SUDEP

Dr. Hemang Shah

Case 3 – Near SUDEP

- 31 yo morbidly obese AAF had new onset seizure was brought to ER.
- Recent fight with common law husband that afternoon, broke TV with fist, had some alcohol (serum alcohol level: 77 mg/dL). +ve ingest of unknown pills. No h/o myoclonic jerks in morning, neurocutaneous stigmata, developmental problems nor family history.
- CSF was OK
- Coded next day during her 4th seizure in ICU, great difficulty with oxygenation. Signs of pulmonary edema.

Case 2 – SUDEP s/p successful epilepsy surgery

- 17 yo RH WM, who had Seizure onset at age of 5. He had SMA seizure once / 3 days and SMA with secondary GTCS once a week – intractable – came to MCG peds epilepsy program (10/31/2005) after finished evaluation at Duke and MUSC.
- Has been tried on valproic acid, zonisamide, carbamazepine, lamotrigine and felbamate.
- V.EEG: Rt. Frontal CPS with SGTC.
- MRI: Normal (12/09/2005)
- Ictal SPECT: Predominant focus of increased activity in the superior-posterior right frontal lobe. (11/22/05)
- Interictal SPECT: relative decrease in activity in the right posterior frontal/anterior parietal region
- Neuropsychological evaluation: Full scale IQ 75 (12-19-2005)
- Invasive EEG: Rt. Frontal + interhemispheric grid implantation with motor mapping (3/9/06)
- Surgery: Rt. Partial lateral frontal lobectomy (3/20/2006)

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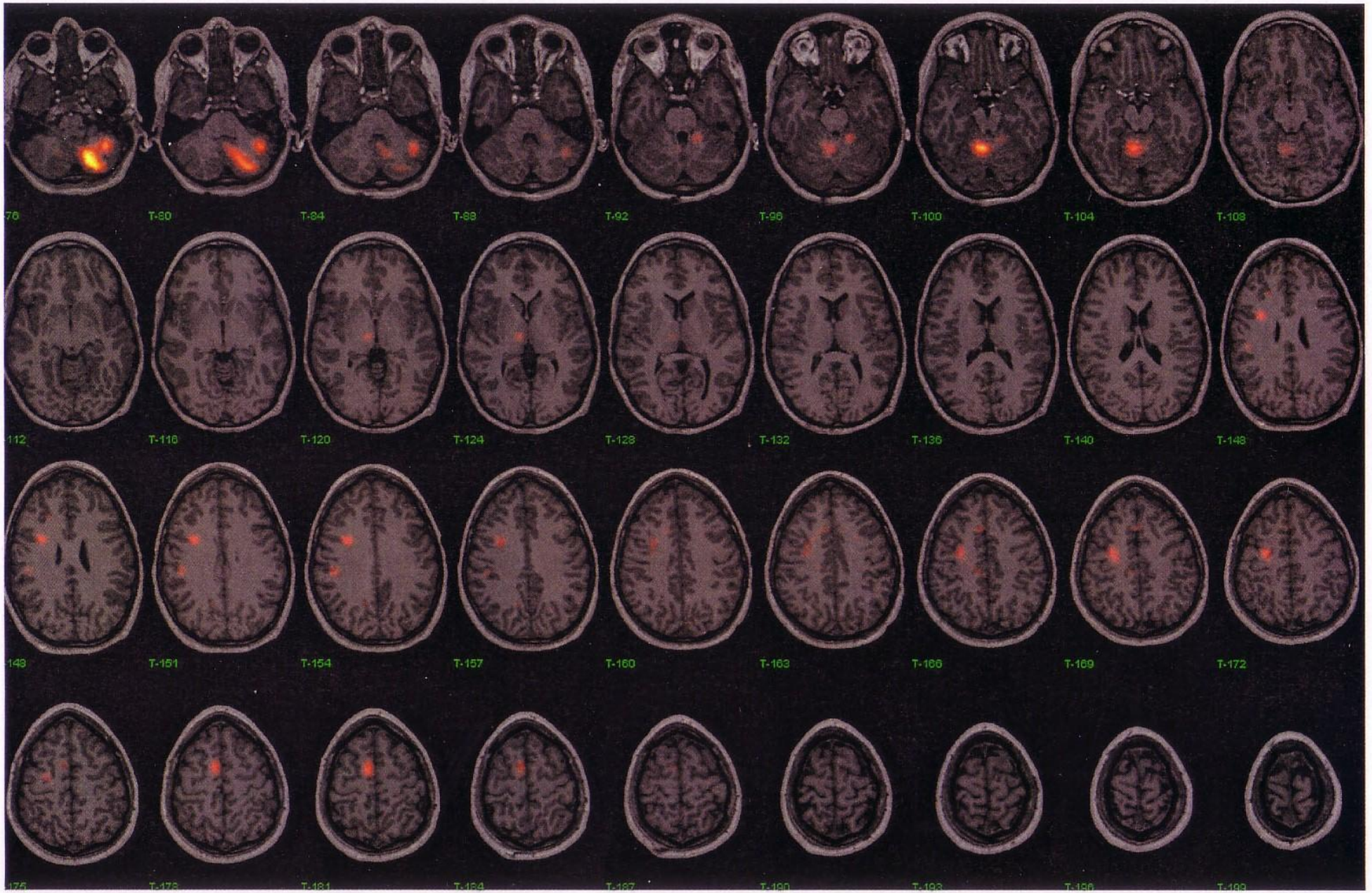

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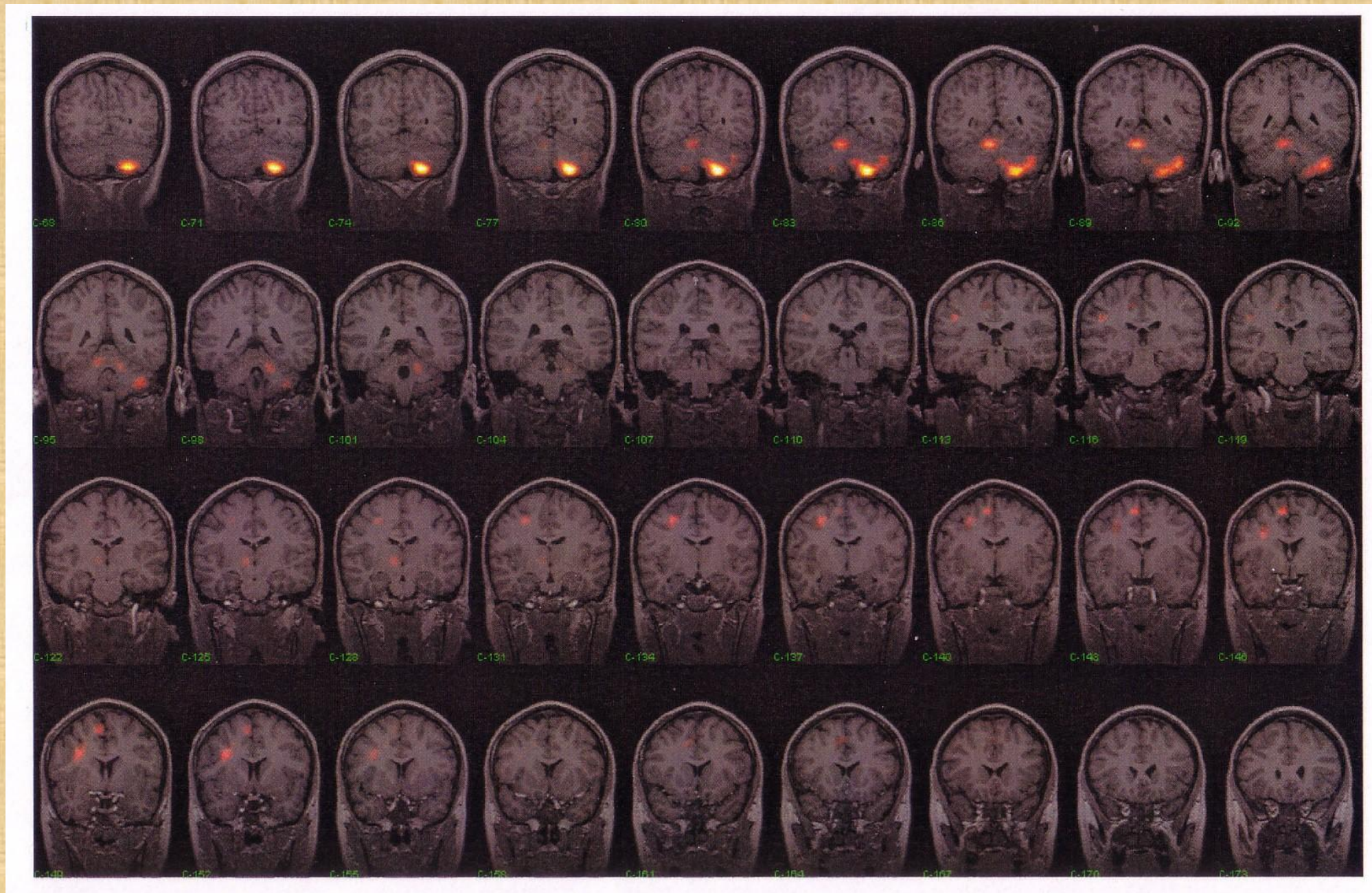

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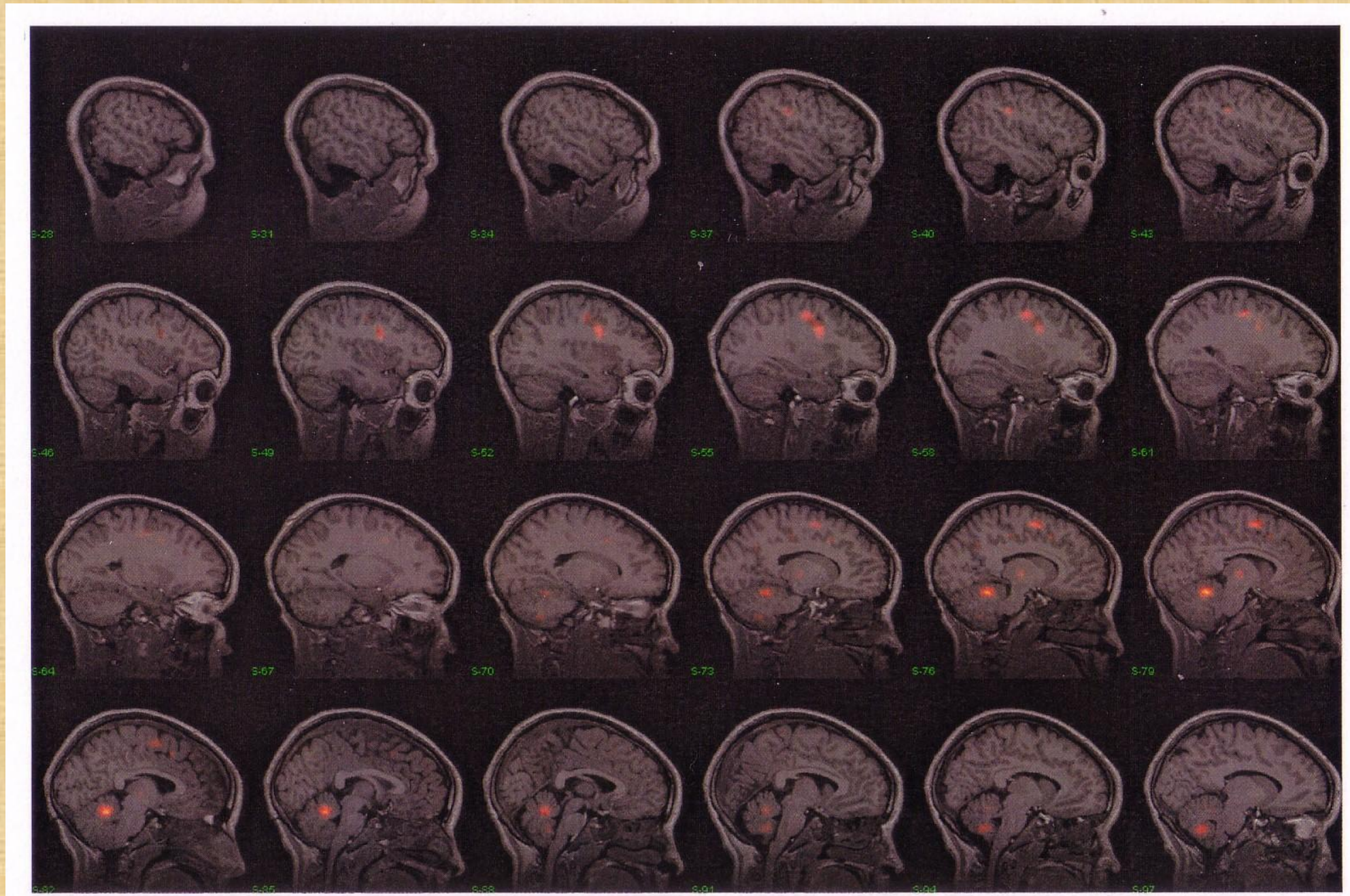

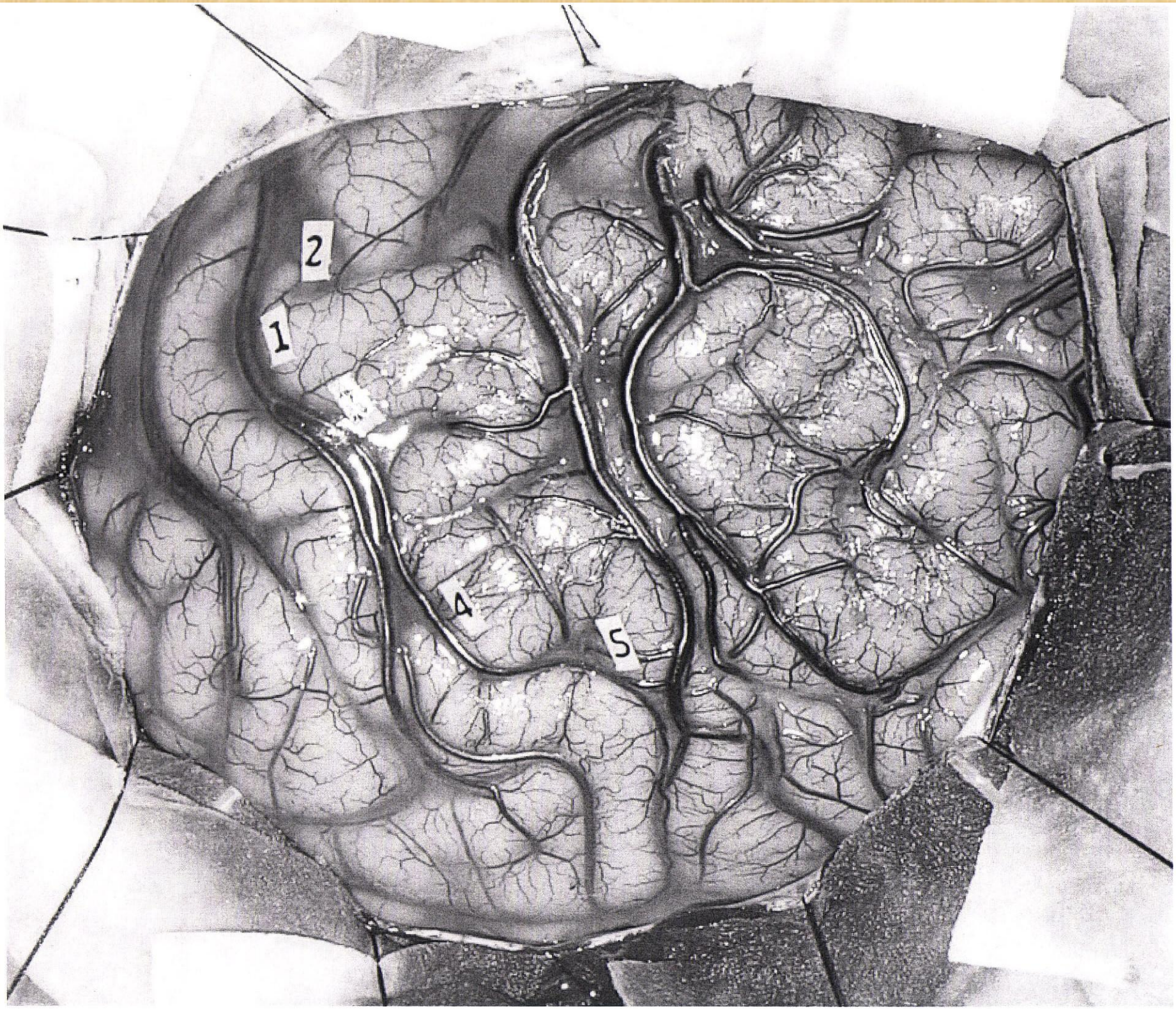
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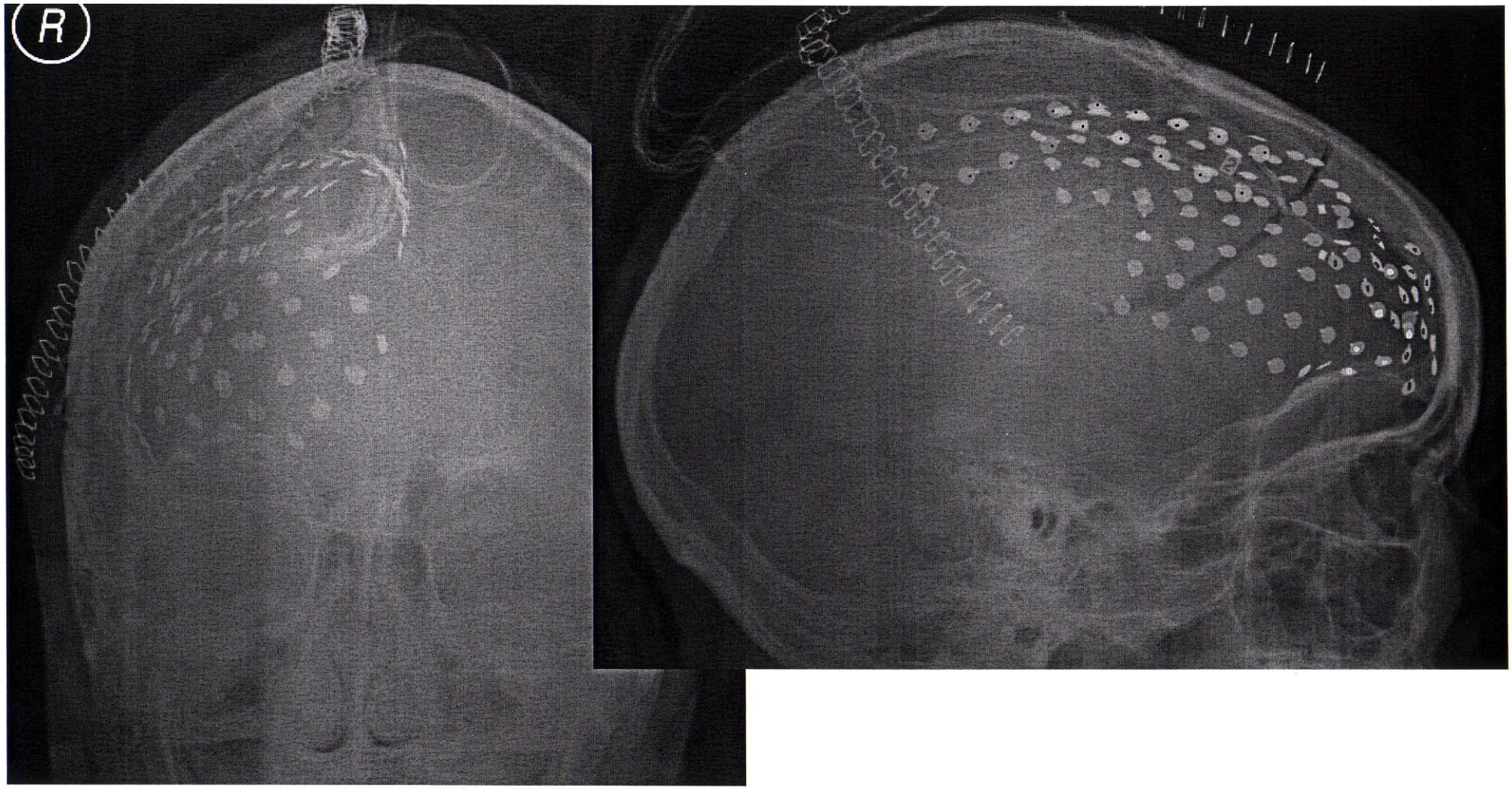
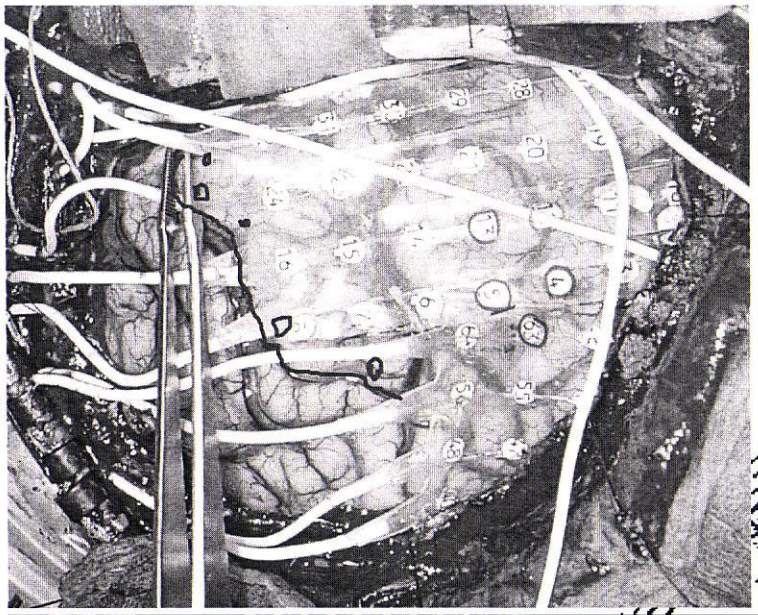
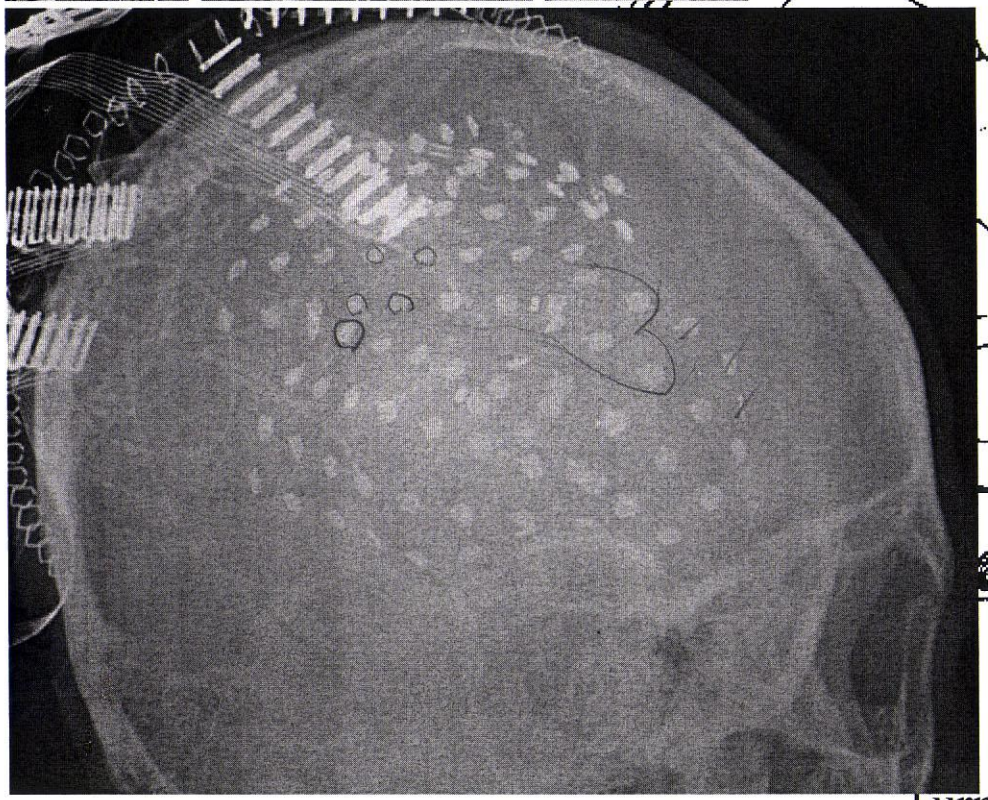
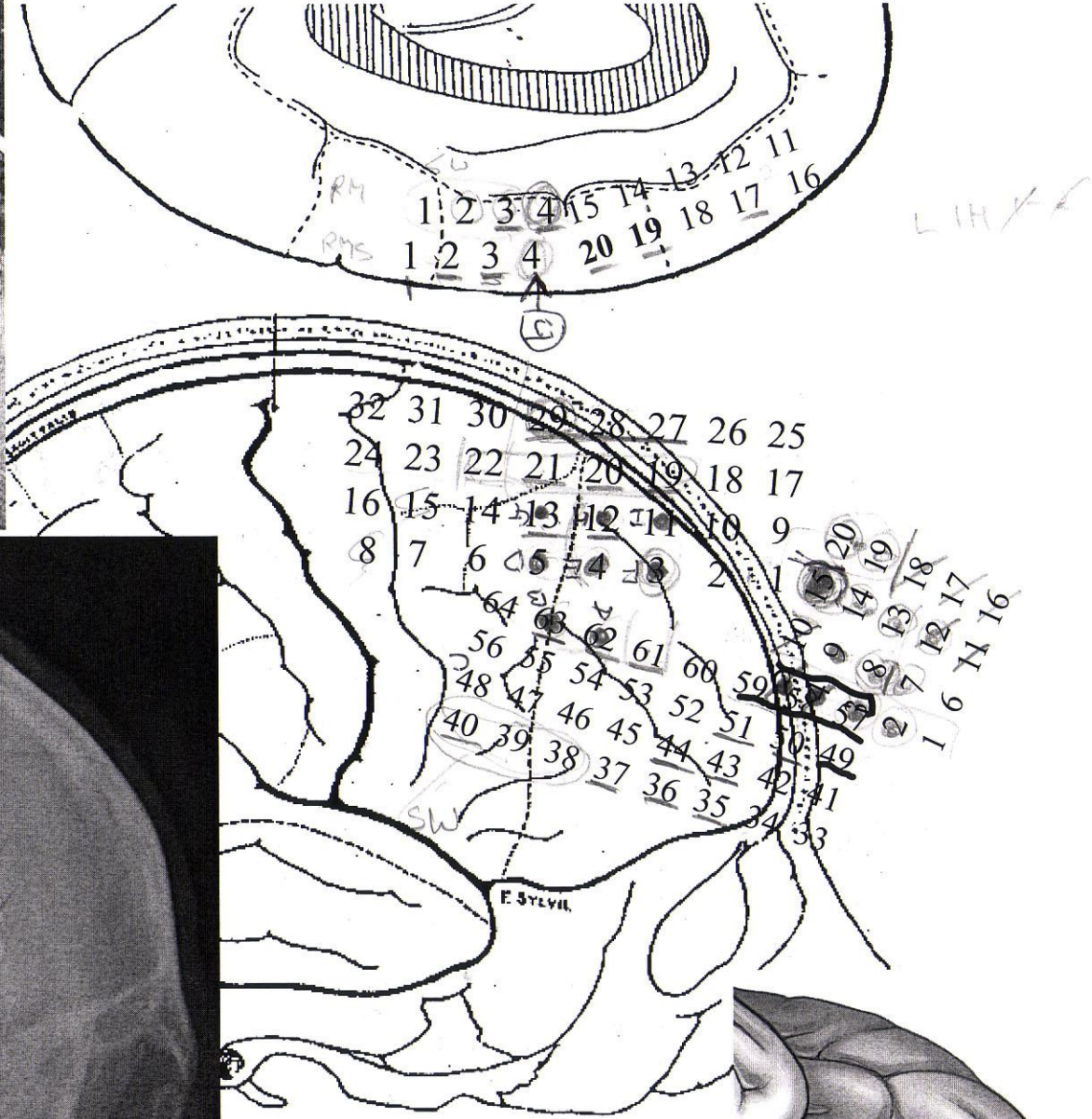
3-14-06 SDG









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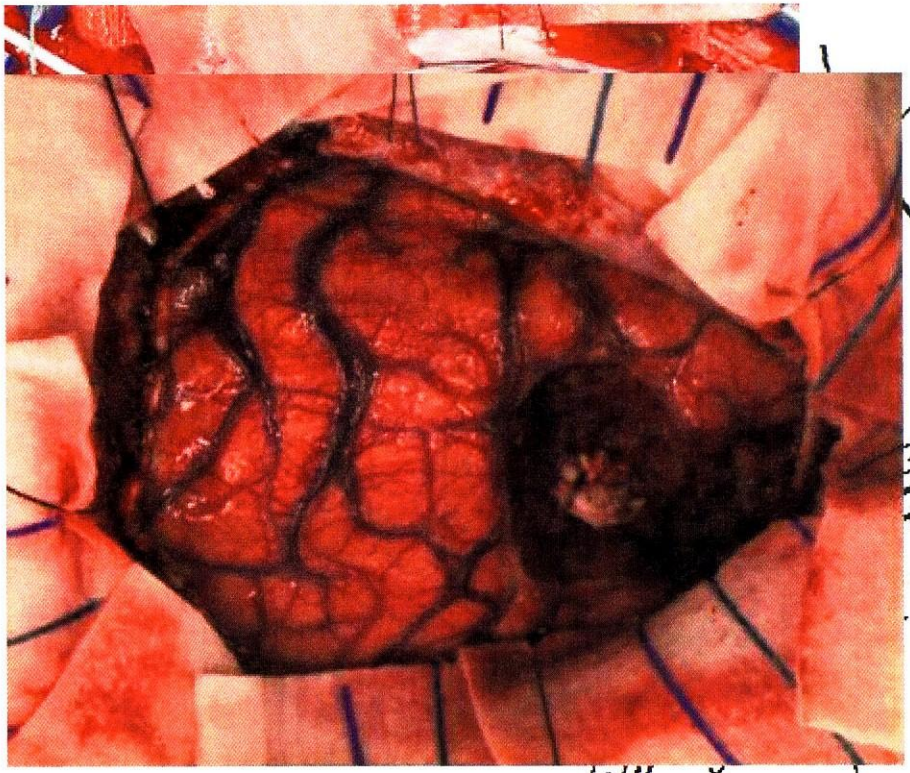
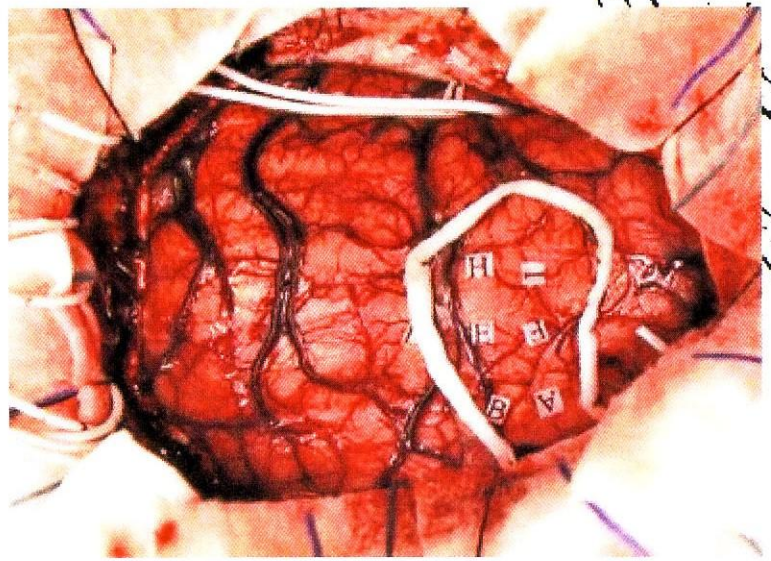
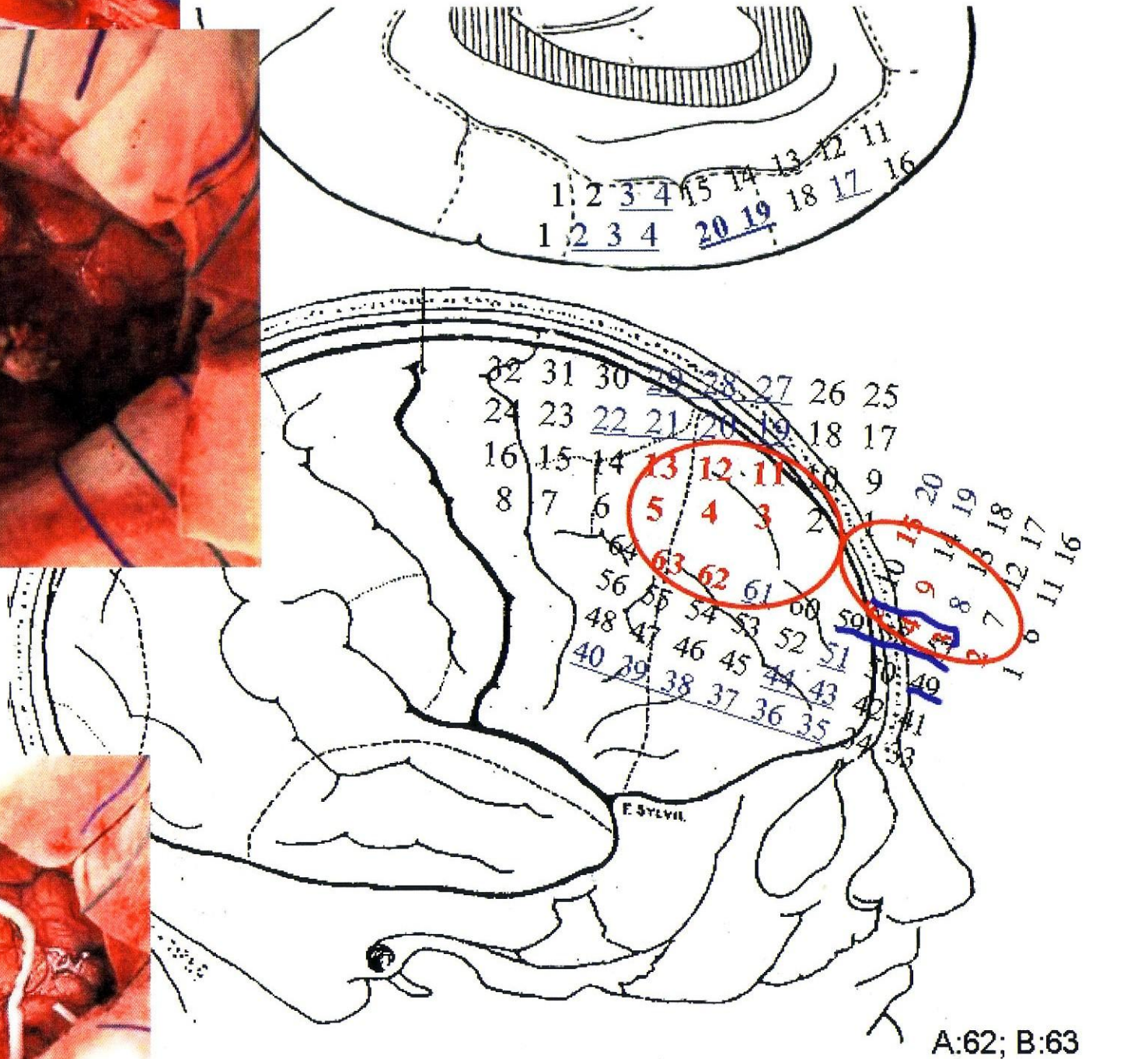






Turner, J 3-14/20-06

Sudden Unexplained Death in Epilepsy: Definition

- Sudden unexplained death in epilepsy (SUDEP) has been defined as “sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause for death” (1).
- Unexpected Vs *Unexplained* : drowning and trauma, sudden

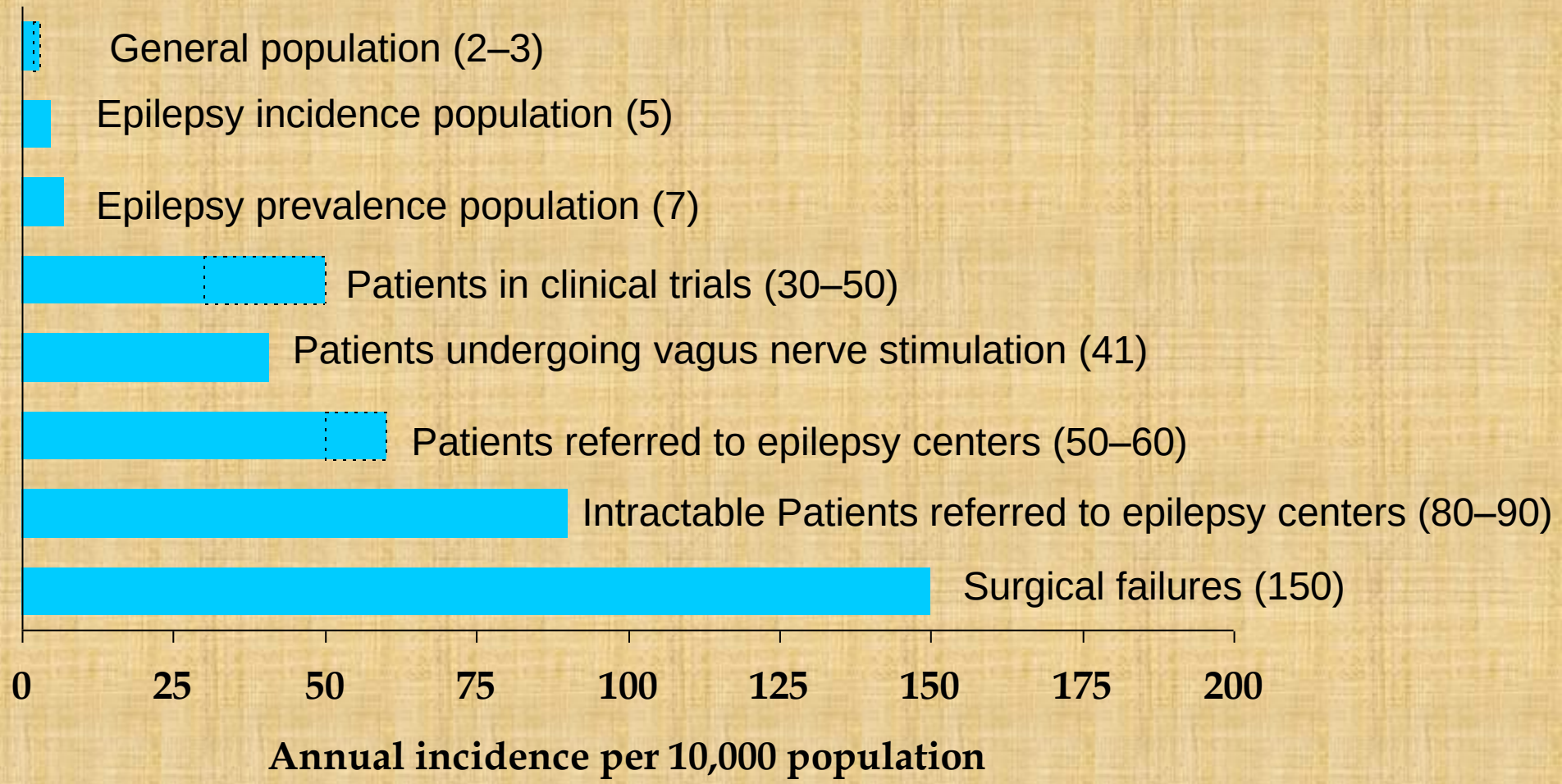
Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. Epilepsia 1997;38(suppl. 11):S6–8.

Sudden Unexplained Death in Epilepsy

- 7-17 % epilepsy pt. died of SUDEP*
- ? 50% refractory epilepsy pt. died of SUDEP
- SUDEP occurs at a rate of 1 in 150 person-years in persons with uncontrolled seizures (Tomson et al., 2005).
- Mechanisms and methods to prevent SUDEP are largely unknown.

** Sudden Unexplained Death in Epilepsy Michael R. Sperling, M.D. Epilepsy Curr. 2001 September; 1(1): 21–23.*

SUDEP incidence



Pathogenesis = Risk Factors + Terminal Events

Close temporal relationship between seizure episodes and SUDEP

- 100 autopsies, 50/50 SUDEP *pt. died in bed and had a seizure.* Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases. Opeskin et al, *Seizure 2003.*
- *Autopsy supported 154 case of SUDEP, risk for SUDEP was 14 times higher if had GTCS within last 3 months.* Case-control study of SUDEP. Langan et al, *Neurology 2005*
- *Multicenter study – but risk of SUDEP was higher only in women.* Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Walczak et al, *Neurology 2001.*

Pathogenesis = Risk Factors + Terminal Events

- *Brain specimens from SUDEP patients had positive stain results for heat shock protein 70 in hippocampal neurons than specimens from control subjects. Note: Heat shock protein 70 is not specific to etiology. No difference for parahippocampal gyrus.* Sudden and unexpected death in epilepsy (SUDEP): evidence of acute neuronal injury using HSP-70 and c-Jun immunohistochemistry. Thom et al. *Neuropath Appl Neurobiol* 2003;

- Other risk factors were: Mental Retardation, Number of AED use.

- Cerebral structure lesion and subtherapeutic AED concentration at last visit were not associated with SUDEP.

Pathogenesis = Risk Factors + Terminal Events

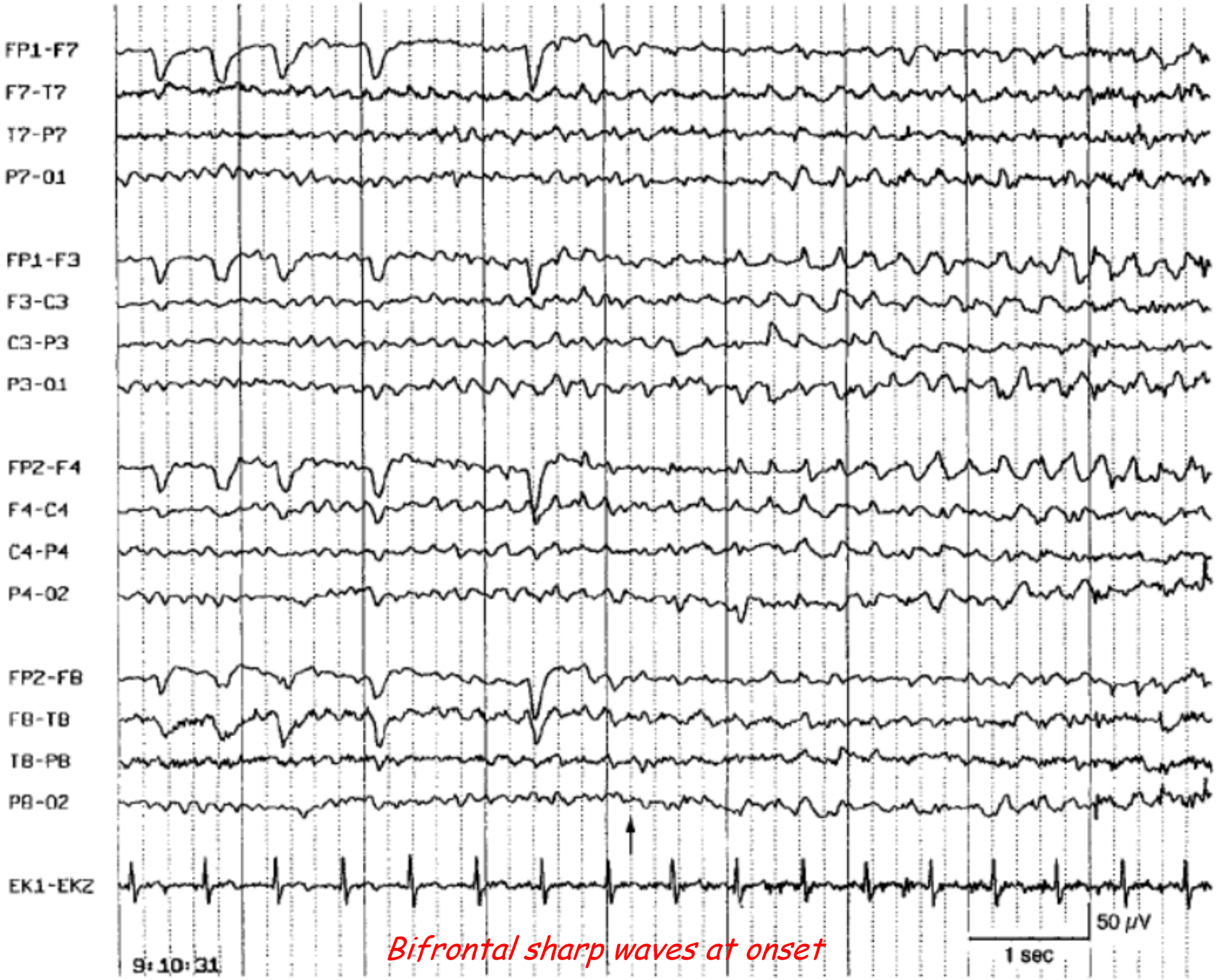
Autonomic dysfunction

- *3 epilepsy pts and 18 control subjects, One had higher baseline HR, hypersympathetic response to valsalva and tilt table.* Ictal bradycardia in partial epileptic seizures: autonomic investigation in three cases and literature review. Tinuper et al. *Brain 2001*

- *Temporal lobectomy reduces the risk of sympathetically mediated tachyarrhythmias and excessive bradycardic counterregulation. There was a reduction of sympathetic cardiovascular modulation and baroreflex sensitivity after surgery.* Hilz et al. Decrease of sympathetic cardiovascular modulation after temporal lobe epilepsy surgery. *Brain* 2002

Pathogenesis = Risk Factors + Terminal Events

- Cardiac arrhythmia and respiratory dysfunction are suspected to be independent primary mechanisms.
- *case report of near SUDEP incident in EMU – 20 yo female – 56 sec long CPS (no secondary generalization) – strong pulse, apnea leading to cardiac arrest.* Postictal central apnea as a cause of SUDEP: evidence from near-SUDEP incident. So EL et al *Epilepsia* 2000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C4-P4
P4-02
FP2-F8
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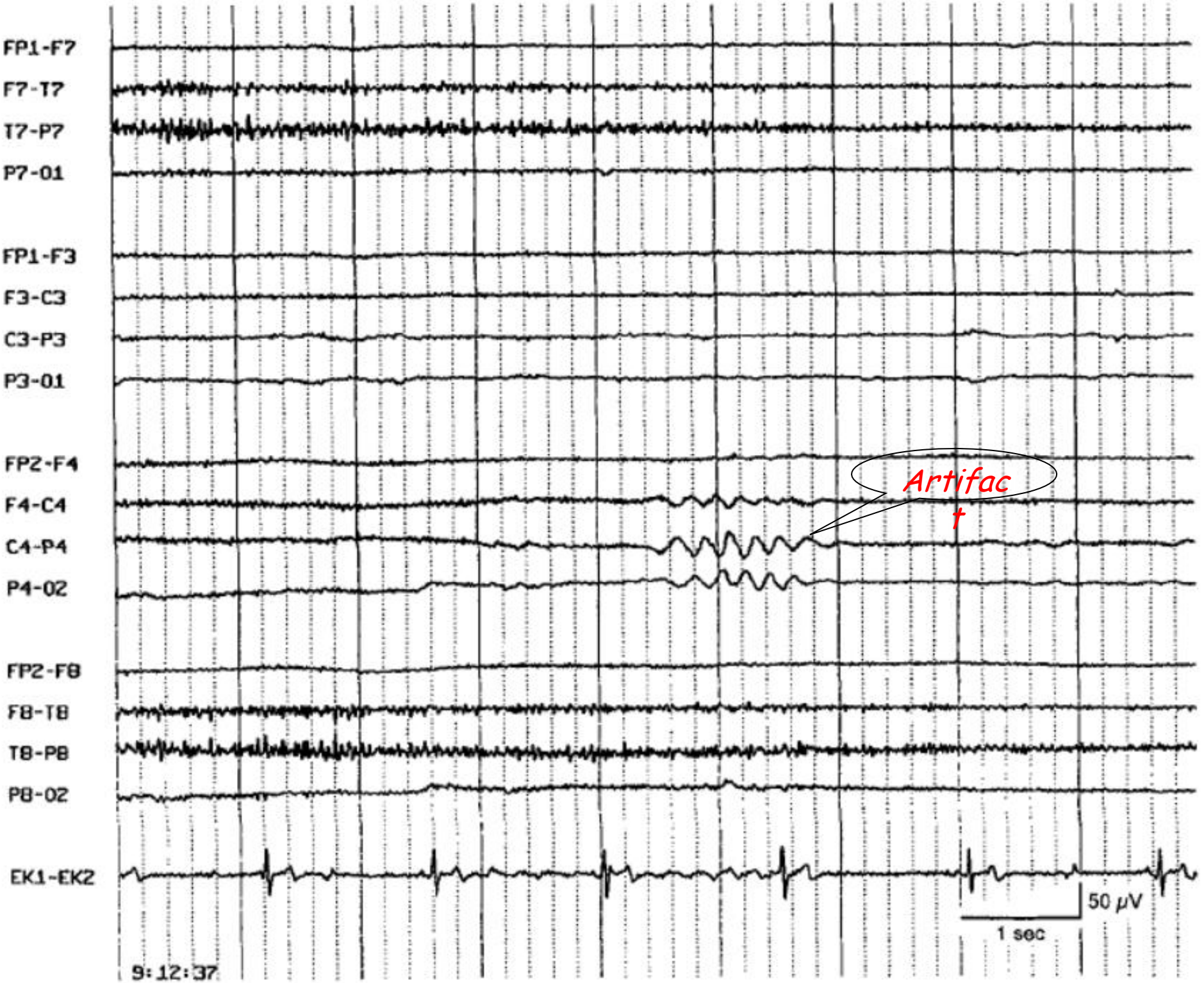
Bifrontal sharp waves at onset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C4-P4
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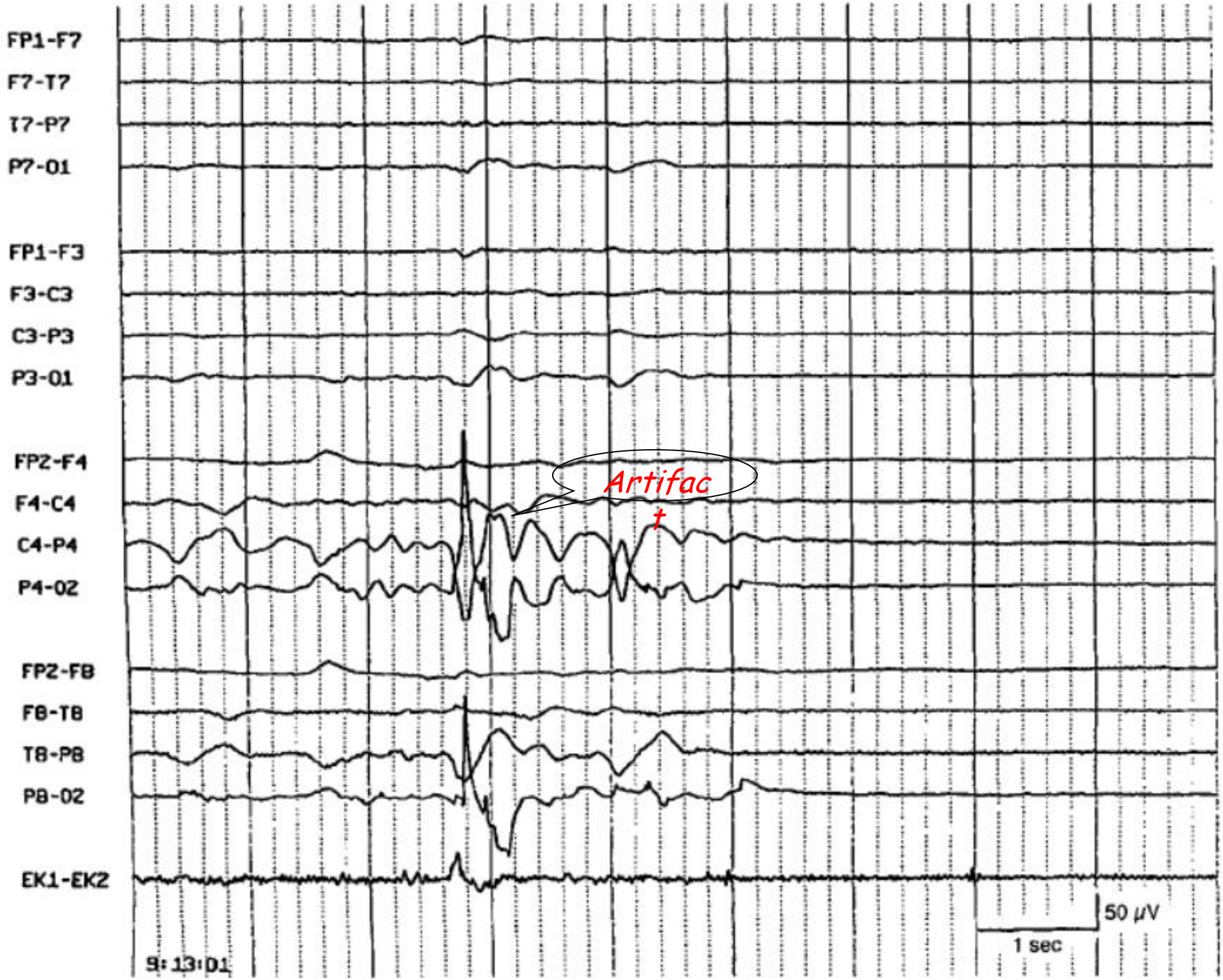
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P4-O2
FP2-F8
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T8-P8
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EK1-EK2
Artifact
50 μV
1 sec
9:13:01

Pathogenesis = Risk Factors + Terminal Events

Central hypoventilation is a cause of SUDEP

- 12/15 witnessed SUDEP events respiratory difficulties were terminal. Sudden unexpected death in epilepsy: a series of witnessed deaths. Langan et al *J Neurol Neurosurg Psychiatry* 2000.

- Johnston et al. The role of hypoventilation in a sheep model of epileptic sudden death. *Ann Neurol* 1995.

- DBA-2J mouse strain, audiogenic seizures. Venit et al. Oxygenation prevents sudden death in seizure-prone mice. *Epilepsia* 2004.

Pathogenesis = Risk Factors + Terminal Events

Seizure related pulmonary edema is a cause of SUDEP

- *Edema more frequent than apnea, edema more commonly seen in near SUDEP.*

- *Case Report: 18 yo with JME otherwise healthy had near SUDEP and SUDEP – hypoxia, acidosis, x-ray showing pulmonary edema.**

* Sudden unexplained death in epilepsy (SUDEP) following previous seizure-related pulmonary edema: case report and review of possible preventative treatment. Swallow et al *Seizure* 2002;11:446–8.

Pathogenesis = Risk Factors + Terminal Events

Seizure related cardiac arrythmia is a cause of SUDEP

- Ictal tachycardia more frequent than bradycardia, asystole. (CPS, GTCS, sub clinical seizures)
- Pattern: Initial steep acceleration at onset of CPS, followed by marked variation during seizure and postictally. Patterns stays same in individual patient.*
- Ictal tachycardia did not favor any hemisphere.**

* Smith PEM, Howell SJL, Owen, Blumhardt LD. Profiles of instant heart rate during partial seizures. *Electr Clin Neurophys* 1989;72:207–217.
** Keilson MJ, Hauser WA, Magrill JP. Electrocardiographic changes during electrographic seizures. *Arch Neurol* 1989;46: 1169–1170.

Cardiac Effects of Seizure

- Seizures associated with ictal asystole and bradycardia are much less frequent* (5/1244 pts who undervent V.EEG), most of them are temporal/frontal in onset and related to apnea**.

- seizure-induced asystole and syncope, placement of a cardiac pacemaker may aid in preventing trauma that is due to falls.***

* Rocamora et al. Cardiac asystole in epilepsy: clinical and neurophysiologic features. *Epilepsia* 2003.
** Nashef et al. Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy. *JNeurolNeurosurg Psychiatry.* 1996.
*** Strzelczyk et al. Ictal asystole in temporal lobe epilepsy before and after pacemaker implantation. *Epileptic Disord* 2008

Cardiac Effects of Seizure

- Electrical stimulation of the human insular cortex suggests that the right hemisphere may have greater sympathetic influence, while the left hemisphere may be associated with greater parasympathetic control*
- patients with refractory epilepsy appear to have a higher risk for seizure-related cardiac rhythm and conduction abnormalities (39%)**
- GTCS, prolonged seizures are risk factors

* Cardiovascular effects of human insular cortex stimulation. Oppenheimer et al. *Neurology* 1992.
** EKG abnormalities during partial seizures in refractory epilepsy. Nei et al. *Epilepsia* 2000;41:542–548.

Cardiac Effects of Seizure

- 40% of patients with refractory epilepsy showed ST segment depression during seizure – cardiac ischemia might occure during seizure.*
- Cardiac troponin levels were not elevated after complex partial or generalized tonic–clonic seizures** – significant ischemia is unlikely to occur. (except patients with CAD***)
- Seizure related rate-rhythm disturbance last longer than seizure and can be cumulative for cluster seizure

* Evidence of cardiac ischemia during seizures in drug refractory epilepsy patients. Tigaran et al. *Neurology* 2003.
** Cardiac troponin levels following monitored epileptic seizures. Woodruff et al. *Neurology* 2003.
*** Myocardial infarction following brief convulsive seizures. Chin et al. *Neurology* 2004

Cardiac Effects of Seizure

- 7/19 patients of refractory epilepsy, showed ictal bradycardia with implantable loop recorder in a prospective study of mean 18 months follow up. 4/7 got pacemaker placement.*
- Patients with ictal asystole identified via video-EEG monitoring, who were implanted with a pacemaker, did not have recurrent asystole or bradycardia sufficient to trigger the pacemaker during a mean follow-up of 5 years.**
- Interictal cardiac abnormalities seem to be same as general population except early morning bradycardia (note SUDEP risk is highest in early morning)

* Cardiac arrhythmias in focal epilepsy: a prospective long-term study. Rugg-Gunn et al *Lancet* 2004.

** Ictal Asystole: a benign condition? Schuele et al. *Epilepsia* 2008.

Cardiac Autonomic Data in Epilepsy

- Cardiovascular autonomic dysregulation, as demonstrated by HR and BP changes during valsalva, worse in refractory epilepsy.
- Epilepsy patients have decreased HR variability, which is associated with arrythmia.
- Temporal lobe epilepsy surgery stabilizes the cardiovascular autonomic control by reducing sympathetic cardiovascular modulation
- Chronic vagal nerve stimulation does not appear to significantly affect overall autonomic tone
- Carbamazepine withdrawal can increase cardiac sympathetic activity during sleep

CARDIAC EFFECTS OF SEIZURES

Maromi Nei, MD

Jefferson Comprehensive Epilepsy Center, Philadelphia, Pennsylvania

Seizures frequently affect the heart rate and rhythm. In most cases, seizure-related cardiac changes are transient and do not appear to cause clinically significant abnormalities for the patient. Great interest in this area of research has been generated because of a possible connection with sudden unexpected death in epilepsy (SUDEP). While there are clear, but rare complications from seizure-related cardiac arrhythmias, such as ictal asystole that causes syncope, the overall risk of seizures on cardiac status and any potential connection between seizures and SUDEP still remain uncertain.

Seizure-Related Cardiac Abnormalities

Considerable interest in seizure-related cardiac abnormalities has developed, particularly since the recognition that the majority of patients with witnessed sudden unexpected death in epilepsy (SUDEP) experience a preceding seizure, suggesting a causal relationship between the seizure and death (1). In adults progression in those individuals. Keilson et al. reported that 93% of 106 lateralized and generalized seizures (in 45 patients who underwent 24-hour ambulatory EEG–EKG monitoring), of at least a 30-second duration, were associated with an ictal tachycardia of greater than 100 beats per minute (6). The investigators found that the ictal tachycardia did not favor one hemisphere over the other.

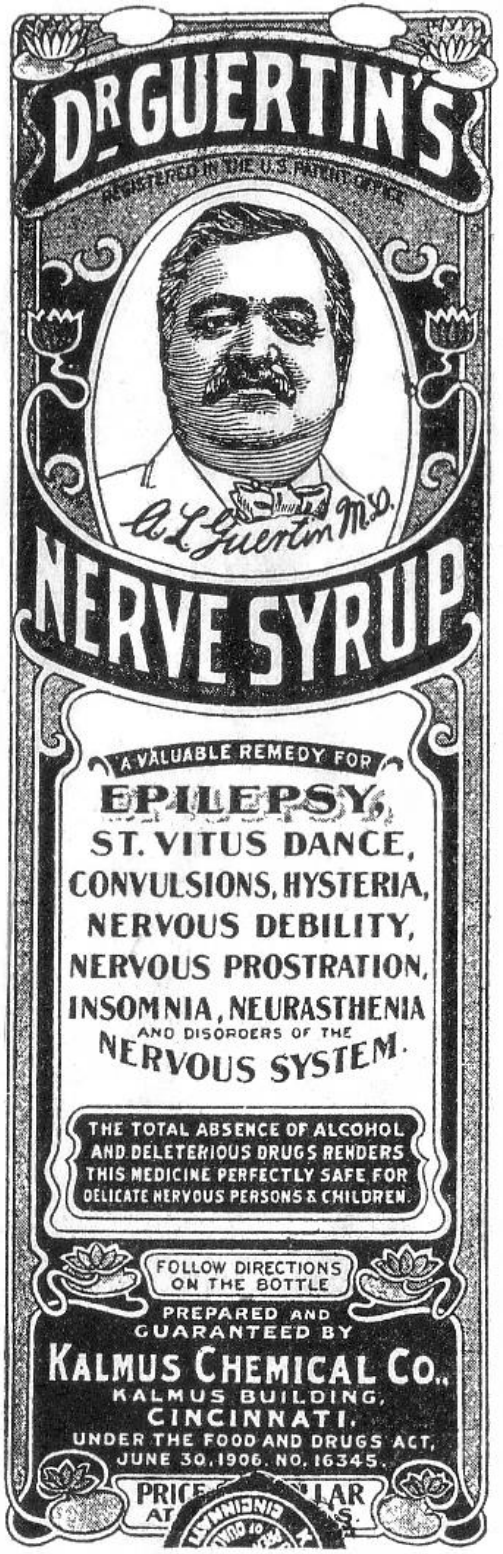
Seizure-related asystole and bradycardia are much less common. In one retrospective analysis, only 5 out of 1244 patients who underwent video-EEG monitoring had ictal asystole (7). Schuele et al. also observed that ictal asystole is rare, seen in only 0.27% of 6825 patients who underwent video-EEG monitoring (8). Tinuper et al. reported 3 cases of ictal bradycardia and reviewed 60 other cases from the literature and found that, most commonly, temporal or frontal lobe seizures are associated with ictal bradycardia and asystole (9). Another study concluded that ictal bradycardia occurred only in the setting of respiratory changes, particularly apnea, suggesting that cardiorespiratory reflexes are important in the generation of ictal bradycardia (10). In contrast, Tinuper et al. found that ictal bradycardia could occur without significant changes in respiration (9). Also notable in this study is the concomitant finding of decreased blood pressure, which may occur before the onset of bradycardia and persist during the seizure. It is important to recognize that seizures may also rarely cause asystole, resulting in a secondary

SUDEP in children

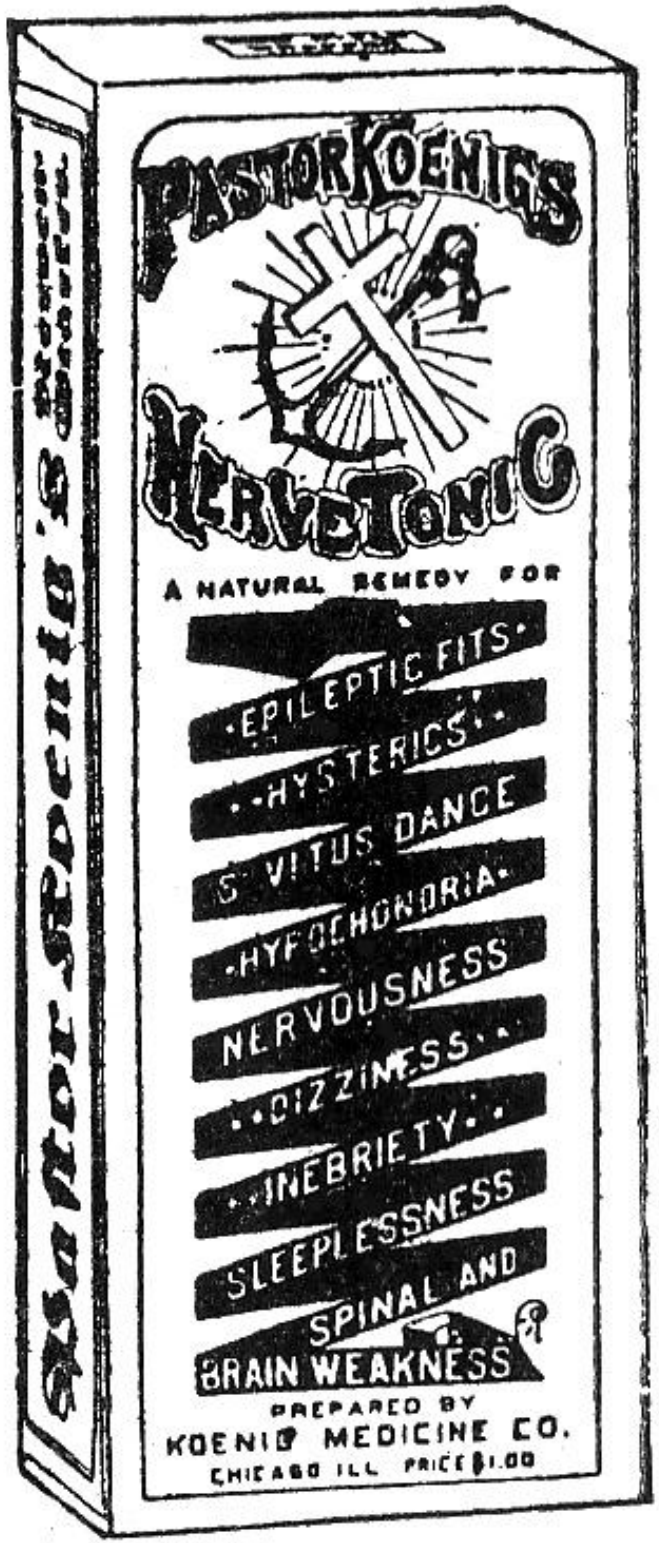
Low sample size to say anything. No information on general population nor control group. Descriptive data suggest kids have similar risk factors as adults. Incidence 1-2.7 deaths per 10,000 person-years (age <14)

- Retrospective case of SUDEP in Canada. Sudden unexplained death in children with epilepsy. Donner et al. *Neurology* 2001

- 5 Cases of SUDEP at EMU in Huston, Texas. Pediatric experience with sudden unexplained death in epilepsy at a comprehensive epilepsy center. McGregor et al. *Epilepsia* 2004



Is SUDEP preventable?



Lessons from SIDS

- Multiple risk factors have been observed, including male gender, prematurity, smoking during pregnancy, winter season, insufficient prenatal care, high parity, prone sleeping position, and certain sleeping environs.*

- American Academy of Pediatrics, initiated the “Back to Sleep” campaign, and the incidence of SIDS has decreased by nearly 50%.

- modification of the crib environs (e.g., removal of soft bedding materials and stuffed toys) to reduce further the risk of suffocation

* Daley KC. Update on sudden infant death syndrome. *Curr Opin Pediatr* 2004;16:227–32.

SUDEP prevention strategies

- Prevention starts with identification of risk factors and terminal events.
- Eighty percent of witnessed SUDEP events were associated with seizures.*
- "heightened supervision" supervision throughout the night was associated independently with reduced risk of SUDEP (odds ratio of 0.4)** - *supervision was defined as having someone present in the bedroom who was at least 10 years old and had at least average intelligence.*

* *Nashef L. Sudden unexpected death in epilepsy: terminology and definitions. Epilepsia 1997;38(suppl. 11):S6–8.*
** Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. *Neurology 2005;64:1131–3.*

SUDEP prevention strategies - position

- Circumstantial evidence: lower rates of SUDEP in children. *(are kids more supervised?)*

- Modification of sleeping position may also prevent SUDEP. * *- case series of 42 SUDEP cases, 71% of patients died in the prone position.*

* Blum AS, Ives JR, Goldberger AL, et al. Oxygen desaturations triggered by partial seizures: implications for cardiopulmonary instability in epilepsy. Epilepsia 2000;41:536–41.

SUDEP prevention strategies - apnea

- Apnea occurred in 45–60% of partial seizures and 100% of generalized convulsive seizures.** - *Apnea lasted up to 70 sec and oxyhemoglobin desaturation as low as 55%*
- Audiogenic seizure mouse model of SUDEP showed that oxygenation reliably prevented death** *- oxygen rich environment – ventilation is problem not oxygenation*
- Evidence of night time supervision and monitors (e.g. Devices for monitoring heart rate, oxygen saturation, and body movements) are *not strong enough to be recommended* by AES***

* Kloster R, Engelskjon T. Sudden unexpected death in epilepsy (SUDEP): a clinical perspective and a search for risk factors. J Neurol Neurosurg Psychiatr 1999;67:439–44.

** Venit EL, Shepard BD, Seyfried TN. Oxygenation prevents sudden death in seizure-prone mice. Epilepsia 2004;45:993

*** Report of the American Epilepsy Society and the Epilepsy Foundation Joint Task Force on Sudden Unexplained Death in Epilepsy

SUDEP prevention strategies – epilepsy surgery

- Patients with epilepsy surgery had lower SUDEP risks than patients who did not undergo epilepsy surgery.* - ?
  No reliable denominator, poor candidates for surgery – (insular, opercular, orbitofrontal locations), poor access.
- The high risk of SUDEP for patients with drug-resistant epilepsy is reduced with *successful* epilepsy surgery.** -
  4 year postoperative follow up – 6/194 SUDEP in unsuccessful surgery Vs 0/199 successful surgery candidates.

*Ryvlin P, Kahane P. Does epilepsy surgery lower the mortality of drug-resistant epilepsy? Epilepsy Res 2003;56:105–20.

** Sperling MR, Feldman H, Kinman J, et al. Seizure control and mortality in epilepsy. Ann Neurol 1999;46:45–50.

SUDEP prevention strategies – pharmacological options for “pill pushers”

- Early use of an α1-adrenergic blocking agents to prevent pulmonary edema.* - block massive catecholamine surge.
- Beta blockers – anti arrythmic but acutely negative ionotropic effect
- Combined – labetalol, carvedilol – low potency alpha blockade.
- How about combined doxazosin + beta blocer? – need to use long term, no data, hypotension problem

* Swallow RA, Hillier CE, Smith PE. Sudden unexplained death in epilepsy (SUDEP) following previous seizure-related pulmonary oedema: case report and review of possible preventative treatment. Seizure 2002;11:446–8.

SUDEP prevention strategies – pharmacological options for "pill pushers"

- *Methods:* DBA/2 mice (75%) exhibited AGS and RA, and ~99% of animals could be resuscitated. The mice exhibiting RA were given a selective serotonin reuptake inhibitor, fluoxetine, 24 h after the initial AGS, and RA susceptibility was evaluated 30 min later. Ten percent of DBA/2 mice exhibited tonic hindlimb extension (TE) without RA, and a serotonin antagonist (cyproheptadine) was administered to these mice.
- *Results:* Fluoxetine (15–25 mg/kg, i.p.) significantly reduced the incidence of RA in DBA/2 mice after AGSs, and this effect was reversible by 72 h. Only the 25-mg/kg dose reduced AGS severity. In mice exhibiting TE without RA, the incidence of RA was significantly increased 30 min after cyproheptadine (1–2 mg/kg i.p.). Most of these mice exhibited AGSs without RA again by 72 h.

* Faingold CL, Raisinghani M, Srinivasan T, et al. A role of serotonin in modulating respiratory arrest in a model of sudden death in epilepsy (SUDEP) in DBA/2 mice [abstract]. Epilepsia 2004;45(suppl. 7);207–8

TABLE 1. *Potential strategies for preventing SUDEP in high-risk patients*

Risk factor or terminal event	Potential strategy
Risk Factor	
Uncontrolled epilepsy	Optimize AED treatment, consider epilepsy surgery
Generalized tonic–clonic seizures	Optimize AED treatment, consider epilepsy surgery
Young adults	Provide prompt medical or surgical treatment
Childhood epilepsy onset	Provide prompt medical or surgical treatment
Low serum AED concentrations	Improve compliance and monitoring
Polytherapy	Reduce AED
Frequent AED adjustments	Stabilize regimen
Substance abuse	Recommend abstention
Mental retardation	Recommend supervision
Unsupervised setting	Recommend supervision
Terminal event	
Seizure occurrence	Recommend supervision; seizure alarm
Pulmonary edema	Recommend recognition and treatment
Apnea or hypoxia	Recommend pulse oximetry monitor; stimulation; and oxygenation
Asystole	Recommend cardiac monitor; pacemaker
Suffocation	Reposition patient; modify environment

Ethical and Legal aspect of SUDEP

- How much discussion we should do about SUDEP?
- More complex measures such as direct supervision and cardiorespiratory monitoring are practicable only with high-risk patients.
- What is our legal obligation about discussing preventive strategies when there is no proof that they work?
- American Epilpesy Society and Epilepsy Foundation - answer

Epilepsia, 50(4):917–922, 2009
doi: 10.1111/j.1528-1167.2008.01906.x

SPECIAL REPORT

Report of the American Epilepsy Society and the Epilepsy Foundation Joint Task Force on Sudden Unexplained Death in Epilepsy

*Elson L. So, †Jacquelyn Bainbridge, ‡Jeffrey R. Buchhalter, §Jeanne Donalty, ¶Elizabeth J. Donner, #Alexandra Finucane, **Nina M. Graves, ††Lawrence J. Hirsch, ‡‡Georgia D. Montouris, §§Nancy R. Temkin, ¶¶Samuel Wiebe, and ##Tess L. Sierzant

*The Department of Neurology, Mayo Clinic, Rochester, Minnesota, U.S.A.; †School of Pharmacy, University of Colorado Health Sciences Center, Denver, Colorado, U.S.A.; ‡Division of Neurology, Phoenix Children's Hospital, Phoenix, Arizona, U.S.A.; §Citizens United for Research in Epilepsy, Chicago, Illinois, U.S.A.; ¶Division of Neurology, The Hospital for Sick Children, Toronto, Ontario, Canada; #The Epilepsy Foundation, Landover, Maryland, U.S.A.; **Medtronic Incorporated, Minneapolis, Minnesota, U.S.A.; ††Department of Neurology, Columbia University, New York, New York, U.S.A.; ‡‡Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, U.S.A.; §§Department of Neurosurgery, University of Washington, Seattle, Washington, U.S.A.; ¶¶Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada; and ##Department of Neurology, St. Joseph's Hospital, HealthEast Care System, St. Paul, Minnesota, U.S.A.

When, What and How SUDEP Should be Discussed?

- Should be SUDEP discussed? :Yes and No
- Yes: The ethical principle of patient autonomy in health care entails the patient's right to know about his or her own medical condition and prognosis.*
- No: In some situations, the physician may have to exercise therapeutic privilege, which is defined as a "unique situation, within medical care, in which it is deemed to be in the patient's best interests for the doctor to withhold information" **

* Black A. (2005) SUDEP: whether to tell and when? *Med Law* **24**:41–49

** Beran RG, Weber S, Sungaran R, Venn N, Hung A. (2004) Review of the legal obligations of the doctor to discuss sudden unexplained death in epilepsy (SUDEP): a cohort controlled comparative cross-matched study in an outpatient epilepsy clinic. *Seizure* **13**:523–528

When, What and How SUDEP Should be Discussed?

- Benefits:
  - Encourage compliance with medical therapy
  - Consideration of epilepsy surgery
  - Reassuring to patients who are at very low risk
  - consistent with the need to accept that some persons with epilepsy have increased risks of morbidity and death*
  - But diminish emphasis on the recommendation that most patients with epilepsy live a normal life

* Berg AT, Shinnar S, Testa FM, Levy SR, Smith SN, Beckerman B. (2004) Mortality in childhood-onset epilepsy. *Arch Pediatr Adolesc Med* **158**:1147–1152

When, What and How SUDEP Should be Discussed?

- When:
  - Only after the diagnosis of epilepsy is made
  - patient's preparedness to receive the information
  - if asked about the risk, adverse effects and prognosis of epilepsy
  - Even if not asked but presence of risk factors
  - priority for patients who are noncompliant and candidates for epilepsy surgery

When, What and How SUDEP Should be Discussed?

- What:
  - Individualizing information according to each patient's risk and to the background of the patients and their families and caregivers in terms of culture, education, emotional state, and support systems.
  - Ongoing research efforts should be mentioned.
- How:
  - as part of global epilepsy care and prognosis
  - Readiness to learn , Preferred learning style, Expectations as a learner, Suitable venue for education and counseling.

Recommended Research Directions in SUDEP

- Although confirming the SUDEP incidence rate in the general population is important, research priorities should be given to identification of causative mechanisms and prevention.
- Good animal models, but no long-term animal studies
- Prospective, multicenter studies are required to enroll a sufficient number of patients with refractory epilepsy
- drug trial databases and national or large community-based databases
- Low autopsy rate of patients with suspected SUDEP and the incompleteness of autopsy information.

Areas for possible investigations

- Age-group–specific incidence rates and the change in risk levels over time;
- Risk factors among high-risk patients with medically refractory epilepsy;
- Role of genetics;
- Role of structural and functional cardiac abnormalities;
- Role of autonomic dysfunction;
- Morphologic, molecular, and biochemical studies of the heart, lungs, and brain of affected patients;
- Role of respiratory mechanisms;
- Role of sleep mechanisms;

Areas for possible investigations

- Role of antiepileptic and nonantiepileptic drug use;
- Role of serotonin and other neurotransmitters;
- Medical and psychologic comorbid conditions;
- Premorbid circumstances of SUDEP (e.g., living situation, sleep position, time of SUDEP event);
- effect of epilepsy surgery in reducing SUDEP risk;
- Role of nocturnal supervision and device-based seizure and apnea detection in preventing SUDEP; and
- Role of long-term implantable devices for monitoring cardiovascular, respiratory, and neurophysiologic functions

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Demystifying Sudden Unexplained Death in Epilepsy—Are We Close?

Elson L. So, M.D.

Section of Electroencephalography, Mayo Clinic, Rochester, Minnesota, U.S.A.

Summary: The cause of sudden unexplained death in epilepsy (SUDEP) is still elusive, despite multiple studies over the past few decades. This review assesses recent progress in the understanding of risk factors (situations that predispose patients to SUDEP) and terminal events (events immediately associated with death) that potentially contribute to SUDEP. Recent studies strongly support a close relationship between seizure episodes (especially generalized convulsions) and SUDEP. The lethal nature of some seizure-induced cardiorespiratory events has been documented fortuitously in rare patient cases, and these events have been consistently reproduced in SUDEP animal models. Nonetheless, SUDEP likely does not have a single cause, and risk factors identified thus far may vary in importance among persons with epilepsy. In the absence of a complete understanding of the pathophysiologic mechanisms underlying SUDEP, potential preventive measures for high-risk patients are offered for consideration. Seizure control is most important for reducing SUDEP risk. Circumstantial data suggest that heightened supervision of patients with frequent seizures may be beneficial. Relatively simple interventions may be sufficient to interrupt potentially lethal events such as periictal suffocation or apnea. However, application of these preventive measures to all epilepsy patients has not been proven to substantially reduce the rate of SUDEP. Additional clinical and laboratory investigations are needed to identify and confirm pathogenic factors and preventive measures. **Key Words:** Epilepsy—Seizure—Sudden death.