

Treatment of Epilepsy with Bipolar Electro-coagulation: An Analysis of Cortical Blood Flow and Histological Change in Temporal Lobe

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Abstract

Background: Bipolar electro-coagulation has a reported efficacy in treating epilepsy involving functional cortex by pure electro-coagulation or combination with resection. However, the mechanisms of bipolar electro-coagulation are not completely known. We studied the acute cortical blood flow and histological changes after bipolar electro-coagulation in 24 patients with intractable temporal lobe epilepsy.

Methods: Twenty-four patients were consecutively enrolled, and divided into three groups according to the date of admission. The regional cortical blood flow (rCBF), electrocorticography, the depth of cortex damage, and acute histological changes (H and E staining, neuronal staining and neurofilament (NF) staining) were analyzed before and after the operation. The *t*-test analysis was used to compare the rCBF before and after the operation.

Results: The rCBF after coagulation was significantly reduced ($P < 0.05$). The spikes were significantly reduced after electro-coagulation. For the temporal cortex, the depth of cortical damage with output power of 2–9 W after electro-coagulation was 0.34 ± 0.03 , 0.48 ± 0.06 , 0.69 ± 0.06 , 0.84 ± 0.09 , 0.98 ± 0.08 , 1.10 ± 0.11 , 1.11 ± 0.09 , and 1.22 ± 0.11 mm, respectively. Coagulation with output power of 4–5 W completely damaged the neurons and NF protein in the molecular layer, external granular layer, and external pyramidal layer.

Conclusions: The electro-coagulation not only destroyed the neurons and NF protein, but also reduced the rCBF. We concluded that the injuries caused by electro-coagulation would prevent horizontal synchronization and spread of epileptic discharges, and partially destroy the epileptic focus.

Key words: Acute Histological Change; Bipolar Electro-coagulation; Electrocorticography; Regional Cortical Blood Flow; Temporal Lobe Epilepsy

INTRODUCTION

Resection of an epileptogenic region is the main surgical procedure for epilepsy. When the epileptogenic region is located within the functionally critical cortex, the resection may result in unacceptable neurological deficits. Therefore, an alternative surgical technique, termed multiple subpial transection (MST), was developed to extend surgery to an epileptic focus located in highly functional cortical areas without inducing significant functional deficits. Recently, Luan *et al.*^[1–3] developed and applied a new method for treating epilepsy specifically located within eloquent areas, which is termed as bipolar electro-coagulation on functional cortex (BCFC). They suggest that in cases where the epileptogenic foci are located in a functional cortex, the combined therapy of foci resection and BCFC, or pure BCFC,

has proven effective and can greatly improve the outcome of the surgery. However, the mechanisms of electro-coagulation are not completely clear. In the present study, we attempted to clarify the mechanisms involved in this technique by evaluating regional cortical blood flow (rCBF) before and after electro-coagulation, electrocorticography (ECoG), and the characteristics of acute histological change.

METHODS

Twenty-four patients were consecutively collected, and divided into three groups according to the date of admission. All patients gave consent for this study. Patients all had intractable temporal lobe epilepsy and were aged 20–42 years. All underwent standard anterior temporal neocortical resections 4.5–7.0 cm along the main temporal gyri.^[4]

Surgical procedure

The anterior temporal lobe was fully exposed before the surgical procedure. Electro-coagulation was performed using bipolar

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coagulation forceps (Company Name: B. Braun, Germany) outside the arachnoid mater, with output power of 4 W. In all cases, electro-coagulations were placed in the central portion of the planned resection. The brain surface was kept clean and moist with saline gauze. There was 45° between the forceps' axis and the brain surface. The direction of electro-coagulation was perpendicular to the long axis of the brain gyrus. The diameter of the tip of the bipolar forceps was 2 mm, and the procedure was performed at an interval of 5 mm. The brain surface was washed immediately after electro-coagulation with room-temperature saline to lower the brain temperature because the electro-coagulation releases heat, and we could clearly see the red and white stripes at regular intervals on the electro-coagulated cortex [Figure 1].

Regional cortical blood flow before and after electro-coagulation

The anterior temporal lobe was fully exposed in the first group of eight patients. Breathing, blood pressure, and heart rate were kept stable, blood gas analysis was checked to ensure it was in the normal range, and the control (nonresected cortex) and experimental areas (the extent of the resection) were selected. Before and after the operation rCBF was detected with a flow laser Doppler perfusion imager (No: 1012, Sweden) for 20 min in both control and experimental areas. There was no operation in control areas and coagulation with output power of 4 W in experimental areas. The brain tissue of experimental areas was also analyzed by the spacing and width of electro-coagulation after resection.

Electrocorticography before and after electro-coagulation

Electrocorticography was recorded before the start of the electro-coagulation procedure in the second group of eight patients. The 2 cm² × 6 cm² cortex of the anterior temporal lobe was coagulated with output power of 4 W. ECoG, with 1 cm² × 6 cm² six-electrode grids, was performed 10 min before and 10 min after electro-coagulation.

Acute histological analysis after electro-coagulation

The electro-coagulations in the last group of eight patients were performed with different output



Figure 1: Red and white stripes at regular intervals were clearly visible on the electro-coagulated cortex (coagulated with output power of 4 W).

powers (2, 3, 4, 5, 6, 7, 8, and 9 W). After electro-coagulations, there were several (8–10) strips in the cortex of anterior temporal lobe. The *en bloc* resection in each case was then immediately performed. Electro-coagulations were recorded photographically. After fixation for at least 3 days in 20% buffered formalin, specimens were grossly analyzed, photographed, and serially sectioned. The plane of the section was parallel to the main gyral axis and perpendicular to the electro-coagulations so that we could assess the full extent of the electro-coagulations. Thereafter, the tissue was embedded in paraffin, sectioned at 5–10 μm and processed for conventional staining techniques and immunocytochemistry using a previously described protocol.^[5-7] H and E were used to assess general pathological features and vascular involvement. Neuronal staining (NeuN staining) was used to study the characteristics of neurons after electro-coagulations. Neurofilament protein staining (NF staining) was used to evaluate axonal bundles in gray matter.

Statistical analysis

Values were expressed as mean ± standard deviation (SD). *t*-test analysis was used to compare the cortical blood before and after the operation and to compare the cortical thickness of coagulated areas in different patients. Statistical analyses were performed with the Statistical Package for the Social Sciences software (version 14.0; SPSS, Inc., Chicago, Illinois, USA). *P* < 0.05 was considered statistically significant.

RESULTS

Regional cortical blood flow

The values before and after electro-coagulation were 474.25 ± 128.13 and 488.97 ± 124.15 Pu in the control group, and 405.55 ± 94.17 and 287.37 ± 23.17 Pu in the experimental group, respectively. Paired *t*-tests showed that the rCBF was significantly reduced in the experimental group after electro-coagulation (*P* < 0.01); there was no statistical significance in the control group (*P* > 0.05). Table 1 shows the change in rCBF before and after electro-coagulation.

Electrocorticography

Every patient had active spiking during ECoG in the coagulated region before the procedure, while the spiking was blocked or almost absent after electro-coagulation [Figure 2].

Table 1: Change in rCBF before and after electro-coagulation (Pu)

Groups	Before electro-coagulation	After electro-coagulation
Control group	474.25 ± 128.13	488.97 ± 124.15
Experimental group	405.55 ± 94.17	287.37 ± 23.17*

Paired *t*-test showed that the rCBF was significantly reduced in the experimental group after electro-coagulation (**P* < 0.01). There was no statistical significance in the control group (*P* > 0.05). rCBF: Regional cortical blood flow.

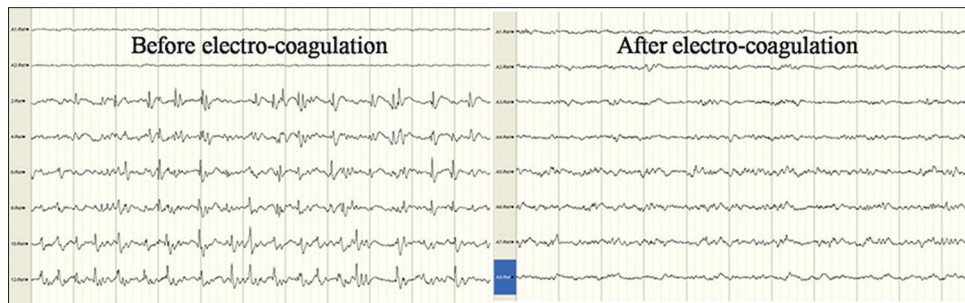


Figure 2: After the procedure, the spiking was nearly absent after electro-coagulation.

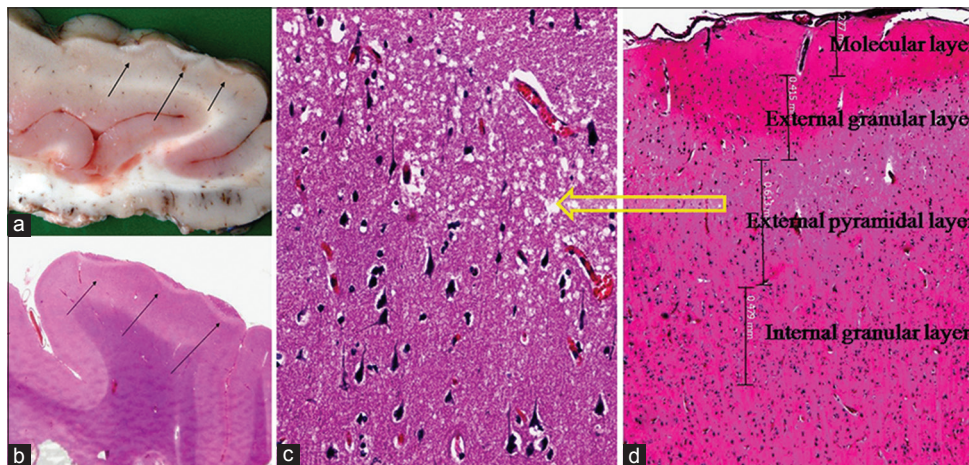


Figure 3: (a) The areas of the cortex after electro-coagulation showed semilunar or arcuate damage (output power of 4 W, arrow). (b) The H and E smear showed that the arcuated damage located in the superficial layers of the cortex (output power of 4 W, arrow). (c) The depth of damage only reached the superficial layers of the external pyramidal layer. The pyramidal cells in the deep layers had normal morphology (output power of 4 W, H and E, original magnification $\times 100$). (d) Histological analysis showed electrocoagulated neural necrosis in the superficial layers and adjacent tissue edema. The deep cortical structures in the electro-coagulated areas were almost normal (output power of 4 W, H and E, original magnification $\times 40$).

Histological analysis

The cortical sections showed semilunar damage after fixation for at least 3 days in 20% buffered formalin [Figure 3a]. The shape of the damaged cortex after electro-coagulation was consistent with the arc current released by bipolar coagulation forceps [Figure 3b].

The diameter of the tip of the bipolar forceps was 2 mm, and this procedure was performed at an interval of 5 mm. The spacing and width of electro-coagulation are shown in Table 2.

Cortical thickness corresponded to the distance between cortical surface and gray-white matter junction at the level of each electro-coagulation. There was no significant difference in cortical thickness in eight patients who underwent electro-coagulation ($P > 0.05$). Depth of electro-coagulation corresponded to the location between the deepest border of the lesion and the cortical surface. For the temporal cortex, the depth of the damaged cortex was, respectively, 0.34 ± 0.03 , 0.48 ± 0.06 , 0.69 ± 0.06 , 0.84 ± 0.09 , 0.98 ± 0.08 , 1.10 ± 0.11 , 1.11 ± 0.09 , and 1.22 ± 0.11 mm with output power of 2–9 W after electro-coagulation. There was increasingly deep damage of the cortex with the increase of coagulation power [Table 3]. When the output power of electro-coagulation

Table 2: Spacing and width of electro-coagulation with 4 W output power (mm)

Patient	Number of strips	Electro-coagulation spacing	Width of electro-coagulation
1	6	4.50 ± 0.42	2.14 ± 0.32
2	5	5.18 ± 0.30	1.88 ± 0.33
3	5	4.58 ± 0.56	2.09 ± 0.52
4	6	4.84 ± 0.47	1.96 ± 0.30
5	6	4.48 ± 0.68	1.66 ± 0.29
6	5	4.88 ± 0.13	1.97 ± 0.45
7	8	4.86 ± 0.49	1.90 ± 0.42
8	7	4.87 ± 0.54	2.09 ± 0.35

was < 4 W, there was incomplete damage of cortical layers I–III. However, when the output power was more than 5 W, the depth of electro-coagulation passed the external pyramidal layer (layer III), reached to the internal granular layer (layer IV), and even the internal pyramidal layer (layer V). Therefore, coagulation with output power of 4–5 W can completely damage the brain tissue in the molecular layer, external granular layer, and the external pyramidal layer.

Histological analysis (H and E) demonstrated that the thermal necrosis was localized within the layers of the

Table 3: Depth of electro-coagulation with different output power (mm)

Patient	Output power (W)	Depth of electro-coagulation	Thickness of cortex	Depth of electro-coagulation/thickness of cortex
1	2	0.34 ± 0.03	3.60 ± 0.53	0.10 ± 0.02
2	3	0.48 ± 0.06	4.00 ± 0.45	0.13 ± 0.02
3	4	0.69 ± 0.06	3.81 ± 0.37	0.18 ± 0.02
4	5	0.84 ± 0.09	3.76 ± 0.45	0.22 ± 0.03
5	6	0.98 ± 0.08	3.68 ± 0.54	0.27 ± 0.05
6	7	1.10 ± 0.11	3.59 ± 0.85	0.33 ± 0.11
7	8	1.11 ± 0.09	3.20 ± 0.69	0.36 ± 0.09
8	9	1.22 ± 0.11	3.85 ± 0.62	0.32 ± 0.06

There were no significant differences in cortical thickness in eight patients who underwent electro-coagulation ($P > 0.05$). There was increasingly deep damage of the cortex with the increase of coagulation power.

electro-coagulated cortex, and did not reach the white matter. After the procedure with output power of 4–5 W, there was no subarachnoid hemorrhage. The arachnoid showed slight changes with a mild shrinkage, the capillaries under the arachnoid disappeared, and those out of the coagulated areas were normal. The larger arteries under the arachnoid and vessel located in the sulci showed no damage. The depth of damage reached the superficial layers of the external pyramidal layer, the neurons showed disintegration, vacuolization, morphological structure deformation, and the pyramidal cells in the deep layers showed normal morphology. No scorched-like tissue was seen in the whole region of electro-coagulation [Figure 3c and d]. Immunohistochemical analysis showed that the neurons and NF proteins in the molecular layer, external granular layer, and external pyramidal layer were completely damaged in the coagulated cortex. The superficial neuron density in the electrocoagulated areas appeared sparse, while the neuron density in the deep cortex and noncoagulated superficial cortex was almost normal [Figure 4a and b]. The NF proteins in electrocoagulated areas were completely destroyed and could not be stained, while NeuN and axonal morphology in the deep cortex and noncoagulated superficial cortex were normal [Figure 4c and d]. However, after the procedure with output power of more than 5 W, the depth of damage reached to the internal granular layer (fourth layer), and even the internal pyramidal layer (fifth layer), while the neurons and NF proteins were correspondingly damaged.

DISCUSSION

Bipolar electro-coagulation is a surgical technique that is applied using bipolar coagulation forceps and can reduce the cortex-related seizures by destroying the epileptic foci and seizure spread with thermal energy. This technique has a similar principle to MST in treating epilepsy.

Morrell *et al.*^[8,9] suggest that although the functional arrangement in the cortex is primarily oriented vertically, the intracortical fibers, which are thought to be responsible for seizure spread, are

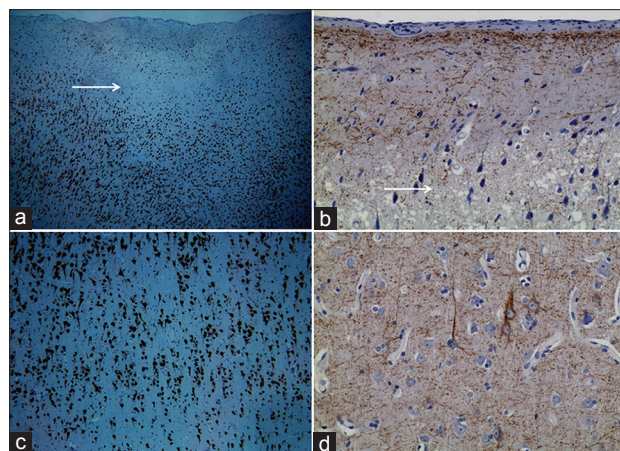


Figure 4: (a-b) The superficial neurons were found sparingly in the electrocoagulated areas (arrow, neuronal [NeuN], original magnification ×40), while the density of deep cortical structures was almost normal (NeuN, original magnification ×100). (c-d) The neurofilament proteins (NFs) in electrocoagulated areas were completely destroyed and could not be stained (arrow) while NeuN and axonal morphology in the deep cortex were normal (NF, original magnification ×200).

oriented horizontally, and therefore, the horizontal fibers can be sectioned without causing cortical dysfunction.^[10] Taking those basic theories into account, Morrell *et al.* introduced MST to treat epilepsy arising from functional cortex.^[8]

Meng and Luan applied bipolar electro-coagulation, which is based on the principles of MST outlined above, on animal models (three monkeys and 50 cats) in 1999, and demonstrated the efficacy of bipolar electro-coagulation in treating epilepsy.^[11,12] They also found that electro-coagulation with output power of 5 W can damage the external molecular layer, external granular layer, and external pyramidal layer. Therefore, the surgical procedures do not cause unacceptable neurological deficits.

The observations from several laboratories show that independent epileptic regions can become synchronous when they are < 5 mm apart. These observations suggest that the transections of the cortex should be performed at 5 mm intervals perpendicular to the long axis of the gyrus to limit seizures and preserve function.^[13,14] Following these findings, the electro-coagulation was carried out at 5 mm intervals perpendicular to the long axis of the gyrus. In accordance with these principles, electro-coagulation was used to treat epilepsy in China.

Luan *et al.*^[1] reported that out of 124 patients with intractable epilepsy, there were 48 cases with extra-temporal lobe epilepsy, 45 subjects were treated with foci resection combined with electro-coagulation on functional cortex, three patients were treated with pure electro-coagulation on functional cortex, and only one case with infantile hemiplegia underwent functional hemispherectomy combined with electro-coagulation of the remaining tissue. The general efficiency of these treatment procedures for the group of 124 patients was 91.7%.^[1] Yang and Luan^[2] compared the efficacy of lesionectomy combined with

electro-coagulation on functional cortex (71 patients) to lesionectomy performed without electro-coagulation on functional cortex (78 patients). The follow-up duration was 2–5 years (mean follow-up duration was 37 months). They demonstrated that the lesionectomy combined with electro-coagulation on functional cortex was significantly more effective than lesionectomy performed without electro-coagulation on functional cortex ($P < 0.01$).^[2] In recent years, we also reported the outcome of pure BCFC. In all 15 patients, the mean time of the postoperative follow-up was 29 months (range 15–93 months). Seven patients developed the hemiparesis after the operation but fully recovered within 1–6 months. An Engel Class I outcome was achieved in 2 (13.3%) patients; Class II, in 6 (40%); Class III, in 3 (20%); and Class IV, in 4 (26.7%). Follow-up electroencephalogram (EEG) was performed in eight patients. Three demonstrated normal EEG.^[3] Those findings documents showed that the bipolar electro-coagulation was effective. In the present study, we attempted to clarify the mechanisms involved in this technique by evaluating the rCBF before and after electro-coagulation, ECoG, and the characteristics of the acute histological change.

Our data showed a significant reduction in rCBF before and after electro-coagulation in the experimental group. Therefore, we concluded that the reduction of rCBF can prevent horizontal synchronization and spread of epileptic discharges. However, we only detected the rCBF for 20 min, and whether a long-term reduction of rCBF occurs still needs investigation.

Every patient had more or less active spiking on the ECoG in the coagulated region before the procedure. The spiking was blocked or almost absent after electro-coagulation. Our previous study also showed 15 patients with pure electro-coagulation. Follow-up EEG was performed in eight patients, and three patients out of eight demonstrated normal EEG.^[3] These data indicated that the EEG had a long-term improvement after electro-coagulation.

Our histologic analyses showed that two factors explained the variability in electro-coagulation. The H and E staining demonstrated increasing deep damage in the cortex with the increase of coagulation power.

The horizontal fibers are mostly located at the midneocortical level,^[8] and coagulation with the output power 4–6 W can completely damage the brain tissue in the molecular layer, external granular layer, and external pyramidal layer. Therefore, output power of 4–6 W can damage the horizontal fibers.

The epileptogenic discharge requires substantial side-to-side or horizontal interaction of cortical neurons, prominent occurrence of fractional spikes believed to be of the dendritic origin, and dendrites located in superficial cortical laminae.^[15-22] The immunohistochemical analysis demonstrated that both neurons and NF proteins in the molecular layer, external granular layer, and the external pyramidal layer were completely damaged. That is to say, coagulation with the output power 4–5 W damaged not only

the neurons that produce epileptogenic discharge, but also the NF proteins that spread the epileptic discharge.

However, the BCFC technique cannot completely control seizures. Animal models (rats) have demonstrated that seizures do not completely disappear because the ictal focus still interacts with subcortical areas through preserved vertical fibers.^[23] In previous studies, it appeared that the lack of adequate damage on the two lateral cortical banks of a gyrus, which reaches down into two adjoining sulci, was also a contributing factor. In time, these residual ictogenic areas may regain enough synchronizing effects to reach the U-shaped fibers again and induce seizures.

There was full damage of layers I–III in the cortex with the output power of 4–5 W. The electro-coagulation not only destroyed the neurons and NF, but also reduced the rCBF. The spikes are significantly reduced after electro-coagulation. We conclude that those injuries can prevent horizontal synchronization and spread of epileptic discharges, and partially destroy the epileptic focus.

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