [20]. However, SUDEP accounts only partly for mortality; a comprehensive epilepsy surgery mortality study of 89 deaths reported only 15 definite or probable SUDEP cases [20]. Much larger cohort studies are required to address whether resection of insular tissue contributes to mortality in general and SUDEP in particular.

Successful temporal lobe surgery undoubtedly mitigates mortality, including the risk of SUDEP, but avoidable insular resection may lead to increased risk in those who are not rendered seizure-free by surgery. As a result, minimally invasive techniques such as laser interstitial thermotherapy and radiofrequency thermocoagulation may be advantageous, particularly for mesial temporal epilepsy with a localized epileptogenic zone. For insular epileptogenic zones, the extent of surgical

resection should be carefully planned to balance risk of continued seizures against avoidable insular resection, both of which may contribute to increased risk of SUDEP. Confirmation of these findings in a larger study is needed, with special emphasis on mortality outcomes in relation to operative approaches and insular involvement.

The sample size was small, and the severity of insular involvement between right and left hemisphere was not equally distributed, with more severe insular damage cases in the left-sided group. In addition, patient records were retrospectively analyzed, with resulting potential attendant biases. Postsurgical imaging studies in the postoperative period were not carried out at a fixed time interval, and thus, scan acquisition was not standardized. We did not assess the impact of medications on HRV since our study was not sufficiently powered to do so. Patients have not been longitudinally followed up for mortality outcomes, and hence, the influence of HRV change on actual SUDEP incidence is unknown but deserving of further study.

Author contributions

Nuria Lacuey, MD. PhD. Study concept, design, analysis, interpretation, and writing.

Vasant Garg, MD. Data collection, analysis of data.

Barbara Bangert, MD. Study supervision.

Johnson P. Hampson, MSBME. Analysis of data, statistical analysis, and graphic design.

Jonathan Miller, MD. Data interpretation and critical revision of the manuscript for important intellectual content.

Samden D. Lhatoo, MD. Study supervision and critical revision of the manuscript for important intellectual content.

Financial disclosure statement

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