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Short communication

Intraoperative real-time guidance using ShearWave Elastography for epilepsy surgery

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ABSTRACT

Purpose: In epilepsy surgery, seizure outcome is determined by the integrity of epileptogenic zone resection. ShearWave elastography (SWE) is a noninvasive imaging technique that generates a quantitative assessment of elasticity values permitting intraoperative real time tissue mapping by differentiating normal and pathological epileptogenic tissue. The aim of this study was to evaluate the contribution of SWE intraoperative guidance on the advancement of epileptogenic zone detection in epilepsy surgery.

Methods: We prospectively analyzed epileptogenic zone resections using SWE guidance for 28 patients with severe and/or disabling drug-resistant focal epilepsy.

Results: Conventional B-mode images visualized echogenicity differences between the epileptogenic lesion and normal brain tissue in 71.4% of cases, while SWE detected a significant difference in stiffness in 92.8% of cases ($p = 0.02$). Regarding cryptogenic epilepsy, none of the 4 MRI-negative focal cortical dysplasias was visualized by B-mode images, while 3 cases were detected by SWE. Postoperative brain MRI showed a complete resection of the epileptogenic zone in all MRI-positive cases. One year after the surgery, 85.7% of the patients were seizure free (ILAE class 1).

Conclusion: Despite some technical limitations, SWE improves the intraoperative detection of epileptogenic lesions and should be considered for all patients with cryptogenic and lesional epilepsy. Naturally this ought to be confirmed by larger case series additionally investigating long-term seizure outcome.

1. Introduction

In epilepsy surgery, seizure outcome is determined by the completeness of epileptogenic zone resection. [1] Our macroscopic intraoperative experience gained from epilepsy surgery suggests that epileptogenic lesions such as focal cortical dysplasia (FCD), hippocampal sclerosis, dysembryoplastic neuroeptihelial tumor (DNET), ganglioglioma, cavernoma and its surrounding gliosis have a stiffer consistence than the surrounding normal brain parenchyma.

ShearWave elastography (SWE) is a noninvasive imaging technique that delivers information on viscoelastic properties of the tissue, thus generating a quantitative assessment of elasticity values. [2] SWE allows intraoperative real time tissue mapping by differentiating normal from pathological tissue [3]. SWE is being used in liver surgery for now several years for the differentiation of focal liver lesions to optimize tumor resection [4]. The first report of the use of SWE guidance in brain surgery was a case of magnetic resonance imaging (MRI)-negative FCD in a child, published by Chan et al. in 2014 [5]. Chauvet et al. (2016) then reported a series of 63 patients investigated with intraoperative SWE for low-grade and high-grade gliomas, metastasis and meningiomas and supported the role of SWE in brain tumor resection [6]. To date, there is no study assessing the interest of SWE for epilepsy surgery. The aim of this study was to evaluate the contribution of SWE intraoperative guidance on the improvement of epileptogenic lesion detection in epilepsy surgery.

2. Methods

Between November 2016 and February 2018, all patients with a drug-resistant focal epilepsy requiring surgery were eligible for

Abbreviations: DNET, dysembryoplastic neuroeptihelial tumor; EEG, electroencephalography; kPa, kilopascal; FCD, focal cortical dysplasia; MRI, magnetic resonance imaging; SWE, shearwave elastography

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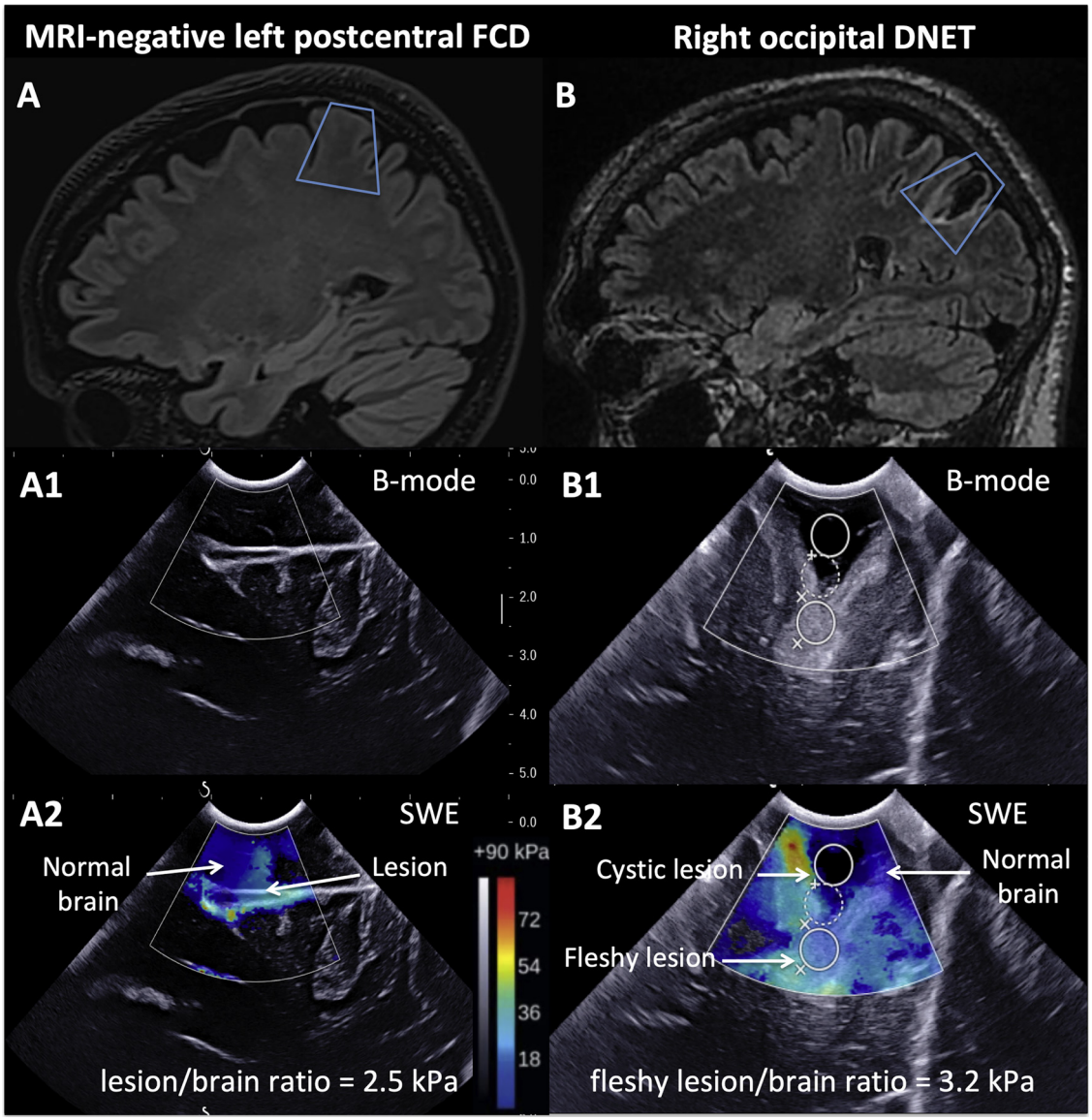

Fig. 1. Example of MRI images (T2-weighted Fluid Attenuated Inversion Recovery, sagittal views), ultrasound images and elastography images for a MRI-negative focal cortical dysplasia (A, A1 and A2 respectively) and for a cystic and fleshy DNET (B, B1 and B2 respectively) in patients with drug-resistant focal epilepsy. Dimensions of ultrasound images: 38.4 mm wide, 40.0 mm depth. Blue trapezium: imaging plan. (A) Imaging of the boundary between epileptogenic lesion (MRI-negative left postcentral focal cortical dysplasia) and surrounding normal brain. The standard ultrasound B-mode image did not show any abnormality (A1). The area of increased stiffness was consistent with the epileptogenic lesion that was previously localized with intracranial EEG monitoring (A2). (B) Imaging of the boundary between epileptogenic lesion (cystic and fleshy right occipital DNET) and surrounding normal brain. The standard ultrasound B-mode image (B1) revealed a cystic and fleshy lesion as suggested by MRI (B). Stiffness map and stiffness quantitative measurements were then done by choosing a region of interest both in the epileptogenic lesion (fleshy tissue) and in the normal parenchyma (B2) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

inclusion in this prospective study. We excluded patients operated for mesial temporal lobe epilepsy associated with hippocampal sclerosis due to the anatomical location of mesial temporal structures because the surgical procedure of amygdalohippocampectomy obviated the need for intraoperative SWE [7,8]. Drug-resistant patients underwent presurgical evaluations. A multidisciplinary team analyzed presurgical data to determine whether surgical treatment was indicated and whether an epileptogenic focus could be clearly localized. If so, strict criteria were used to define a single-stage surgical resection, avoiding intracranial electroencephalographic (EEG) recordings when possible. Intracranial EEG recordings, performed using depth electrode stereo-electroencephalography (SEEG), were limited to atypical presentations and were mainly indicated in MRI-negative patients, in case of discordance between electro-clinical data and imaging or in multifocal lesions. Ethical considerations were previously validated by our institutional ethics committee, "Comité de Protection des Personnes – Ile-de- France VI – Pitié-Salpêtrière".

Intraoperatively, ultrasound images and stiffness maps were acquired with an ultrafast ultrasonic device (Aixplorer®, Supersonic Imagine, Aix-en-Provence, France) using the same probe (SuperMicroConvex® SMC 12-3, 2.78 x 0.91 cms, Supersonic Imagine, Aix-en-Provence, France). Conventional B-mode images and stiffness maps were recorded during surgery after dural opening, with the same probe, in order to monitor epileptogenic zone resection. The stiffness was color-coded in kilopascals (kPa) and displayed over the B-mode image.[1] The coldest coloration represented the softest elasticity, and the hottest represented the hardest. All stiffness images have the same scale, from 1 kPa (dark blue) to 90 kPa (dark red). Stiffness

quantification, evaluated by a mean value and its standard deviation (Young's modulus), was then done by choosing a region of interest both in the epileptogenic lesion and in the normal parenchyma. At least 3 stiffness quantifications comparing the lesion to normal brain tissue were recorded for each patient giving access to a ratio in kPa. Due to anisotropy, the stiffness of the normal brain can vary depending on the direction of the white matter fibers. Therefore, the stiffness quantifications were done in at least 2 perpendicular planes. We considered a significant difference in the stiffness and the positivity of the epileptogenic zone screening if this ratio was > 2. In previously published papers, this threshold was often arbitrarily set at 1.5. For more specificity, we have chosen to set it at 2. Lesion and normal brain elasticity were quantified and recorded with full objectivity by the same neurosurgeon (B.M.). At the end of the operation, final ultrasound imaging was performed with B-mode and SWE to confirm the quality of the resection.

All resected tissue samples were examined and classified histologically. Postoperative brain MRI was systematically performed to assess the extent of epileptogenic zone resection. Postoperative seizure outcomes were assessed using the ILAE classification.

Statistical analysis was performed with SPSS, version 21 (IBM, Armonk, NY, U.S.A.). Differences between groups were assessed with the χ^2 test for categorical variables. A probability $p < 0.05$ was considered statistically significant.

3. Results

We analyzed epileptogenic zone resections using SWE guidance in 28 patients with severe and/or disabling drug-resistant focal epilepsy. Mean age at surgery was 28.2 ± 9.4 years (range, 18–61.5); and the female/male ratio was 1.1. Mean age at the time of the first seizure was 13.1 years (± 5.7, range, 1.8–42.4 years) and mean seizure frequency just before surgery was 5 ± 4 seizures per month (range = 1–35). Patients treated with three or more antiepileptic drugs at the time of surgery reached 78.6%. Intracranial EEG records were necessary in 8 patients (28.6%) before epileptogenic zone resection. Four of our patients had negative MRI exploration (cryptogenic epilepsy, 14.3%). Epileptogenic lesions comprised cavernomas (n = 8, 28.6%), FCDs (n = 7, 25%, of which 4 cases were MRI-negative), DNETs (n = 6, 21.4%), gangliogliomas (n = 3, 10.7%), posttraumatic lesions (n = 2, 7.1%), and other forms of cortical malformations (n = 2, 7.1%, a case of early lipofuscin accumulation in frontal lobe epilepsy and a case of nodular heterotopia), as disclosed in the neuropathological examination.

During surgery, echogenicity and stiffness maps as well as stiffness values were recorded for every patient as shown for two patients in Fig. 1. Normal brain measurement was obtained in all cases. A global mean elasticity of 8.5 ± 2.1 kPa was observed for normal brain tissue for all patients combined. Conventional B-mode images visualized echogenicity differences between the epileptogenic lesion and the normal brain in 71.4% (n = 20) of cases, while SWE detected a significant difference in stiffness in 92.8% (n = 26) of cases (χ^2 test, p = 0.02). Classification into categories was then performed using histological results. The 3 cases of FCD visible on MRI were detected by SWE with a mean ration of 3.9 ± 0.8 kPa. Regarding cryptogenic epilepsy, none of the 4 MRI-negative FCD was visualized by B-mode images, while 3 cases were detected by SWE with a mean ratio of 2.8 ± 0.6 kPa. Table 1 compares the sensitivity of conventional B-mode images versus SWE mode for detecting epileptogenic lesions according to histology. Neither infections nor postoperative complications related to surgery were observed. Postoperative brain MRI showed in all cases a complete resection of the epileptogenic lesion or suspected epileptogenic zone as previously defined by presurgical evaluation. With a one-year follow-up, seizure outcome was classified as ILAE class 1 in 24 patients (85.7%), ILAE class 2 in one patient (3.6%), ILAE class 3 in one patient (3.6%) and ILAE class 4 in two patients (7.1%).

Table 1
Comparison between conventional B-mode images versus SWE mode in the detection of epileptogenic lesions according to histology. The SWE mode is more sensitive than conventional B-mode to detect epileptogenic lesions (χ^2 test, p = 0.02). The stiffness ratio (in kPa) between the epileptogenic lesion and the normal surrounding brain is shown for each histological type of epileptogenic lesion.

Epileptogenic lesion	n	B-mode sensitivity	SWE sensitivity	Epileptogenic lesion/ normal brain stiffness ratio (kPa)
MRI- FCD	4	0%	75%	2.8 ± 0.6
MRI + FCD	3	33.3%	100%	3.9 ± 0.8
Cavernoma /	8	100%	100%	8.2 ± 2.1
gliosis		75%	100%	2.7 ± 0.8
DNET	6	100%	100%	4.9 ± 3.8
Ganglioglioma	3	100%	100%	4.3 ± 3.5
Posttraumatic lesion	2	50%	100%	3.2 ± 0.8
Others	2	50%	50%	2.5 ± 1.2
Total	**28**	**71.4%**	**92.8% (p = 0.02)**	–

4. Discussion

Improving the quality of epileptogenic zone resection is an ultimate goal in epilepsy surgery. During the presurgical evaluation, several examinations can improve detection rates of epileptogenic zones: 3 T MRI scan, interictal positron emission tomography, subtraction ictal single photon emission computed tomography and in some cases intracranial EEG recording. [9] Intraoperatively, some technologies, such as the surgical navigation system or MRI control may help to localize the epileptogenic zone. However neurosurgeons cannot always discriminate normal tissue from the epileptogenic lesion. This case series is the first on SWE of epileptogenic lesions and demonstrates that the stiffness of the most frequent lesions differs from the surrounding normal brain (p = 0.02). With our experience, we suggest that SWE is effective especially for suspected MRI-negative FCDs (cryptogenic epilepsy), MRI-positive FCDs and cavernomas with surrounding gliosis.

SWE emerges as an efficient tool to detect epileptogenic zones by measuring the stiffness and has significant benefits. Despite the results of a small series published in 2011 suggesting the interest of intraoperative B-mode ultrasonography to detect FCD, [10] we detected FCD for only one of 7 patients (MRI-positive case) with this conventional mode. Our results showed that SWE is more powerful than B-mode in terms of detecting epileptogenic lesions. Moreover, stiffness measurements do not excessively prolong the duration of surgery since three measures take a matter of minutes. Concerning safety, we did not report any side effects related to intraoperative ultrasonography. Finally, unlike other intraoperative image-guided neuronavigation systems, SWE is not impacted by brain shift and provides dynamic real-time images [11].

Despite promising results, this study has some limitations. First, ultrasonography is an operator-dependent tool. The differences in skill between operators may result in distinct results. However, contrary to other ultrasound modes, [12] SWE does not require an external force and thereby minimizes intra-operator and inter-operator variability. Second, SWE is not suitable for some surgical cases. Depth and/or obstacle may forbid shear wave propagation; stiffness values and stiffness maps cannot therefore be acquired. For example, when performing transcortical or transylvian selective amygdalohippocampectomy for mesial temporal lobe epilepsy, a stiffness measurement cannot be achieved for the amygdalohippocampal complex. By contrast, this can be measured when an anterior temporal lobectomy is performed.[5] In the future, probe miniaturization could permit substantial improvements for deep-seated lesions elastographic analysis. However, once presurgical evaluation has clearly defined the epileptogenic focus in the

mesial temporal structures (e.g. mesial temporal sclerosis), SWE is of little avail to localize the epileptogenic zone. Finally, even if SWE showed benefits in the detection of epileptogenic lesions and on the improvement of surgical resection, seizure outcome following SWE resection guidance should be assessed and compared to outcomes following resection with conventional neuronavigation tools.

In conclusion, the use of SWE improves intraoperative detection of the epileptogenic zone allowing the neurosurgeon to visualize the lesion and its boundaries in most cases. SWE can further reinforce surgical intraoperative guidance in the perspective of complete resection. Therefore, SWE should be considered in all patients with cryptogenic and lesional epilepsy. This must be confirmed in larger case series additionally investigating seizure outcome.

Ethical publication statement

We confirm that we have read the Journal position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosures

On behalf of all authors, the corresponding author states there is no conflict of interest.

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