SEEG-guided radiofrequency thermocoagulation (SEEG RF-TC): from in vitro and in vivo data to technical guidelines

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Abstract

Background: Deep brain electrodes have been used for the last ten years to produce bipolar SEEG-guided radiofrequency thermo-coagulation (SEEG RF-TC). However, this technique is based on empirical knowledge. The aim of this study is threefold: 1) provide in vivo animal data concerning the effect of bipolar RF-TC on brain and its safety 2) assess the parameters of this procedure (current delivery and dipole selection) which produce the most efficient lesion and 3) provide technical guidelines.

Methods: First we achieved in vivo RF-TC on rabbit brain with several conditions (power delivered and lesioning duration) and analyzed their influence on the lesion produced. Only a difference in terms of volume was found and type of histological lesions was similar whatever the settings were. We then performed multiple RF-TC in vitro on egg albumen first with several parameters of radiofrequency then with different dipole spatial selections. The endpoint was the size of the radiofrequency thermo-lesion produced.

Results: Using unfixed parameters of radiofrequency current delivery and increasing it until the power delivered by the generator collapsed produced significantly larger lesions (p = 0.008) than other conditions. Concerning the dipole selection, the use of contiguous contacts on electrodes lead to lesions with a higher volume (p = 7.7 x 10^{-13}) than those produced with noncontiguous ones.

Conclusion: Beside the target selection in SEEG RF-TC, which are summarized based on a literature review, we report the optimal parameters: radiofrequency-current must be increased until the power delivered collapses and dipoles should be constituted by contiguous electrode contacts.

Introduction

Many physical principles have been used to perform brain lesions as a treatment tool, such as focused ultrasounds, cryogenics, chemical lesions, focused electromagnetic waves and radiofrequency (RF). Heating by RF has become popular for intracranial use since the second part of the XXth century, probably due to the possibility to perform well-circumscribed lesions, to obtain stimulation and recording in the same time, to have an impedance monitoring and to its easy adaptation on stereotactic and scopic systems[1]. RF lesioning is based on the spreading of a RF current between the two poles of a dipole. This creates an oscillation in each given point of the electric field *(E-field)* between these two poles which induces the nearby charged ions in the electrolyte to move back and forth in space at the same high frequency creating an ionic oscillation current named *j*. RF-TC is the result of the frictional heating within the tissue resulting from *J-field*. The power deposition and the elevation of temperature are directly linked to the *J-field*[2, 3].

In 2004, it has been proposed to use the electrodes of stereo-electroencephalography (SEEG) to perform SEEG-guided RadioFrequency-ThermoCoagulation (RF-TC) of the epileptogenic zone[4] in drug resistant epileptic patients who are ineligible for a conventional surgical resection of the ictal onset zone because of the proximity of a functional area or the implication of a too large epileptic network.

Despite the growing popularity of SEEG-guided RF-TC (SEEG RF-TC)[5- 9], there is lack of studies related to its physical effect and to the optimal required settings of the RF-generator. There is yet a need for such studies, as all data available in literature involve monopolar RF-TC[10-14] and as, unlike the usual monopolar stereotactic lesional devices, SEEG electrodes do not have any thermocouples, making it impossible to monitor the temperature during the procedure.

The aim of our study is to assess the safety of SEEG-guided RF-TC based on in vivo animal data and to determine the optimal parameters of radiofrequency and the most appropriate spatial selection of a dipole to perform a RF-TC lesion in the central nervous system using an SEEG electrode.

Materials and Methods

Materials

Radiofrequency thermo-lesions were performed (figure 1) using a generator system model RFG-3 manufactured by Radionics (Radionics Medical Products, Burlington, MA USA) and electrodes manufactured by Dixi (Dixi Medical, Besancon, France). Electrodes had from 5 to 18 contacts and each of them had a 2mm length and a 0.8 mm diameter. The inter-contact spacing was 1.5mm.

In vivo model was rabbit (Oryctolagus cuniculus, provided by Charles River laboratoire, B.P 109 69592 l'Arbresle, France). According to the European guidelines (ISO 10993-6) on animal experimentation for safety studies, at least five days of acclimatization were required and animal housing (BIOMATECH, study 44607) was in accordance with European directive ECC/86/609.

In vitro model was chosen based on data available in the literature[12,15]. Therefore, coagulations were made by using the electrodes previously described deeply plunged in egg white and distant from more than 2.5 cm from the wall of the container used for the experiment.

Methods

First part (in vivo): we first focused on safety (figure 2). Therefore, we initially aimed at obtaining histological data on the brain tissue involved by RF-TC. We performed RF-TC lesions with different settings in terms of power delivering and lesioning duration. Eight rabbits were divided into four groups, and RF-TC lesions were performed in both hemispheres: Group 1 – standard power and standard lesioning time (5W, 30s); Group 2 – extreme power and standard lesioning time (10W, 30s); Group 3 standard power and extreme lesioning time (5W, 90s); Group 4 - extreme power and extreme lesioning time (10W, 90s).

Rabbit were sacrificed immediately after the end of the RF-TC procedure (by means of intravascular injection of Vetoquinol) and an histopathological examination of their brain, focused on the brain tissue lesions, and on the integrity of the electrodes, was performed (BIOMATECH study) in order to provide a qualitative comparison between each group. Furthermore, the size of lesion obtained in each group was compared to those obtained with similar setting in egg white. In this way we aimed to determine whether there is a relation

between in vivo and in vitro RF-TC in order to perform numerous in vitro lesions allowing statistical analysis without to have to sacrifice too many animals.

Second part (in vitro): we aimed to determine the optimal radiofrequency parameters (i.e. intensity, in mA, and voltage, in V, from which the power, in W, does result) required to obtain the largest possible lesion size. We performed 55 RF-TC using, either a given power during rooted time, or the maximal available power without time limit. Coagulations using fixed parameters were performed at 0.94W (18.75V, 50mA), 1.88W (25V, 75mA), 3.75W (37.5V, 100mA) and 7.50W (50V, 150mA) during 30s (power delivered was progressively increased with a constant linear velocity which took from 5 to 10s). These settings were defined according both to the literature and to data resulting from our empiric experience. As the size of a lesion resulting from RF-TC never kept growing over 30s of procedure, we decided to not perform procedure over that term.

For RF-TC done without rooted parameters, the power was increased (in the same way than in other conditions) until its delivery spontaneously fell down.

Third part (in vitro): using the best parameters found in the second part of the study, our goal was then to find out the best spatial choice of electrode contacts. We thus performed two series of 38 coagulations. In the first series we used contiguous electrode contacts to create a dipole and in the second one we employed a dipole made of two electrode contacts separated by another one.

In the three parts of our study the criteria used to evaluate the efficiency of the RF-TC was volume, measured in mm^3. For lesions having a ball aspect (figure 2), volume was obtained by the following calculation: $\frac{4}{3} \pi R^3$ (where R is the radius), and for those which had a confluent cylindrical aspect: $\pi R^2 H$ (where H is the length of the coagulated volume).

In the two last (in vitro) parts of the study, external temperature monitoring was performed. As no thermocouple device is available for bipolar RF-TC, in vivo temperature monitoring was not possible.

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Statistics

Statistics were implemented on Matlab R2011a v7.12.0 (The MathWorks, Inc., Natick, Massachusetts, USA). Means were compared using a two-tailed Welch's t-test for unpaired

samples. Since multiple comparisons were done, type I errors were controlled by means of a False Discovery Rate procedure.

Ethics

In vivo animal study section has been approved by the institutional review board of BIOMATECH (study n° 44607).

Results

First part – in vivo experiment

For all the procedures (n=16), the power delivered by the generator fell down before 30s (from 5 to 30 s), just after that a slight crack could be heard. Whatever the setting and the lesioning duration, we did not see any alteration of the electrode itself. Brain tissue lesions were limited to the parenchyma adjacent to the part of the electrode on which the RF-TC was performed.

Comparison between the four groups found similar histological lesions (figure 3): 1) a loss of the tissular structure associated with signs of liquefaction and bleeding; 2) edema and fibrinous exsudates; 3) focus of cellular necrosis. The size of the lesions was not the same in each group: 105 mm^3 in the groups 2 and 4, and 35mm^3 in groups 1 and 3. This suggests that there is a correlation between the quantity of power delivery and the size of the lesion.

We found that the diameter of a lesion produced in rabbit brain was the double than one produced with the same parameter in egg white.

Second part – in vitro evaluation of settings

During the procedure performed with fixed parameters, we first noticed that the lesion stopped growing in the ten first seconds of the initially planned lesioning duration (30s). No lesion was noticed for a power of 0.94W (18.75V, 50mA). Concerning the other parameters settings, the higher the delivered power was, the larger the volume was (figure 4).

When unfixed radiofrequency parameters were used, we did not notice any increase of the volume lesion after the delivered power spontaneously fell down, which happened in all cases before 10s. The mean power required to reach this point was 9.6W (standard deviation (STD): 1.8W) obtained by a mean voltage of 54.2V (STD: 5.6V) and a mean intensity of 176.9mA (STD: 21.4mA). The mean volume of RF-TC lesion was 32.9mm^3(STD/ 9.7mm^3).

The volume obtained with unfixed parameters was significantly higher than the volume obtained in all other conditions (table 1).

Third part – in vitro evaluation of the most appropriate configuration of the dipole

As the use of unfixed RF parameters allowed to produce the largest RF-TC, we use that condition in the last part of this study, in which intensity and voltage were increased until they spontaneously collapsed, either on contiguous contacts, or on distant contacts (figure 5).

We noticed that coagulations performed on adjacent electrode contacts had a confluent cylindrical form, whereas those executed on non-adjacent electrode contacts resulted in a succession of ball-shaped lesions, thus giving at the end an aspect of pearl necklace (figure 6).

We found that the lesion volume obtained after RF-TC done on adjacent electrode contacts (mean: 32.9 mm^3) was significantly superior to those (mean 11.9 mm^3) obtained with the other condition (p = 1.2 x 10^{-16}, t-val 11.2).

The temperature could be measured by means of an external monitoring. It ranged from 78 to 82°.

Discussion

Our in vivo and in vitro data, in addition to allow us to propose practical guidelines for the realization of SEEG-guided RF-TC, provide evidence that performing RF-TC using SEEG electrodes is an efficient, reliable, reproducible, and safe lesioning technique. It is indeed possible to assert that: i) There is a clear linearity between energy supply and lesion size. ii) The lesion size cannot exceed a maximal volume, which is known and constant, even if the lesioning parameters are set to the highest possible point. iii) The electrodes are not damaged by RF-TC, so that there is no cause for concern about a possible alteration of the brain-electrode interface, which could have led to a risk of adhesion between brain tissue and electrode.

One of our main goals was to assess the value of our in vitro model (egg white), especially in order to minimize the number of animals included in the study, and therefore sacrificed. We noticed that there is a linear correlation between the volume of a RF-TC lesion produced in rabbit brain tissue and in egg white, thus raising the value of this classical in vitro model, already used in literature. It became then simpler to determine the optimal settings, which are likely to create as large and reproducible post- RF-TC lesions as possible. Histological data could obviously be obtained only from in vivo model.

We showed in vitro that increasing the intensity and voltage of the delivered current until these parameters spontaneously collapse provides larger lesions than using fixed parameters, even for a longer spell. One can note that the mean power delivery resulting from the maximal settings conditions (9.6W) was higher than the one resulting from the highest fixed parameters (7.5W) setting condition. These different fixed parameters had been determined in our protocol in order to test different power ranges than those used in the empiric procedure described in our initial experiments (i.e. 50V; 120mA actually resulting in a power of 6W)[4]. It is now possible to say that these previous empiric parameters did finally not lead to the constitution of lesions as large as possible. Worth to be said, although it was not planed on our protocol, we also tried to test even higher parameters than the highest ones of our study, going very fastly to the maximal settings our generator could reach, looking for a possible stronger effect. In doing so, we noticed that using such massively increased parameters led in fact to a rapid collapse of the delivered power, similar to what happens when using unfixed parameters, thus resulting in a lesion of a usual size. This can be explained by the fact that thermocoagulation does, by definition, result in a coagulation of the proteins of the surrounding tissues, thus resulting in a coagulation necrosis around the electrode contacts. As a result, a proportional raise of tissular impedance (that we could observe) happens simultaneously. We assume that, from a certain power strength, reached when unfixed parameters are used (in our study, the mean power required to reach this point was 9.6W), this raise of tissular impedance becomes so elevated, that it does finally prevent the power from being delivered by the RF generator. However, as we found significant differences between the initial impedance of each of the electrode contacts, we considered impedance as being a non-relevant parameter for SEEG RF-TC procedure guidance.

This constitutes an important point in favour of the safety of SEEG-guided RF-TC (thermo-SEEG) procedure, as it demonstrates that it is impossible to unintentionally create lesions of excessive size. Interestingly, in vivo and in vitro data available in literature related to monopolar RF-TC suggest that lesion appears after about 60s of lesioning duration[12,16] and that temperature raises proportionally to exposure duration[1], which is incongruent with our findings. This may be related to a less spred delivery of power in bipolar condition, than in monopolar condition.

The results of the third part of our study were somewhat surprising as we instinctively thought that using non-adjacent contacts to create a dipole would provide a larger lesion as the *E-field* is bigger than it is when using two adjacent contacts. We found the opposite. A possible explanation is that a too high distance between the contacts constituting the dipole does not allow the production of a confluent lesion, but produces only two smaller separate spherical lesions, each of them centered on an electrode contact.

The bipolar RF-TC technique, performed by means of SEEG electrode, studied here, is an alternative to monopolar RF-TC performed by means of a classical lesioning probe. Its main advantages are: one the one hand, to be performed on the same electrodes than those used for an the SEEG procedure itself, thus avoiding any additional bleeding risk related to another electrode insertion, and, on the other hand, to create lesions with sharp limits, which is valuable when the lesion is close to vascular structures. Conversely, monopolar RF-TC allows the use of larger electrodes which can create larger lesions[12,17,18]. Other stereotactic techniques, sometimes used in the field of epilepsy surgery may have the advantage, either to provide a real time monitored lesion (laser ablation[19]), or to be less invasive (radio-surgery[20]) but they do not offer the possibility to be in-situ guided by intracranial electrophysiological findings and they require a dedicated procedure.

Technical guidelines - Conclusion

We propose the following technical and practical guidelines for the realisation of SEEG-guided RF-TC:

Parameters of radiofrequency current: when performing SEEG-guided RFTC, we recommend, in order to obtain the highest possible lesional volume, not to use standard fixed parameters, as it had been proposed in previous, more empiric, works, but to progressively (in a few seconds) increase the power delivered until the intensity and the voltage spontaneously fall down.

Selection of dipole: according to our results, we recommend to always select adjacent electrode contacts to create a dipole. These two recommendations constitute prerequisite conditions to obtain the largest possible lesional volume, which is to be desired to maximize the clinical effect of SEEG RF-TC. They must however be added to other, already published[4,5,7,9,21,22], technical guidelines, deriving from the clinical experience gained with this technique.

Target location: the selected adjacent contacts have to be located in cortical areas showing either a low amplitude fast pattern or spike-wave discharges at the onset of the seizures. Interictal paroxysmal activities can obviously help to locate the ictal onset zone (especially in case of dysplasia) but are insufficient, if isolated, to be considered as a SEEG-guided RF-TC target. Our overall SEEG RF-TC experience always fulfilled this recommendation, and involves now more than 160 patients over a 10-years period. Briefly: as far as seizure outcome is concerned, nearly half (48%) of the patients showed a long-term improvement, while 7% became seizure free for more than 1 year. Thus, SEEG RF-TC can be considered as a major option of palliative treatment in patients for whom resective surgery is risky, or even not feasible.

Target evaluation: All the possible targets must be functionnally evaluated by bipolar electrical stimulations (low and high frequency pulse stimulation up to 3mA) done during the video-SEEG recording session. RF-TC should obviously not be done on dipoles which, when stimulated, do provide a neurological deficit. We consider this recommendation as being crucial for the safety of any SEEG RF-TC procedure. In our experience indeed, 6 patients (3%) experienced a post SEEG RF-TC motor impairment (transient in most cases, and without any associated neuropsychological impairment). In 2 cases, the deficit could clearly be forecast by the stimulations done on contacts located in the motor area, and it actually occurred as expected in both cases (these patients had been informed and maintained their

choice to undergo SEEG RF-TC because of their life-threatening epilepsy).Observance of this latter recommendation is therefore essential.

Acknowledgments

Disclosure

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Figure 1: a. Connection between the electrode and the radiofrequency generator by the mean of a dipole selector (manufactured by Dixi medical). b. Connection between the electrode and the dipole selector.

Figure 2: study design. The first part (a.) is an in vivo experiment and the two others (b. and c.) are in vitro experiments.

Figure 3: RF-TC performed with SEEG electrode on rabbit brain. a. The green arrow points an SEEG electrode/brain interface without RF-TC. b. The red dotted line shows the sharp limit of the RF-TC lesion. c. The red double arrow shows the radius'lesion and the yellow one indicates the diameter of the SEEG electrode. d. Dotted arrows correspond to the lead length and double arrow shows the inter-lead gap.

Figure 4: Mean volume of RF-TC obtained using fixed parameters during a 30s period in the four groups. Each point corresponds to a group and is associated to the value of the parameter used (e.g: 1.88; 2.7 corresponds to a power of 1.88W associated to a mean volume of 2.7 mm^3 which are the results of the second group).

Figure 5: Schema displaying the electric field (*E-field*) which oscillates according to the current density *(j)* produced by current (*i*); a. dipole made of two adjacent contacts of an electrode; b. dipole made of two distant contacts separated by a third electrode.

Figure 6: Visual aspect of multiple RF-TC performed on adjacent contacts (a.) and on separated contacts (b.).

Table 1: Comparisons between volumes of the post-RF-TC lesions obtained using unfixed parameters and the four couples of fixed parameters.

	Mean volume - fixed parameters (mm^3)	Mean volume - unfixed parameters (mm^3)	p	t-value
Unfixed parameters compared to 18.75V; 50mA	0	32.9	4.3×10^{-22}	20.9
Unfixed parameters compared to 25V; 75mA	2.7	32.9	8.3×10^{-21}	19.2
Unfixed parameters compared to 37.5V; 100mA	7.4	32.9	1.6×10^{-10}	12.9
Unfixed parameters compared to50V; 150mA	16.5	32.9	0.004	4.4
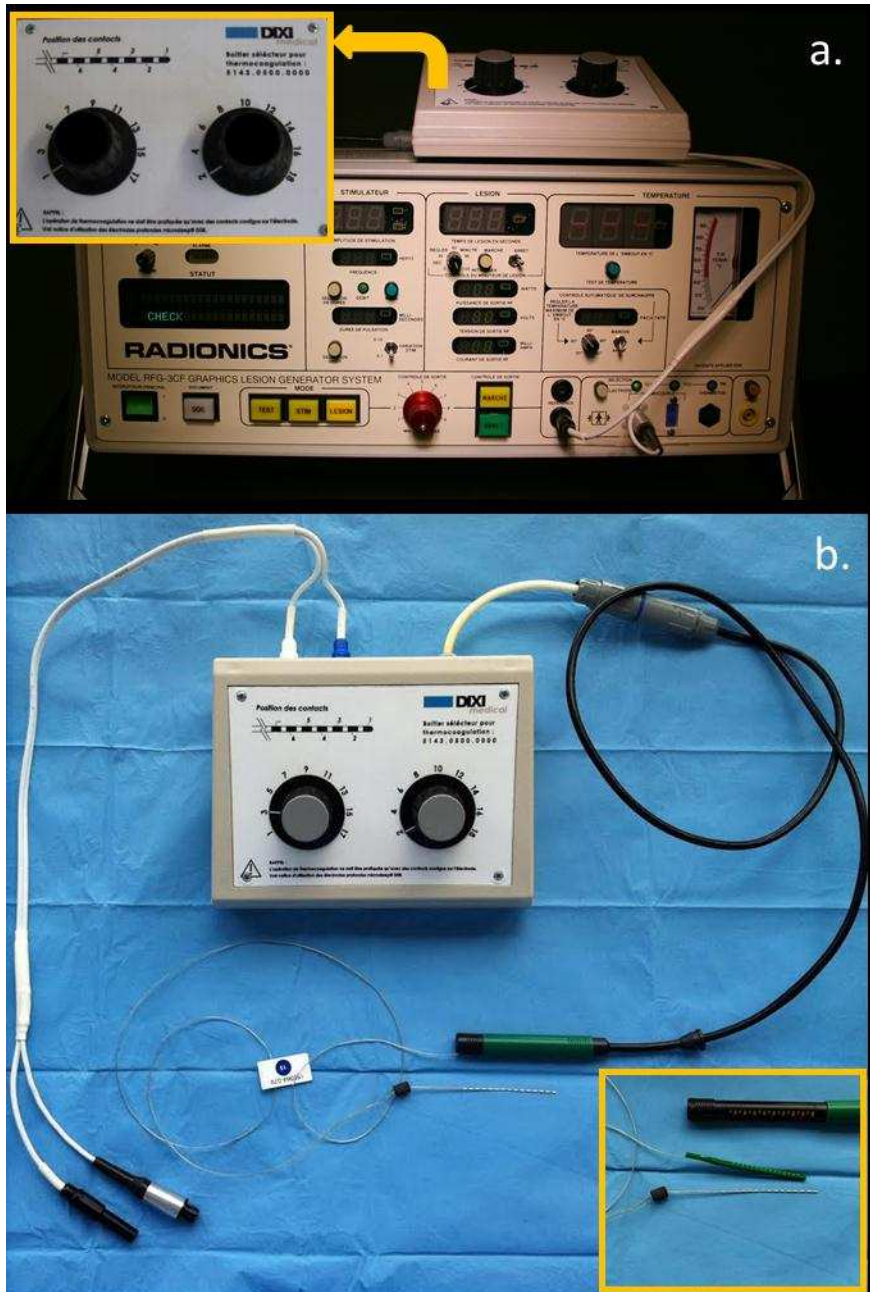
a- In vivo experiment

4 groups of 2 rabbits (n=16 hemispheres)

1. 5W / 30s
2. 10W / 30s
3. 5W / 90s
4. 10W / 90s

Objective:
- *Safety - histopathological examination*
- *In vivo effect of power delivering and lesioning duration*
- *Relation between in vitro and in vivo lesion sizes*
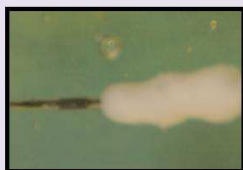
b- In vitro experiment *1 - radiofrequency parameters*

5 in vitro conditions of RF-TC lesions

1. 18.75V; 50mA (0,94W)
2. 25V; 75mA (1,88W)
3. 37.5V;100mA (3,75W)
4. 50V; 150mA (7,50 W)
5. Unfixed parameters

Objective:
- *to determine the optimal radiofrequency parameters required to obtain the largest possible lesion size.*

c- In vitro experiment *2 - spatial parameters*

2 in vitro conditions of RF-TC lesions

1. contiguous electrode contacts to create a dipole
2. two electrode contacts separated by another one to create a dipole

Objective:
- *to determine the best spatial choice of electrode contacts required to obtain the largest possible lesion size.*

Relation between the mean volume of lesion and the power delivered
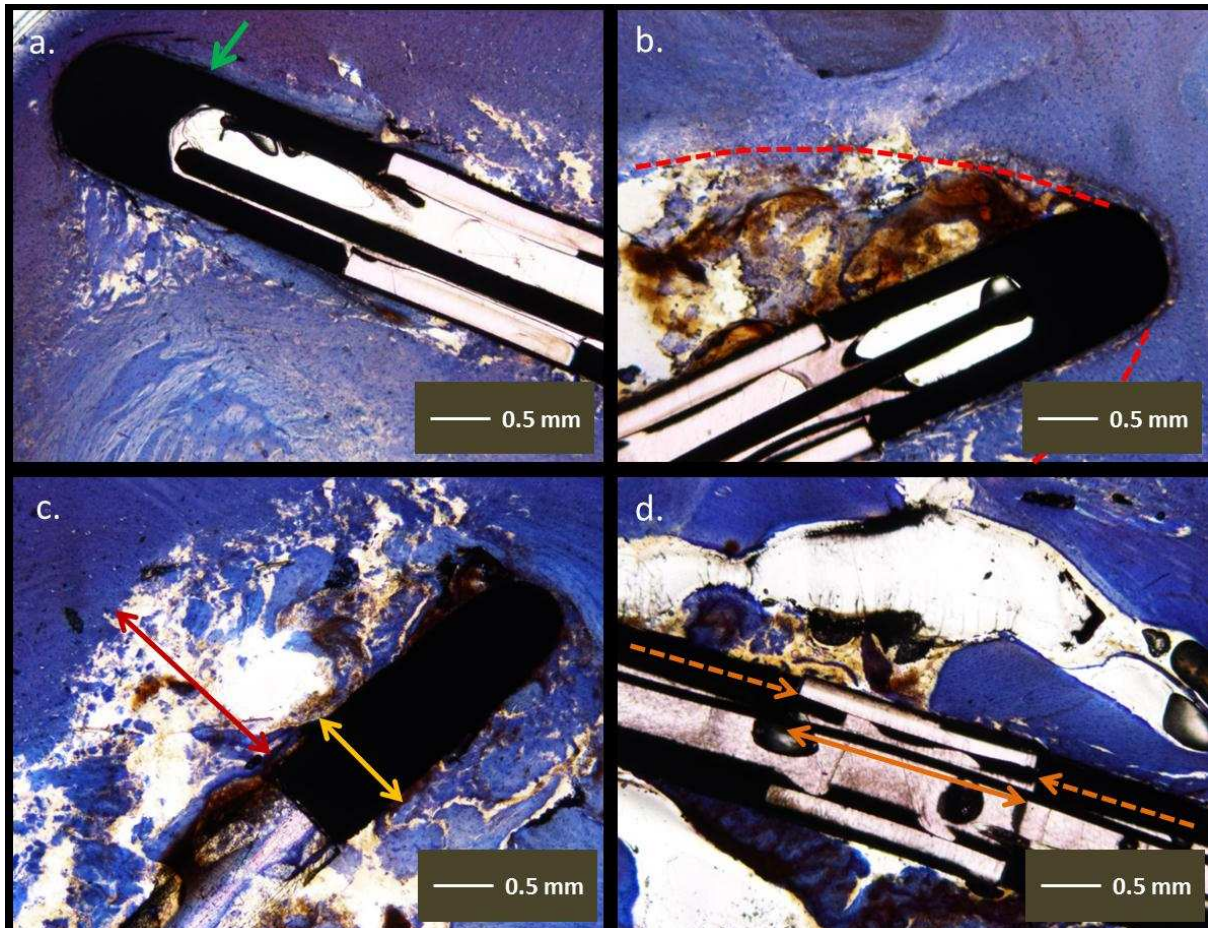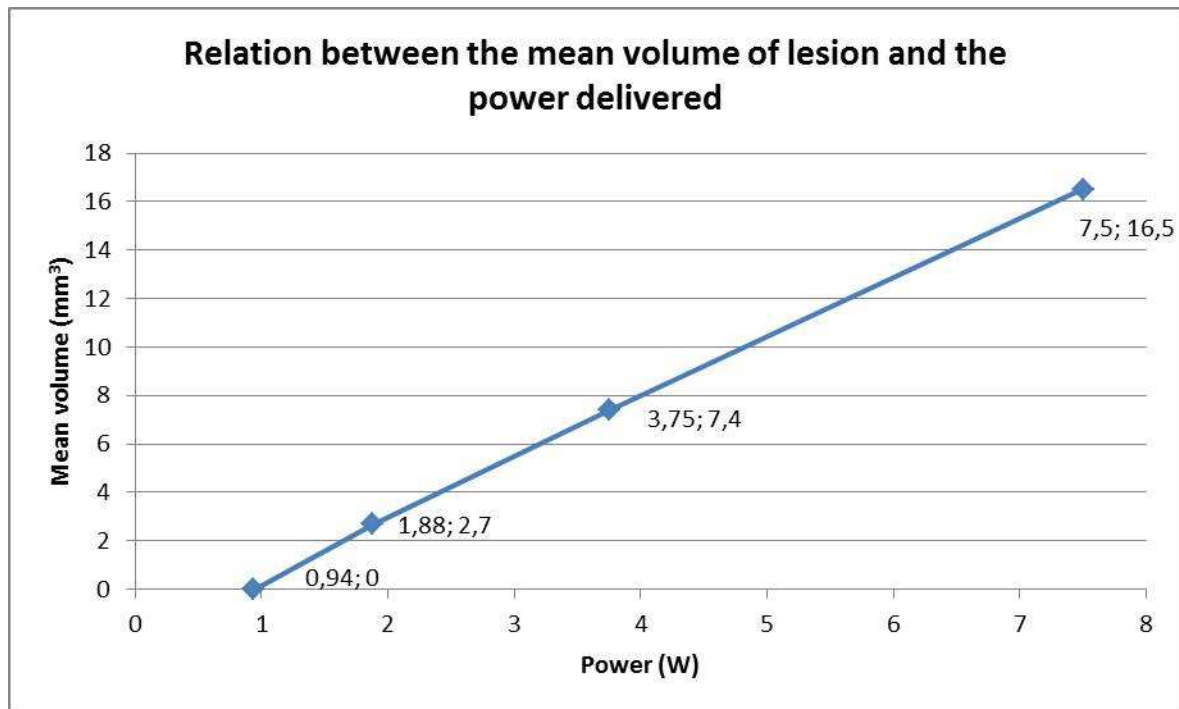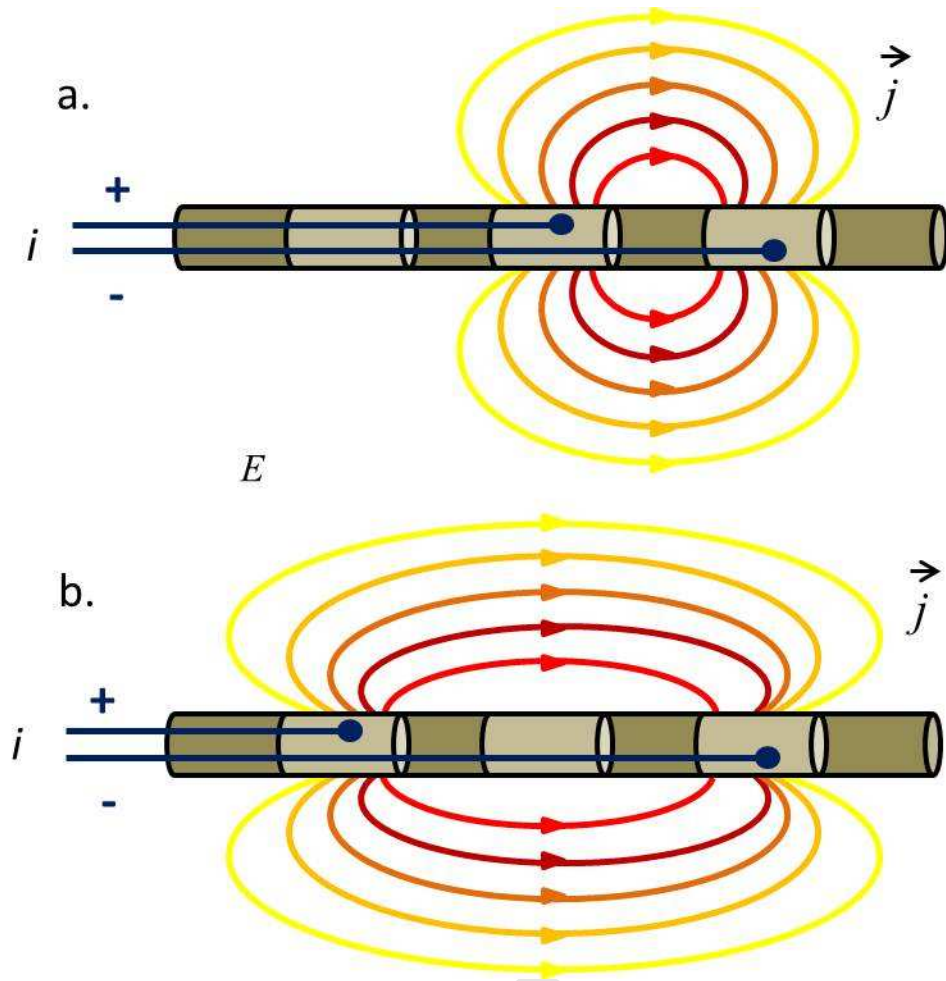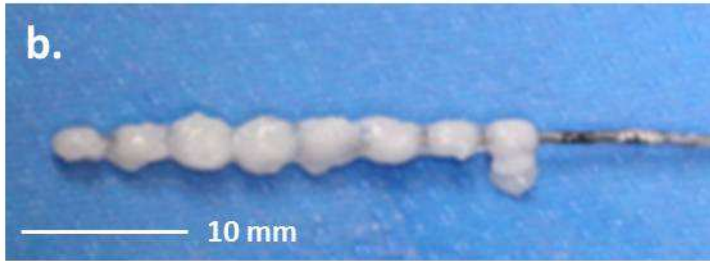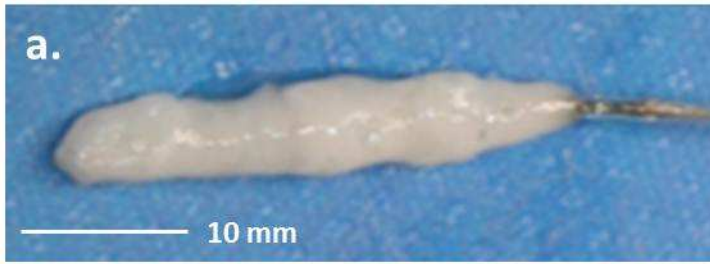
Abbreviation

SEEG: stereo-electro-encephalography

RF-TC: radiofrequency thermo-coagulation

SEEG-guided radiofrequency thermo-coagulation: SEEG RF-TC

Highlights

- SEEG-RF-TC produces safe and sharp in vivo lesions
- There is a linear correlation between in vivo and in vitro models
- Radiofrequency-current must be increased until the power delivered collapses
- Dipoles should be constituted by contiguous electrode contacts