Refractory Status Epilepticus

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Disclosures

- Research support from NIAID, NINDS, AHA, Zoll, Edge
- Consultant for USAMRICD (nerve agent protection)

- Many of the treatments discussed are not approved by the FDA for SE.

Guidelines for the Evaluation and Management of Status Epilepticus

Gretchen M. Brophy · Rodney Bell · Jan Claassen · Brian Alldredge · Thomas P. Bleck · Tracy Glauser · Suzette M. LaRoche · James J. Riviello Jr. · Lori Shutter · Michael R. Sperling · David M. Treiman · Paul M. Vespa · Neurocritical Care Society Status Epilepticus Guideline Writing Committee

Abstract Status epilepticus (SE) treatment strategies vary substantially from one institution to another due to the lack of data to support one treatment over another. To provide guidance for the acute treatment of SE in critically ill patients, the Neurocritical Care Society organized a writing committee to evaluate the literature and develop an evidence-based and expert consensus practice guideline. Literature searches were conducted using PubMed and studies meeting the criteria established by the writing committee were evaluated. Recommendations were developed based on the literature using standardized assessment methods from the American Heart Association and Grading of Recommendations Assessment, Development, and Evaluation systems, as well as expert opinion when sufficient data were lacking.

Keywords Status epilepticus · Seizure · Guideline · EEG · Antiepileptic treatment

Introduction

Status epilepticus (SE) requires emergent, targeted treatment to reduce patient morbidity and mortality. Controversies about how and when to treat SE have been described in the literature [1–3]. The Neurocritical Care Society Status Epilepticus Guideline Writing Committee was established in 2008 to develop evidence-based expert consensus guidelines for diagnosing and managing SE. Co-chairs were selected by the Neurocritical Care Society, with ten additional neurointensivists and epileptologists from across the United States included on the committee. After the committee prepared an initial set of guidelines

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Refractory SE (RSE)

- Patients who do not respond to standard treatment regimens for status epilepticus are considered to be in RSE [32]. For the purposes of these guidelines, patients who continue to experience either clinical or electrographic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable antiepileptic drug (AED) will be considered refractory.
- Controversies exist regarding the definition of RSE, including:
    - The number of AEDs patients need to have failed. Most experts agree that patients should be considered in RSE after failure of adequately dosed initial benzodiazepine and one AED.
    - Duration of SE after initiation of treatment. Most experts no longer consider duration to be a criterion for classification of RSE.

The real meaning of the VA cooperative trial is that the speed of first treatment is much more important than the drug selected.

DVA cooperative study of SE: treatment success

response rates (%)	Overt SE	Subtle SE
LRZ	64.9	17.9
PB	58.2	24.2
DZ + PHT	55.8	8.3
PHT alone	43.6	7.7
means	55.5	14.9

DVA cooperative study of SE:
treatment success by *initial* EEG pattern

pattern	**percent successfully treated**
discrete seizures	75
waxing and waning	30
continuous seizure pattern	24
brief suppressions	8
periodic discharges	7

Only the first conventional anticonvulsant has a reasonable chance of working in SE.

VACSP 265: lorazepam arm (overt SE)

drug	***response rate (%)***
lorazepam	64.9
phenytoin	7.2
phenobarbital	2.1
other drugs	17.5

VACSP 265: phenobarbital arm (overt SE)

drug	***response rate (%)***
phenobarbital	58.2
phenytoin	3.3
lorazepam	2.2
other drugs	25.3

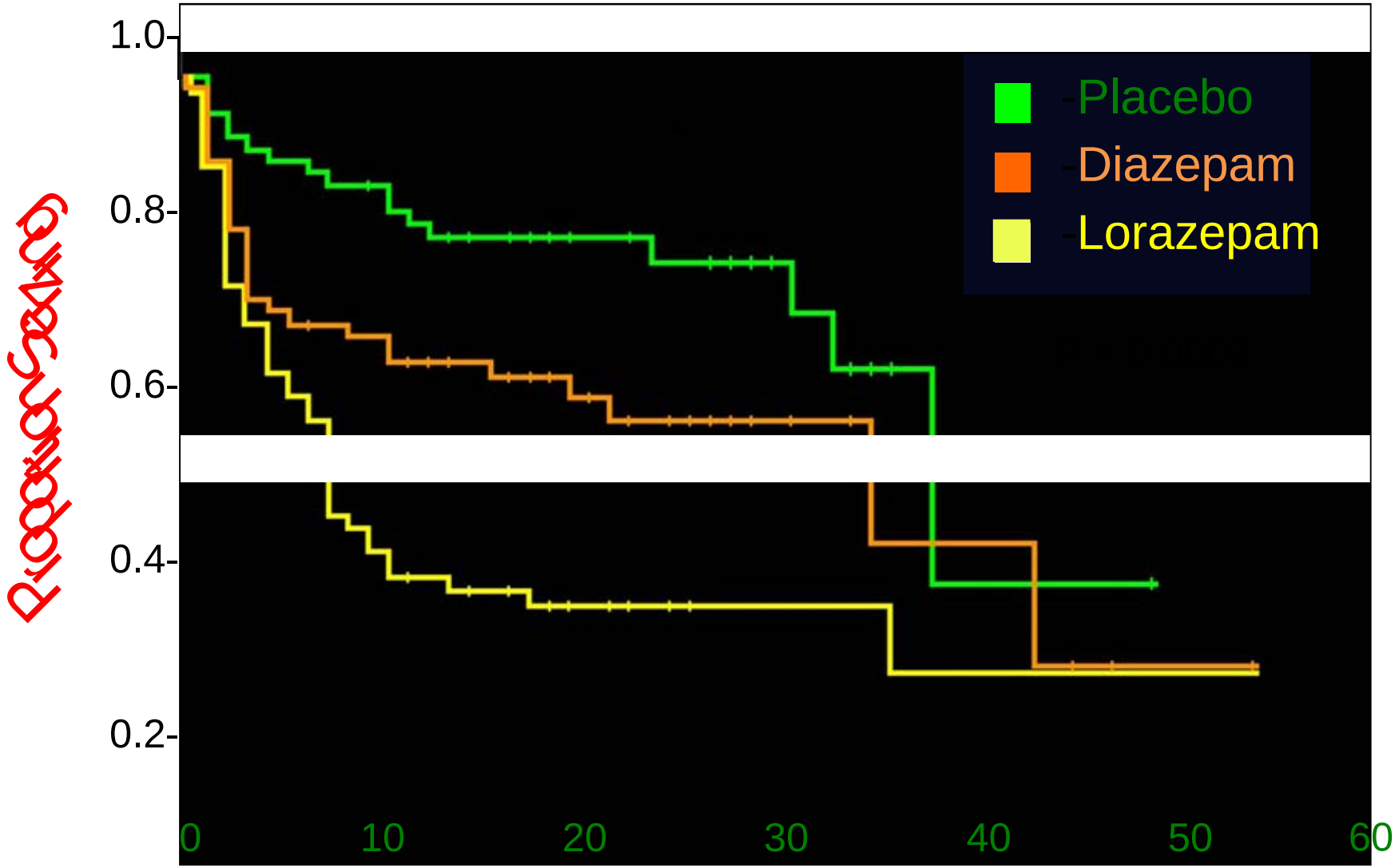
VACSP 265: diazepam/phenytoin arm (overt SE)

drug	***response rate (%)***
diazepam/phenytoin	55.8
lorazepam	3.2
phenobarbital	2.1
other drugs	23.2

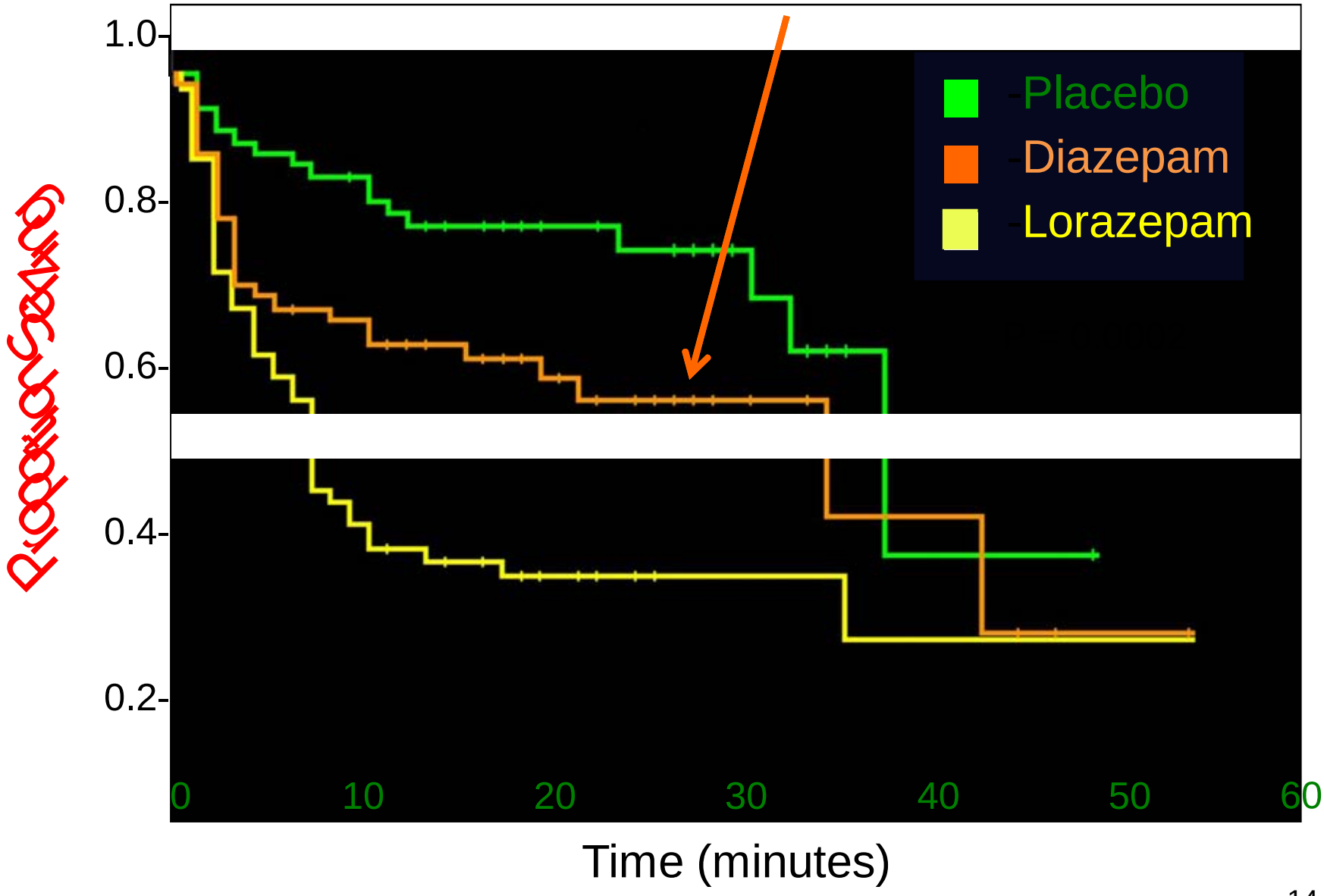
VACSP 265: phenytoin arm (overt SE)

drug	***response rate (%)***
phenytoin	43.5
lorazepam	13.9
phenobarbital	3.0
other drugs	26.7

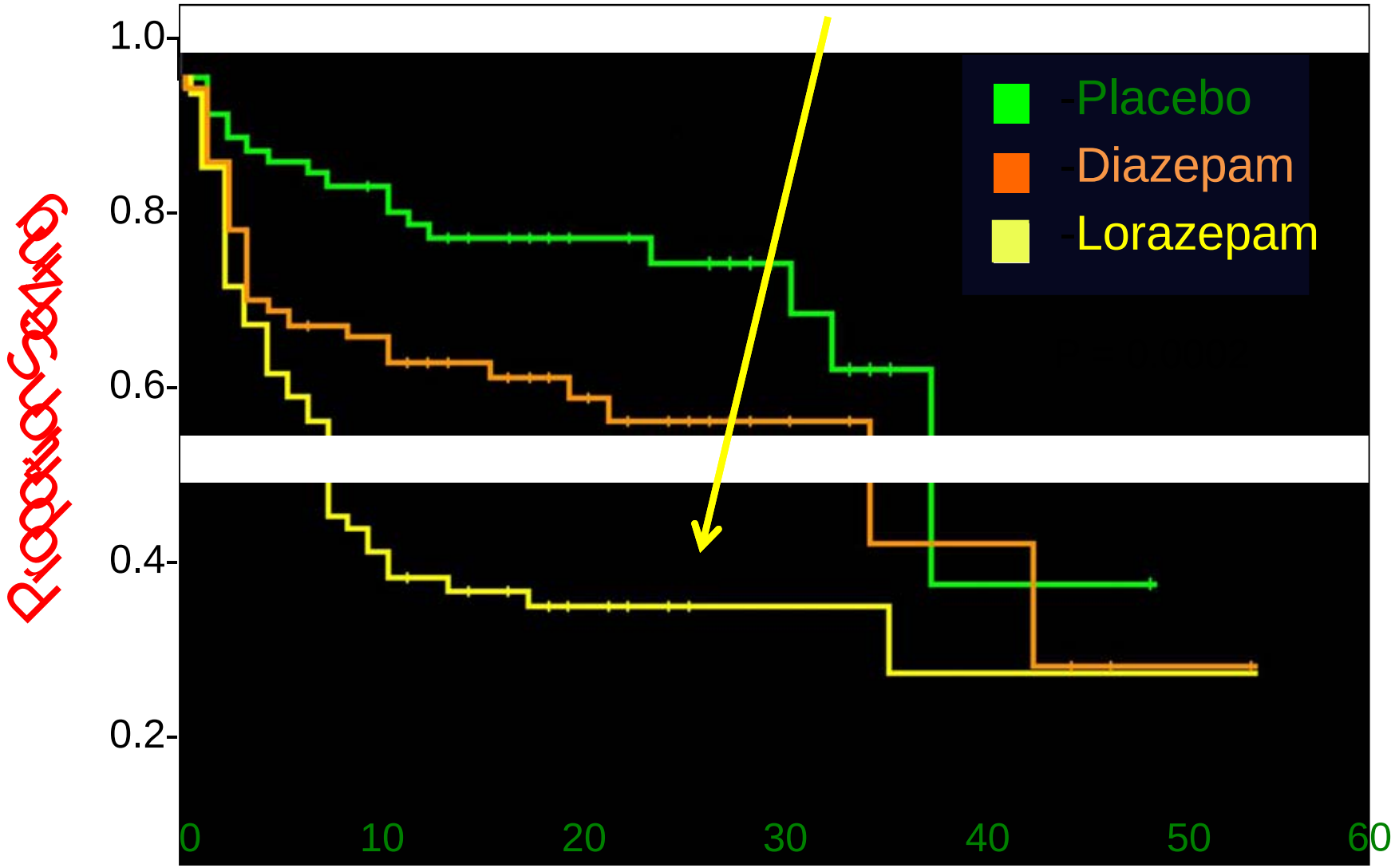
Time to end of status

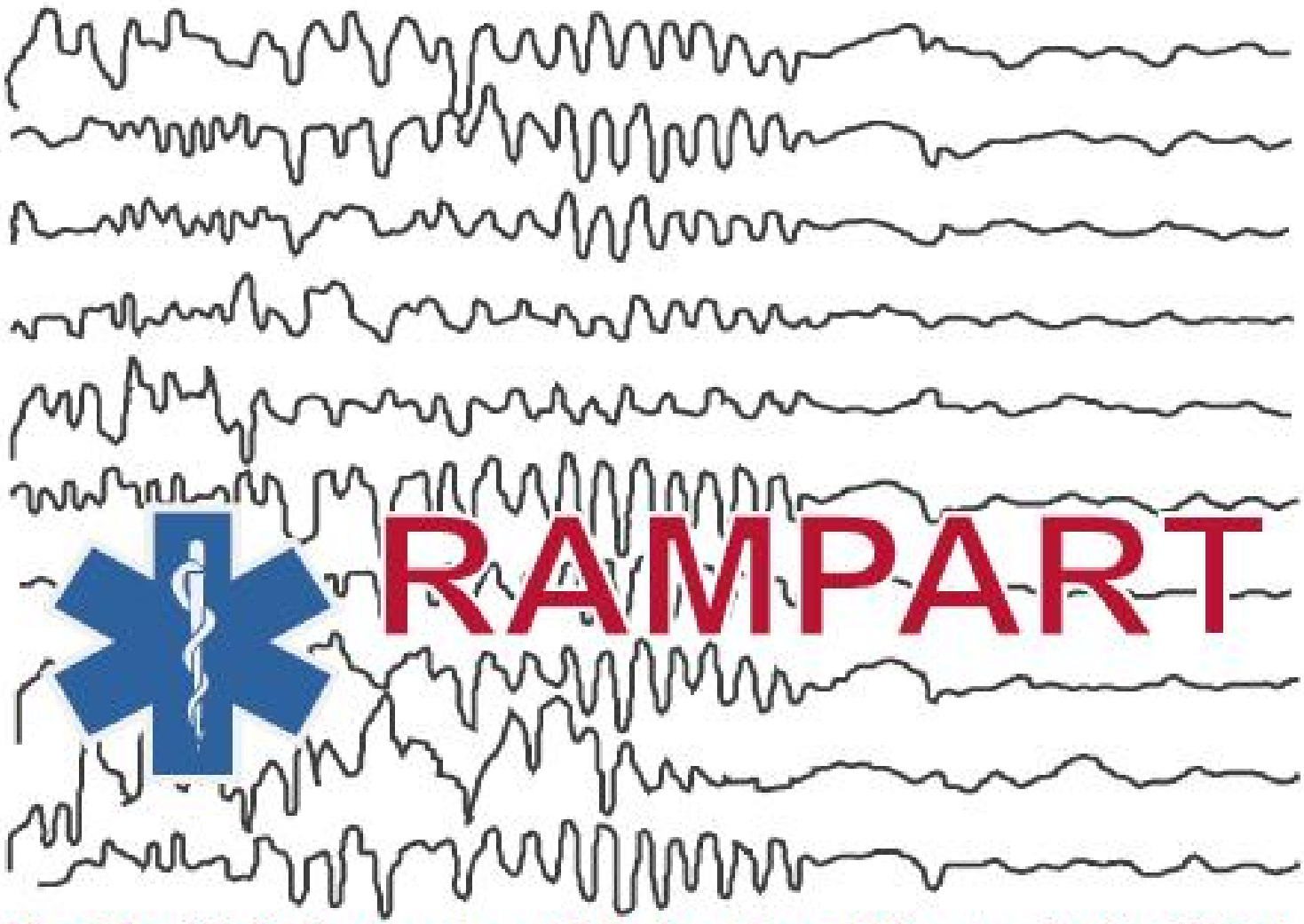


Proportion refractory to diazepam



Proportion refractory to lorazepam




RAMPART
The Rapid Anticonvulsant Medications Prior to Arrival Trial

Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., Arthur Pancioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators*

ABSTRACT

BACKGROUND

Early termination of prolonged seizures with intravenous administration of benzodiazepines improves outcomes. For faster and more reliable administration, paramedics increasingly use an intramuscular route.

METHODS

This double-blind, randomized, noninferiority trial compared the efficacy of intramuscular midazolam with that of intravenous lorazepam for children and adults in status epilepticus treated by paramedics. Subjects whose convulsions had persisted for more than 5 minutes and who were still convulsing after paramedics arrived were given the study medication by either intramuscular autoinjector or intravenous infusion. The primary outcome was absence of seizures at the time of arrival in the emergency department without the need for rescue therapy. Secondary outcomes included endotracheal intubation, recurrent seizures, and timing of treatment relative to the cessation of convulsive seizures. This trial tested the hypothesis that intramuscular midazolam was noninferior to intravenous lorazepam by a margin of 10 percentage points.

RESULTS

At the time of arrival in the emergency department, seizures were absent without rescue therapy in 329 of 448 subjects (73.4%) in the intramuscular-midazolam group and in 282 of 445 (63.4%) in the intravenous-lorazepam group (absolute difference, 10 percentage points; 95% confidence interval, 4.0 to 16.1; P<0.001 for both noninferiority and superiority). The two treatment groups were similar with respect to need for endotracheal intubation (14.1% of subjects with intramuscular midazolam and 14.4% with intravenous lorazepam) and recurrence of seizures (11.4% and 10.6%, respectively). Among subjects whose seizures ceased before arrival in the emergency department, the median times to active treatment were 1.2 minutes in the intramuscular-midazolam group and 4.8 minutes in the intravenous-lorazepam group, with corresponding median times from active treatment to cessation of convulsions of 3.3 minutes and 1.6 minutes. Adverse-event rates were similar in the two groups.

CONCLUSIONS

For subjects in status epilepticus, intramuscular midazolam is at least as safe and effective as intravenous lorazepam for prehospital seizure cessation. (Funded by the National Institute of Neurological Disorders and Stroke and others; ClinicalTrials.gov number, NCT00809146.)

From the Department of Emergency Medicine, University of Michigan, Ann Arbor (R.S., W.B.); the Department of Medicine, Division of Biostatistics and Epidemiology, Medical University of South Carolina, Charleston (V.D., Y.P.); the Department of Neurology, University of California, San Francisco, San Francisco (D.L.); the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD (R.C.); and the Department of Emergency Medicine, University of Cincinnati, Cincinnati (A.P.). Address reprint requests to Dr. Silbergleit at the Department of Emergency Medicine, Suite 3100, 24 Frank Lloyd Wright Dr., Ann Arbor, MI 48105, or at robert.silbergleit@umich.edu.

*The Neurological Emergencies Treatment Trials (NETT) investigators are listed in the Supplementary Appendix, available at NEJM.org.

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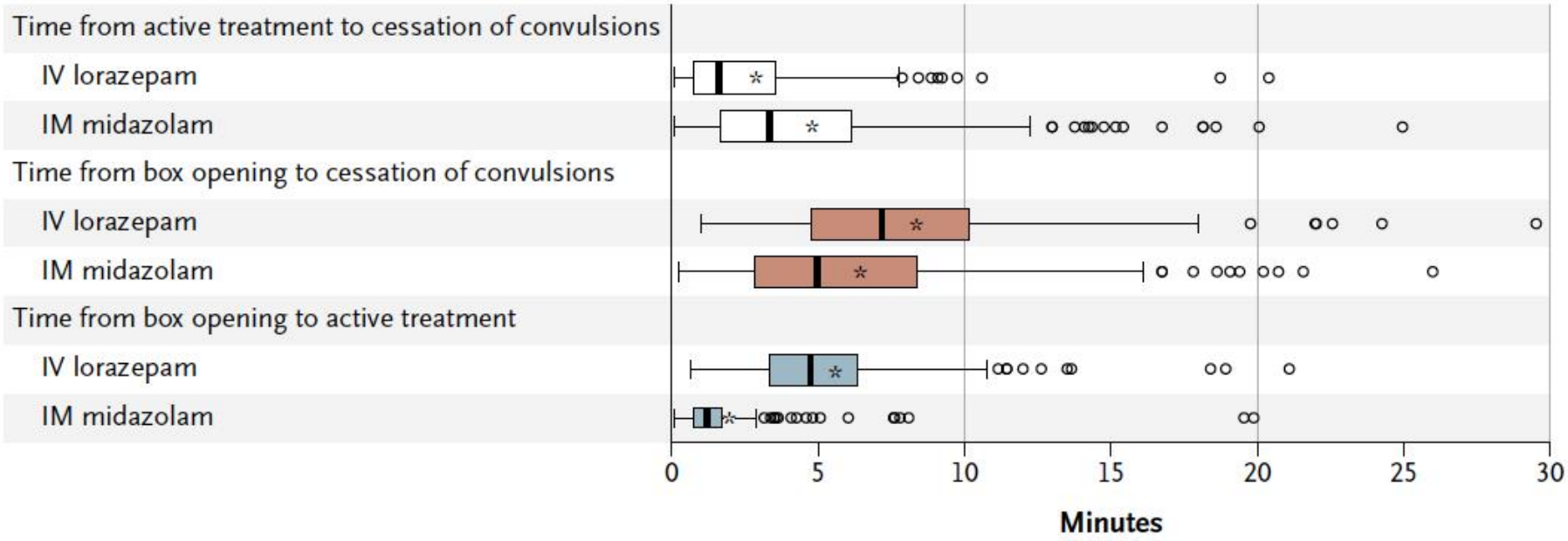

Figure 3. Intervals between Active Treatment and Cessation of Convulsions, Box Opening and Cessation of Convulsions, and Box Opening and Active Treatment.

The shorter time to IM drug administration was offset by the faster onset of action after IV drug administration, resulting in similar latency periods until convulsions were terminated. Time to IV administration includes the nominal time (about 20 seconds) needed to administer the drug by means of IM autoinjector. Asterisks indicate means, boxes interquartile ranges, bold vertical lines within boxes medians, I bars 1.5 times the interquartile range, and circles outliers.

We need a clinical trial to guide the choice of second-line agents

Proposed second-line agents

- Phenytoin/fosphenytoin
- Valproate
- Levetiracetam
- Lacosamide
- Topiramate
- Verapamil

Established SE Treatment Trial (ESETT) proposal

- Use Neurologic Emergency Treatment Trial network and additional sites
- Randomize after BZ failure to
  - Phenytoin/fosphenytoin
  - Valproate
  - Levetiracetam
- Parallel studies in US and Europe to obtain answers faster

European Journal of Neurology 2011 doi:10.1111/j.1468-1331.2011.03606.x

REVIEW ARTICLE

IV Valproate in generalized convulsive status epilepticus: a systematic review

F. Brigo[a,*], M. Storti[b,*], A. Del Felice[a], A. Fiaschi[a] and L. G. Bongiovanni[a]

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Keywords:
clinical trials randomized controlled, clinical trials systematic review/meta-analysis, Status epilepticus, valproic acid

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Accepted 4 November 2011

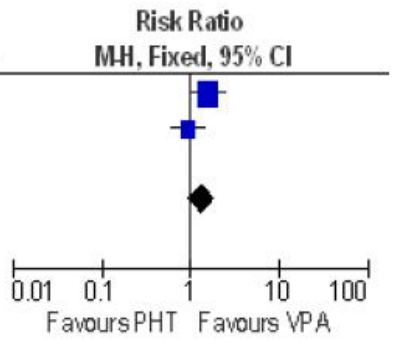
Aim of this review was to evaluate efficacy and safety of intravenous valproate (IV VPA) in the treatment of generalized convulsive status epilepticus (GCSE) in patients of any age, synthesizing available evidences from randomized controlled trials (RCTs). RCTs on IV VPA administered in patients (no age restriction) for GCSE at any stage were searched in MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials. Studies were selected and data independently extracted. Following outcomes were considered: clinical seizure cessation after drug administration, seizure freedom at 24 h, and adverse effects. Outcomes were assessed using standard methods to calculate risk ratio (RR) with 95% confidence intervals. Five trials met inclusion criteria. Two different comparisons were available (IV VPA versus phenytoin (PHT), IV VPA versus IV Diazepam), but only the former included more than one study with enough information to permit a meta-analysis. Compared with PHT, VPA had statistically lower risk of adverse effects (RR 0.31, 95% CI 0.12–0.85), with no differences in GCSE cessation after drug administration (RR 1.31, 95% CI 0.93–1.84) and in seizure freedom at 24 h (RR 0.96, 95% CI 0.88–1.06). This review suggests that IV VPA has a better tolerability than PHT in treatment of GCSE, without any statistically significant differences in terms of efficacy. More rigorous RCTs of VPA versus an appropriate comparator, in a well-defined population with a systematic definition of SE, are however required to conclude about efficacy and tolerability of VPA in clinical practice.

IV VPA versus IV PHT

(a) *Clinical seizure cessation after drug administration*

Study or Subgroup	VPA Events	VPA Total	PHT Events	PHT Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Misra et al. 2006	23	35	14	33	60.7%	1.55 [0.97, 2.46]	2006
Gilad et al. 2008	13	18	7	9	39.3%	0.93 [0.59, 1.46]	2008
Total (95% CI)		**53**		**42**	**100.0%**	**1.31 [0.93, 1.84]**	
Total events	36		21				

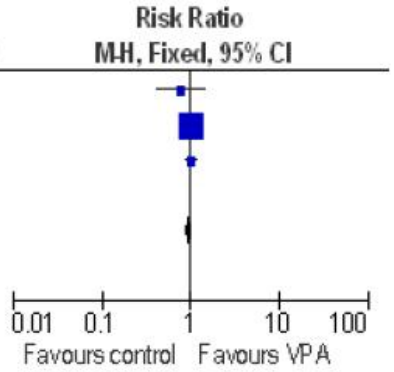
Heterogeneity: Chi² = 2.71, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 1.53 (P = 0.13)



(b) *Seizure freedom at 24 hours*

Study or Subgroup	VPA Events	VPA Total	PHT Events	PHT Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Misra et al. 2006	10	23	8	14	14.9%	0.76 [0.40, 1.46]	2006
Agarwal et al. 2007	45	45	43	43	66.5%	1.00 [0.96, 1.04]	2007
Gilad et al. 2008	18	18	9	9	18.6%	1.00 [0.85, 1.17]	2008
Total (95% CI)		**86**		**66**	**100.0%**	**0.96 [0.88, 1.06]**	
Total events	73		60				

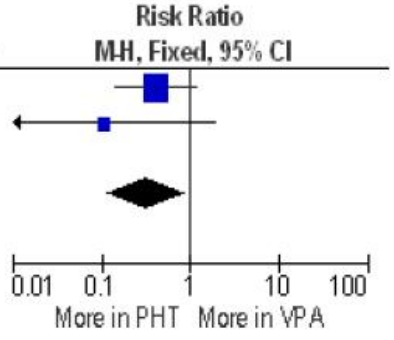
Heterogeneity: Chi² = 3.33, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 0.74 (P = 0.46)



(c) *Total of adverse effects*

Study or Subgroup	VPA Events	VPA Total	PHT Events	PHT Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Misra et al. 2006	4	23	6	14	69.5%	0.41 [0.14, 1.19]	2006
Gilad et al. 2008	0	18	2	9	30.5%	0.11 [0.01, 1.99]	2008
Total (95% CI)		**41**		**23**	**100.0%**	**0.31 [0.12, 0.85]**	
Total events	4		8				

Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 2.28 (P = 0.02)



Available online at www.sciencedirect.com
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Epilepsy & Behavior
www.elsevier.com/locate/yebeh

Brief Communication

Intravenous levetiracetam: Treatment experience with the first 50 critically ill patients

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Available online 4 March 2008

Abstract

Levetiracetam (LEV) is a broad-spectrum antiepileptic drug with no known interactions and a favorable profile of adverse events. These properties make it a good candidate for use in critically ill patients. An intravenous formulation of LEV was recently approved. The present study retrospectively assesses the safety and efficacy of LEV in the first 50 critically ill patients treated with intravenous LEV. Indications for use were seizure prophylaxis, acute symptomatic seizures, and all forms of status epilepticus. There were no major adverse effects, although less prominent changes may have been masked by the already severely compromised condition of these patients. Two patients (4%) had transiently lowered platelet counts (55,000 and 82,000, respectively). Efficacy, defined as cessation of seizure activity or prevention of its recurrence, was observed in 41 of 50 patients (82%). Antiepileptic treatment of critically ill patients with LEV seems to be effective and safe according to the data for this small cohort, but this observation warrants further prospective investigation in a larger number of patients.

Terminated 65% of SE
(few initial, most refractory)

neurocritical care society Neurocrit Care (2010) 12:165–172
DOI 10.1007/s12028-009-9304-y

ORIGINAL ARTICLE

Prospective, Randomized, Single-Blinded Comparative Trial of Intravenous Levetiracetam Versus Phenytoin for Seizure Prophylaxis

Jerzy P. Szaflarski · Kiranpal S. Sangha · Christopher J. Lindsell · Lori A. Shutter

Published online: 7 November 2009

Abstract

Background Anti-epileptic drugs are commonly used for seizure prophylaxis after neurological injury. We performed a study comparing intravenous (IV) levetiracetam (LEV) to IV phenytoin (PHT) for seizure prophylaxis after neurological injury.

Methods In this prospective, single-center, randomized, single-blinded comparative trial of LEV versus PHT (2:1 ratio) in patients with severe traumatic brain injury (*s*TBI) or subarachnoid hemorrhage (NCT00618436) patients received IV load with either LEV or fosphenytoin followed by standard IV doses of LEV or PHT. Doses were adjusted to maintain therapeutic serum PHT concentrations or if patients had seizures. Continuous EEG (cEEG) monitoring was performed for the initial 72 h; outcome data were collected.

Results A total of 52 patients were randomized (LEV = 34; PHT = 18); 89% with sTBI. When controlling for baseline severity, LEV patients experienced better long-term outcomes than those on PHT; the Disability Rating Scale score was lower at 3 months ($P = 0.042$) and the Glasgow Outcomes Scale score was higher at 6 months ($P = 0.039$). There were no differences between groups in seizure occurrence during cEEG (LEV 5/34 vs. PHT 3/18; $P = 1.0$) or at 6 months (LEV 1/20 vs. PHT 0/14; $P = 1.0$), mortality (LEV 14/34 vs. PHT 4/18; $P = 0.227$). There were no differences in side effects between groups (all $P > 0.15$) except for a lower frequency of worsened neurological status ($P = 0.024$), and gastrointestinal problems ($P = 0.043$) in LEV-treated patients.

Conclusions This study of LEV versus PHT for seizure prevention in the NSICU showed improved long-term outcomes of LEV-treated patients vis-à-vis PHT-treated patients. LEV appears to be an alternative to PHT for seizure prophylaxis in this setting.

Keywords Levetiracetam · Phenytoin · Fosphenytoin · Seizure prevention · ICU · SAH · TBI · Long-term outcomes · GCS · GOS · DRS

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Introduction

Seizures in the setting of acute brain injury are common; the chance of seizure occurrence depends, in part, on the

mortality (LEV 14/34 vs. PHT 4/18; $P = 0.227$)

LEV mortality 14/34 = 41%
PHT mortality 4/18 = 22%
Fisher's exact test p = 0.22

Power analysis suggests sample size of 440 to test mortality difference

neurocritical care society Neurocrit Care
DOI 10.1007/s12028-011-9662-0

ORIGINAL ARTICLE

Safety and Efficacy of Lacosamide in the Intensive Care Unit

Sunil Cherry · Lilith Judd · Juan Carlos Muniz · Hoda Elzawahry · Suzette LaRoche

Results LCM was administered in 24 patients including 13 episodes of refractory status epilepticus (RSE) occurring in 10 patients and for treatment of isolated seizures or following resolution of RSE in an additional 14 patients. Seizure cessation was achieved in 5/13 (38%) episodes of RSE (mean 11.2 h) while there was at least a 50% decrease in seizure frequency in 7/13 (54%). 11/14 patients (76%) who received LCM for treatment of isolated seizures or prevention of seizure recurrence remained seizure free. Three patients experienced a decline in systolic blood pressure (>20 mmHg) while one patient experienced unexplained fever and one patient had elevation of liver function tests.

neurocritical care society Neurocrit Care
DOI 10.1007/s12028-008-9092-9

ORIGINAL ARTICLE

Hypothermia for Refractory Status Epilepticus

Jesse J. Corry · Rajat Dhar · Theresa Murphy · Michael N. Diringer

Abstract

Introduction Status epilepticus (SE) can be refractory to conventional anticonvulsants, requiring anesthetic doses of medications to suppress seizures. This approach carries significant morbidity, is associated with a high fatality rate, and may not always control SE. Hypothermia has been shown to suppress epileptiform activity experimentally, but has not previously been used as a primary modality to control SE in humans.

Methods Four patients with SE refractory to benzodiazepine and/or barbiturate infusions were treated with hypothermia (target temperature: 31–35°C) using an endovascular cooling system. All received continuous EEG monitoring, three were on midazolam infusions and one had recurrent seizures on weaning from pentobarbital.

Results Therapeutic hypothermia was successful in aborting seizure activity in all four patients, allowing midazolam infusions to be discontinued; three achieved a burst-suppression pattern on EEG. After controlled rewarming, two patients remained seizure-free, and all four demonstrated a marked reduction in seizure frequency. Adverse events included shivering, coagulopathy without bleeding, and venous thromboembolism. Two death occurred, neither directly related to hypothermia; however, immunosuppression related to the use of barbiturates and hypothermia may have contributed to an episode of fatal sepsis in one patient.

Conclusions Hypothermia was able to suppress seizure activity in patients with SE refractory to traditional therapies with minimal morbidity. It appears promising as an alternative or an adjunct to anesthetic doses of other agents, but requires further study to better evaluate its safety and efficacy.

Keywords Induced hypothermia · Status epilepticus · Endovascular cooling · Barbiturates

Introduction

Status epilepticus (SE) affects up to 150,000 patients each year in the United States, with a mortality between 3 and 33% [1–8]. Initial treatment with benzodiazepines, phenytoin, and/or phenobarbital fails to terminate SE in 30–50% of cases, with cases of longer duration becoming more difficult to treat [6, 9–12]. Even infusions of anesthetic doses of agents, such as midazolam, pentobarbital, and propofol that are traditionally used to control refractory SE, fail in 8–21% of cases [13]. Refractory SE has a greater mortality than SE that can be controlled by first-line interventions [8]. Furthermore, prolonged seizures pose a

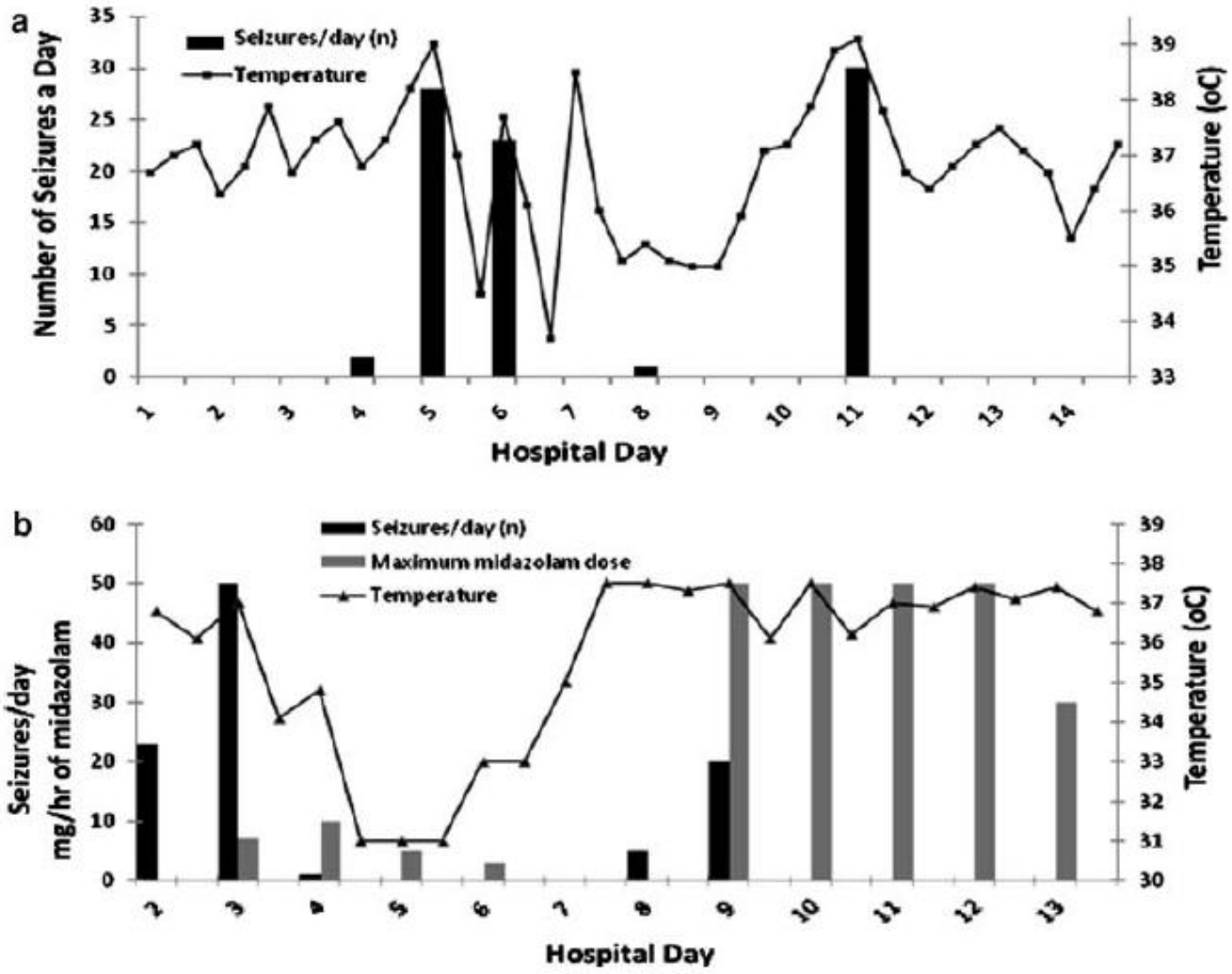
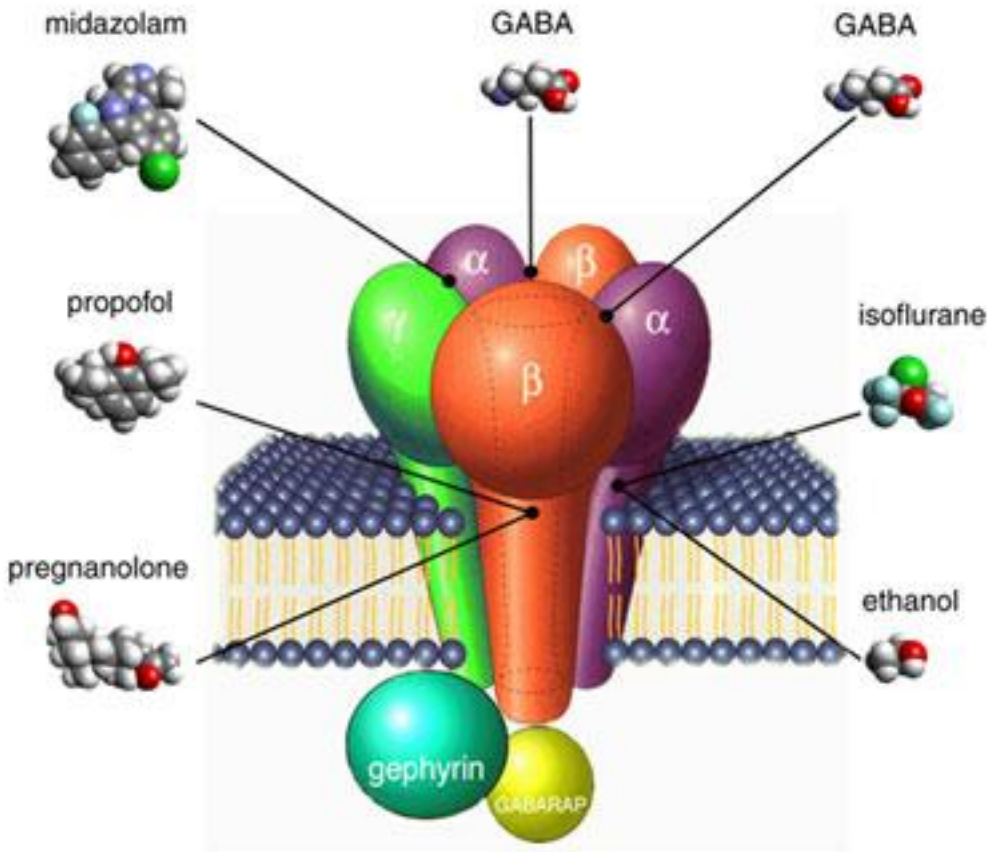
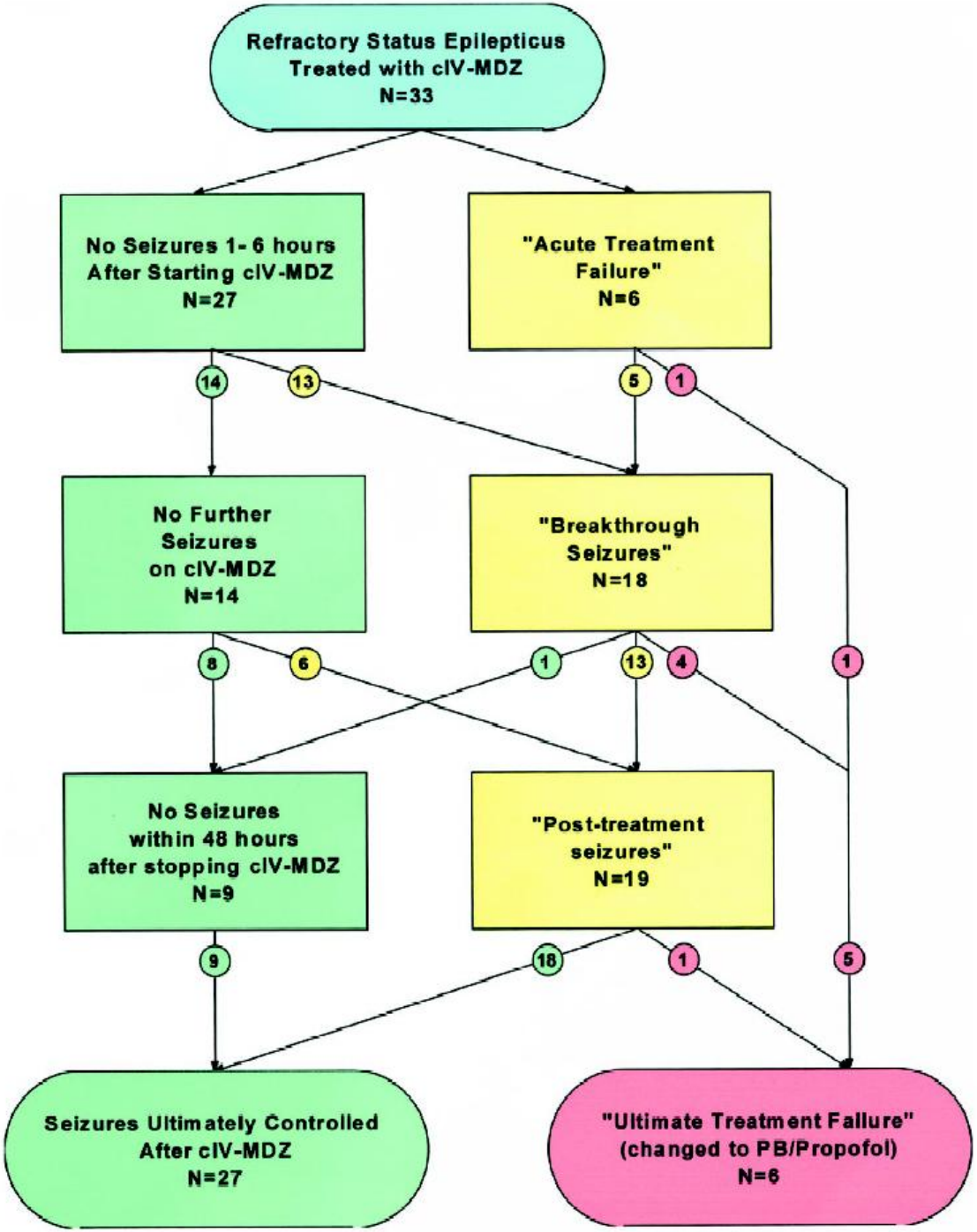


Fig. 2 Correlation between temperature and number of seizures. (a) Demonstrates the relationship of temperature to the number of seizures in patient 3. Hypothermia was initiated on day 7 and the patient was warmed on the 9th day. (b) Demonstrates this relationship in patient 4. Hypothermia was initiated on day 3, and the endovascular cooling catheter was turned off on day 7


midazolam
GABA
GABA
propofol
isoflurane
pregnanolone
ethanol
α
β
γ
β
α
gephyrin
GABARAP

High-dose benzodiazepines

- Midazolam
  - loading dose: 0.2 mg/kg
  - maintenance: 0.1 - 2.0 mg/kg/hr (2.0 - 40 µg/kg/min)
  - goal: seizure suppression
- Lorazepam
  - up to 9 mg/hr
  - goal: seizure suppression



Response of RSE patients to continuous midazolam infusion (range of 0.1-0.4 mg/kg/hr)

Claassen *et al*
Neurology 2001:57:1036-1042

Propofol

- Consider an initial dose of 3-5 mg/kg
- Maintenance dose, 1 mg/kg/hr (~15 µg/kg/min); increase to achieve seizure control
  - onset of action in 3 to 5 minutes; duration of action is only 5 to 10 minutes after the drug has been stopped.
  - up to 15 mg/kg/hr (250 µg/kg/min) has been used.

Stecker *et al* **Epilepsia** 1998;39:18-26

Midazolam vs. propofol

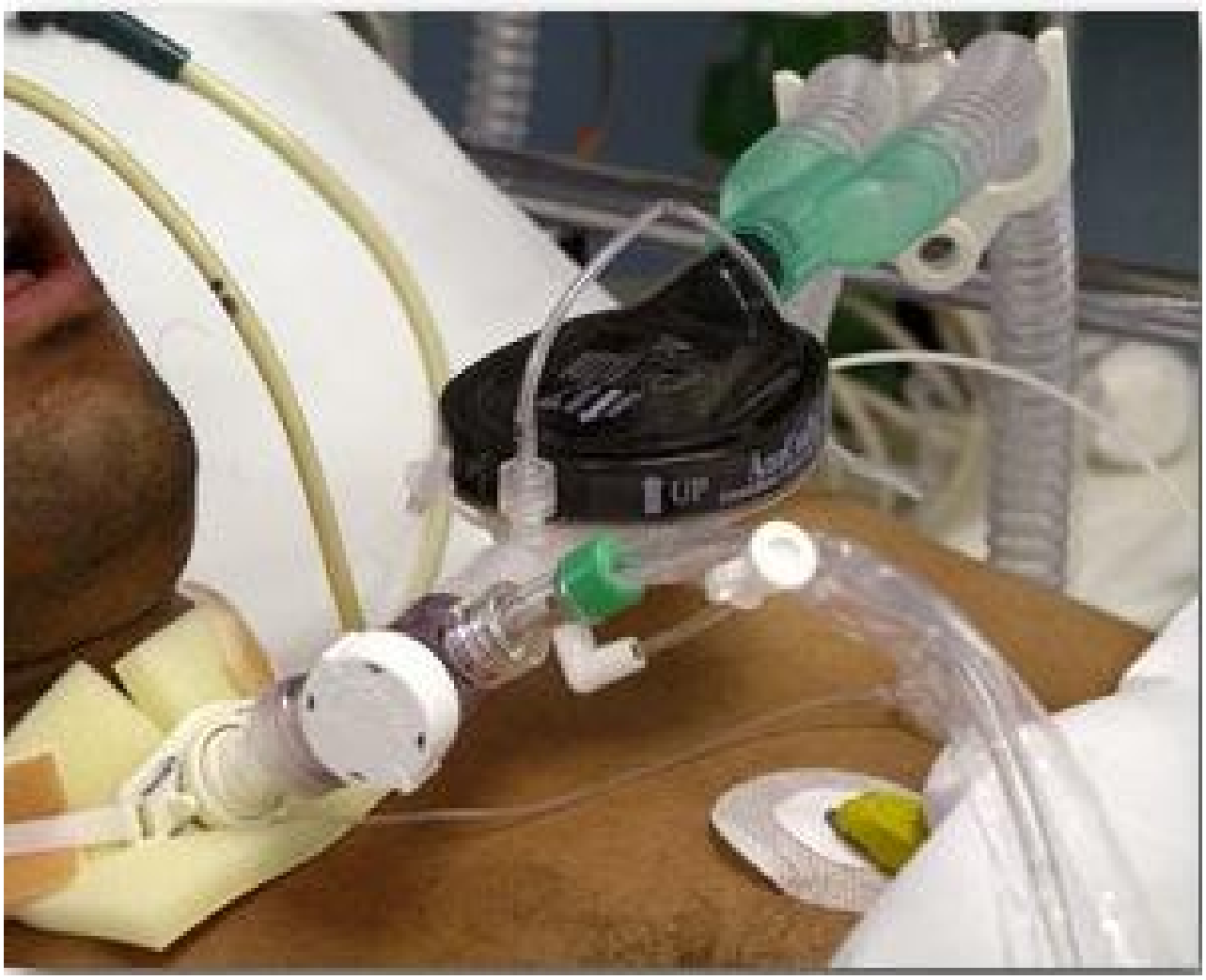
- Retrospective review of 20 RSE cases with continuous EEG monitoring
  - 14 propofol, 6 midazolam
  - Overall mortality:
    - 57% propofol, 17% MDZ (NS)
    - Subgroup with APACHE II scores > 20 did show a statistically significantly higher mortality with propofol

Prasad A et al **Epilepsia** 2001;42:380-386

Other approaches to RSE

- lidocaine
- high-dose phenobarbital
- paraldehyde
- clonazepam
- isoflurane
- magnesium
- surgery
  - resection
  - subpial transection
  - vagus nerve stimulator

AnaConDa device for recirculating volatile anesthetic gases in the ICU



neurocritical care society Neurocrit Care
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ORIGINAL ARTICLE

Electroconvulsive Therapy for Refractory Status Epilepticus: A Case Series

Hooman Kamel · Susannah Brock Cornes · Manu Hegde · Stephen E. Hall · S. Andrew Josephson

Abstract

Background Status epilepticus refractory to conventional anti-epileptic drugs typically has a poor prognosis, but patients may recover well if seizures can be stopped. Case reports suggest that electroconvulsive therapy (ECT) may stop seizures in patients with refractory status epilepticus, and we sought to examine its effectiveness in a series of patients.

Methods Three consecutive patients with refractory status epilepticus at our institution were treated with ECT after other therapies had failed.

Results ECT stopped seizures in 2 of 3 patients. One patient had complete neurological recovery; the other was left with mild cognitive impairment and epilepsy, but returned to independent living.

Conclusion ECT may be an effective therapy for refractory status epilepticus and warrants further study for this indication.

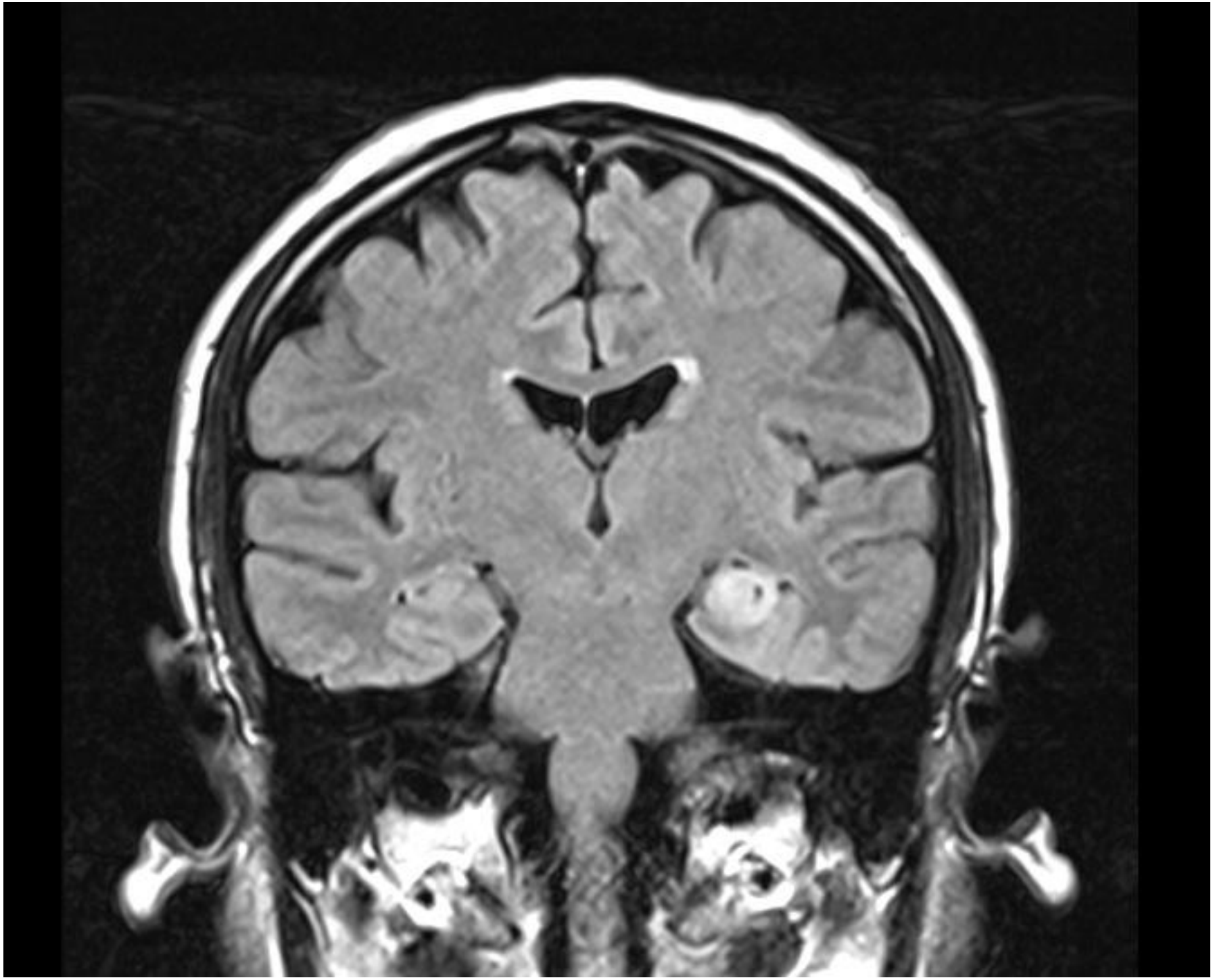
Introduction

Status epilepticus is a potentially devastating medical emergency that affects 60,000–120,000 Americans per year [1]. It is classically defined as a seizure that lasts more than 30 min, or repeated seizures that prevent the patient from regaining full consciousness [2]. Thus defined, its mortality is approximately 25%, compared to less than 5% from seizures shorter than 30 min. Its treatment is particularly relevant to the neurocritical care community, because it often requires prolonged use of anesthetic agents in an intensive care unit (ICU) [3].

Most patients with status epilepticus are successfully treated with benzodiazepines and conventional anti-epileptic drugs such as phenytoin, but some require anesthetic agents such as propofol, midazolam, or pentobarbital to suppress seizures [3, 4]. This requires endotracheal intubation, admission to an ICU, and continuous electroencephalographic (EEG) monitoring. Anesthetic agents are important

Our increasing recognition of inflammatory causes of SE suggests that we need to pay early attention to treating the etiology of SE

('source control')



Epilepsia, 50(Suppl. 12): 58–60, 2009
doi: 10.1111/j.1528-1167.2009.02352.x

Status epilepticus due to paraneoplastic and nonparaneoplastic encephalitides

Josep Dalmau

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Table 1. Antibodies associated with encephalitides and seizures

Antibody	Syndrome	Clinical significance	Location of epitopes	Response to immunotherapy
Hu	Limbic, cortical encephalitis	High	Intracellular	Infrequent
CV2/CRMP5	Limbic encephalitis	High	Intracellular	Infrequent
Ma2	Limbic, diencephalon, upper brainstem encephalitis	High	Intracellular	Moderate
Amphiphysin	Limbic encephalitis, stiff-person syndrome	High	Intracellular	Poor
GAD	Limbic encephalitis, refractory epilepsy, stiff-person syndrome	Moderate	Intracellular	Moderate
VGKC (Kv1.1, Kv1.2)	Limbic encephalitis, Morvan's syndrome	High	Extracellular	Frequent
NMDAR (NR1)	Psychosis, dyskinesias, autonomic instability, hypoventilation	High	Extracellular	Frequent
NMDAR (NR2B or Gluϵ2)	Multiple types of encephalitides	Unclear[a]	Extra and intracellular	N/A
NMDAR (NR2A/2B)	Neuropsychiatric lupus	Low	Extracellular (DWEYS)[b]	N/A
AMPAR (GluR1/2)	Limbic encephalitis (frequent relapses)	N/A[c]	Extracellular	Frequent
AMPAR (GluR3)	Rasmussen's encephalitis	Low	Extracellular?	Infrequent/moderate
Thyroid peroxidase, thyroglobulin	Hashimoto's encephalitis	Low	Intracellular	Frequent

Italics indicate syndromes that are almost always paraneoplastic.

CRMP5, collapsin response mediator protein-5; GAD, glutamic acid decarboxylase; VGKC, voltage-gated potassium channels; NMDAR, *N*-methyl-D-aspartate receptor, AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.

[a]Described in multiple unrelated disorders, including among others: limbic encephalitis, nonspecific encephalitis, viral encephalitis, and degenerative disorders.

[b]DWEYS pentapeptide consensus sequence present in NR2A and NR2B.

[c]N/A: not available, too early to assess significance.

The Frequency of Autoimmune *N*-Methyl-D-Aspartate Receptor Encephalitis Surpasses That of Individual Viral Etiologies in Young Individuals Enrolled in the California Encephalitis Project

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Background. In 2007, the California Encephalitis Project (CEP), which was established to study the epidemiology of encephalitis, began identifying cases of anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. Increasing numbers of anti-NMDAR encephalitis cases have been identified at the CEP, and this form rivals commonly known viral etiologies as a causal agent. We report here the relative frequency and differences among encephalitides caused by anti-NMDAR and viral etiologies within the CEP experience.

Methods. Demographic, frequency, and clinical data from patients with anti-NMDAR encephalitis are compared with those with viral encephalitic agents: enterovirus, herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV), and West Nile virus (WNV). All examined cases presented to the CEP between September 2007 and February 2011 and are limited to individuals aged ≤30 years because of the predominance of anti-NMDAR encephalitis in this group. The diagnostic costs incurred in a single case are also included.

Results. Anti-NMDAR encephalitis was identified >4 times as frequently as HSV-1, WNV, or VZV and was the leading entity identified in our cohort. We found that 65% of anti-NMDAR encephalitis occurred in patients aged ≤18 years. This disorder demonstrated a predilection, which was not observed with viral etiologies, for females ($P < .01$). Seizures, language dysfunction, psychosis, and electroencephalographic abnormalities were significantly more frequent in patients with anti-NMDAR encephalitis ($P < .05$), and autonomic instability occurred exclusively in this group.

Discussion. Anti-NMDAR encephalitis rivals viral etiologies as a cause of encephalitis within the CEP cohort. This entity deserves a prominent place on the encephalitic differential diagnosis to avoid unnecessary diagnostic and treatment costs, and to permit a more timely treatment.

Clinical Infectious Diseases 2012;54(7):899–904

Immunomodulatory therapy

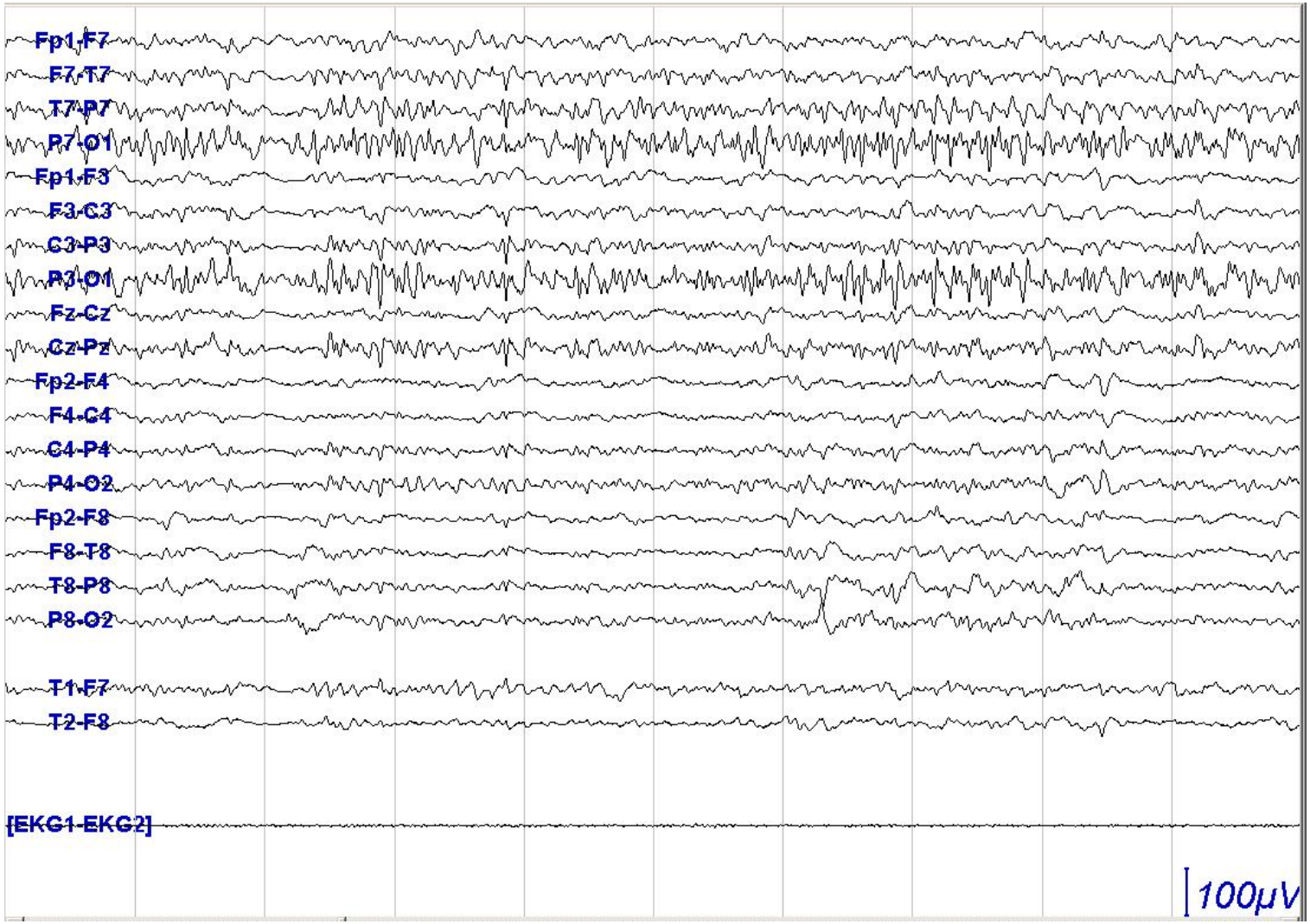
- With or without a definitive diagnosis of an immunologic cause of status
- Choices:
  - Steroids
  - IgIV
  - Plasma exchange
  - Calcineurin antagonists and other antirejection drugs
  - Cytotoxic agents

We need to prevent or ameliorate secondary injury (sometimes from our treatment) while controlling SE

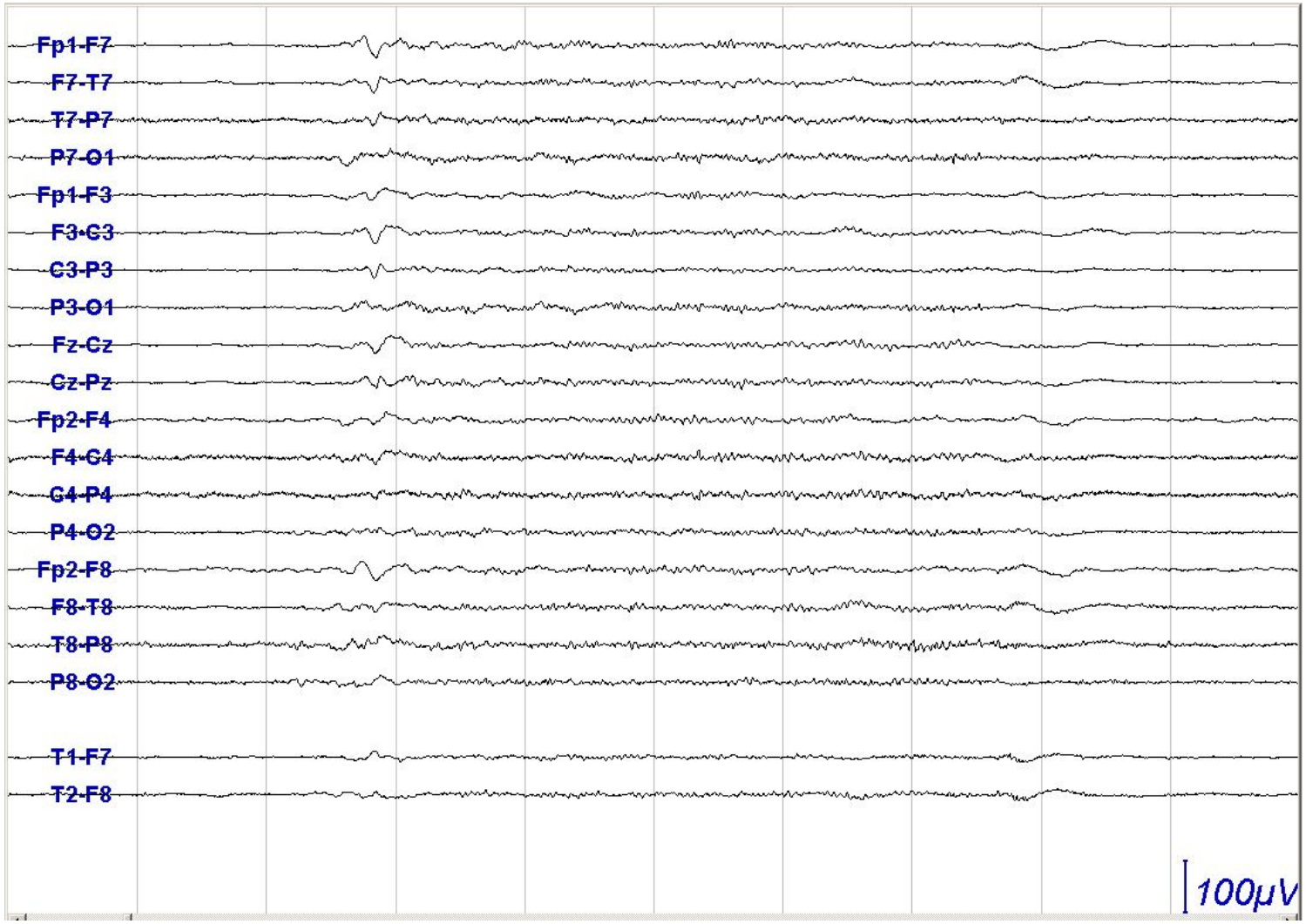
Ketamine

- for refractory CPSE
  - dose uncertain
  - general (dissociative) anesthetic dose 1 - **5** mg/kg, with infusion of 1 – 5 mg/kg/hr (20 - 80 μg/kg/min)
  - administer with a benzodiazepine in an attempt to decrease later psychiatric side effects

Patient 2 before ketamine



Patient 2 after ketamine



neurocritical care society Neurocrit Care
DOI 10.1007/s12028-011-9668-7

PRACTICAL PEARL

Early Ketamine to Treat Refractory Status Epilepticus

Andreas H. Kramer

Fig. 1 Continuous EEG (*top*) and 12 h compressed density spectral array (CDSA) tracing (*bottom* T3-01 and T4-02). The CDSA *x* axis represents time, the *y* axis designates EEG frequencies between 0 and 30 Hz, and the *color* indicates the "power" (higher with increasing brightness). Nearly continuous seizure activity was seen over the left hemisphere during the initial 4 h (represented by the *yellow bar*), with corresponding peaks visualized using CDSA. During this time, the patient received escalating doses of midazolam and propofol (see text for details). He was also given levetiracetam and had previously already been loaded with phenytoin. The *yellow asterisk* indicates the time point corresponding to the 10 s raw EEG tracing, just prior to administration of 50 mg of ketamine, followed a 40 mg per hour infusion. Over the subsequent 8 h (represented by the *red bar*), with an incremental dose of ketamine, the frequency, amplitude, and duration of seizures gradually decreased (colour figure online)

Burst-suppression myths

- EEG burst-suppression has been demonstrated to be necessary for RSE control
- achieving burst-suppression means that the patient will not have seizures
- the burst-suppression pattern is easily recognized and taught, even for non-neurologists

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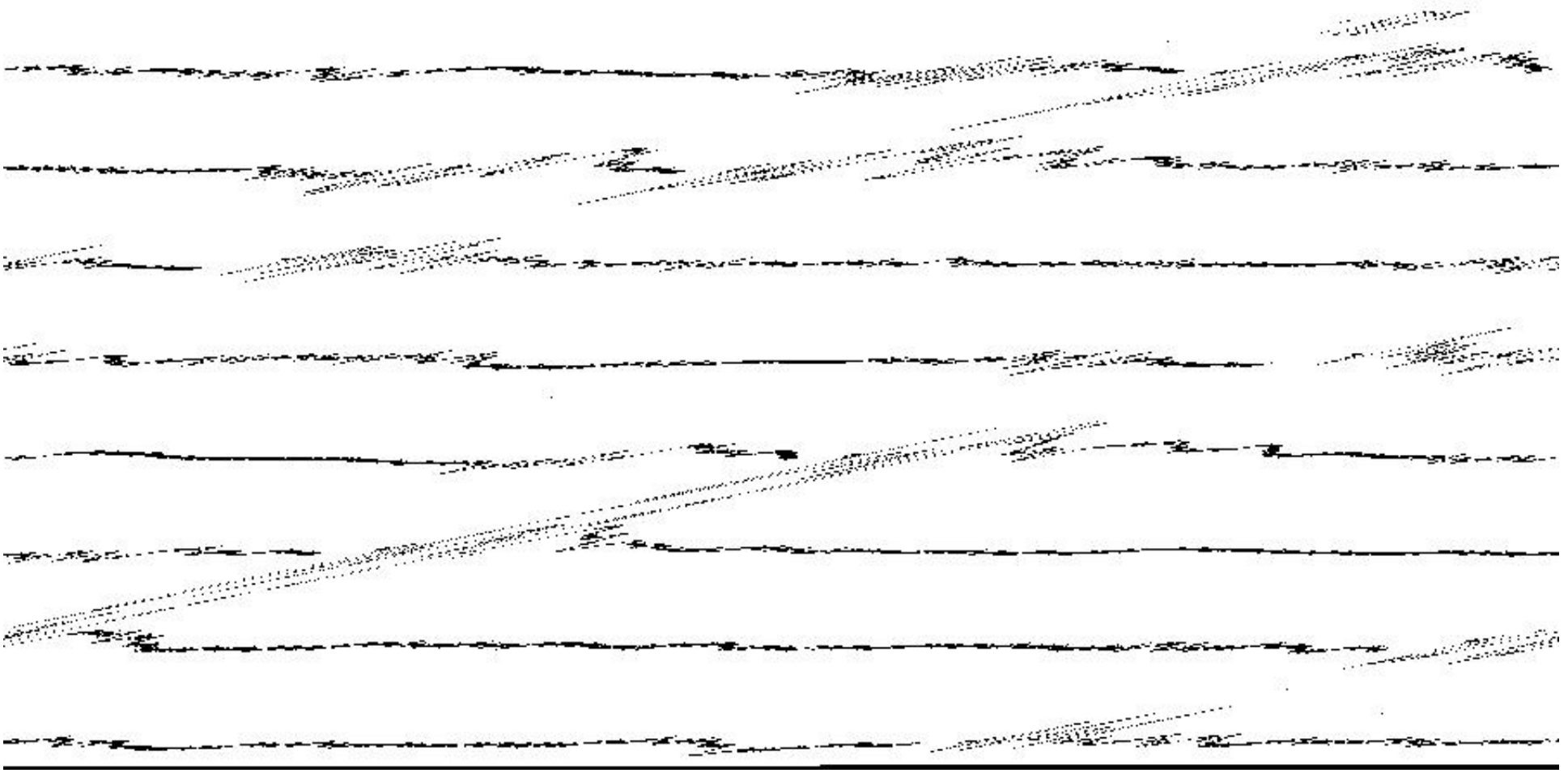

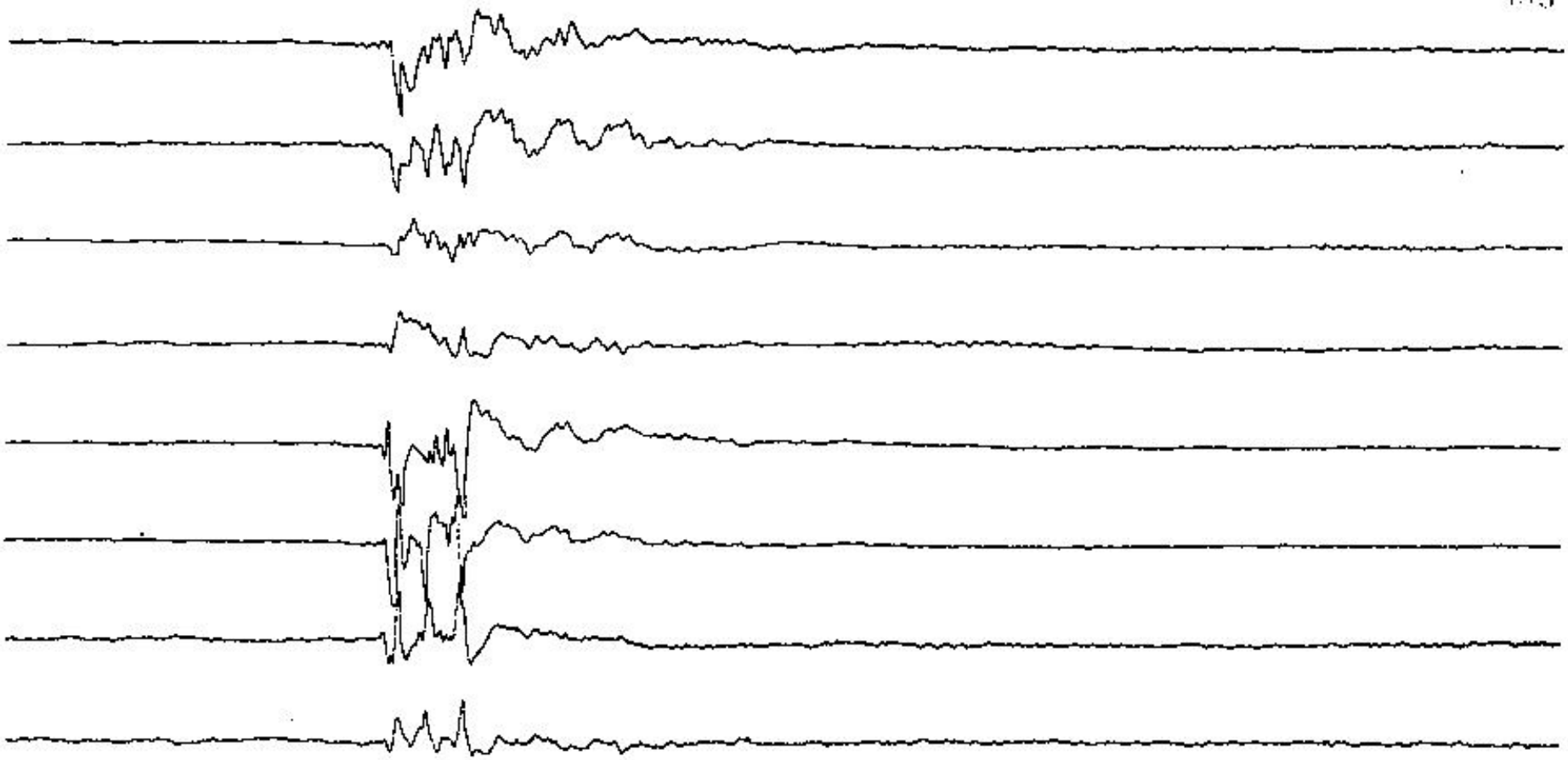

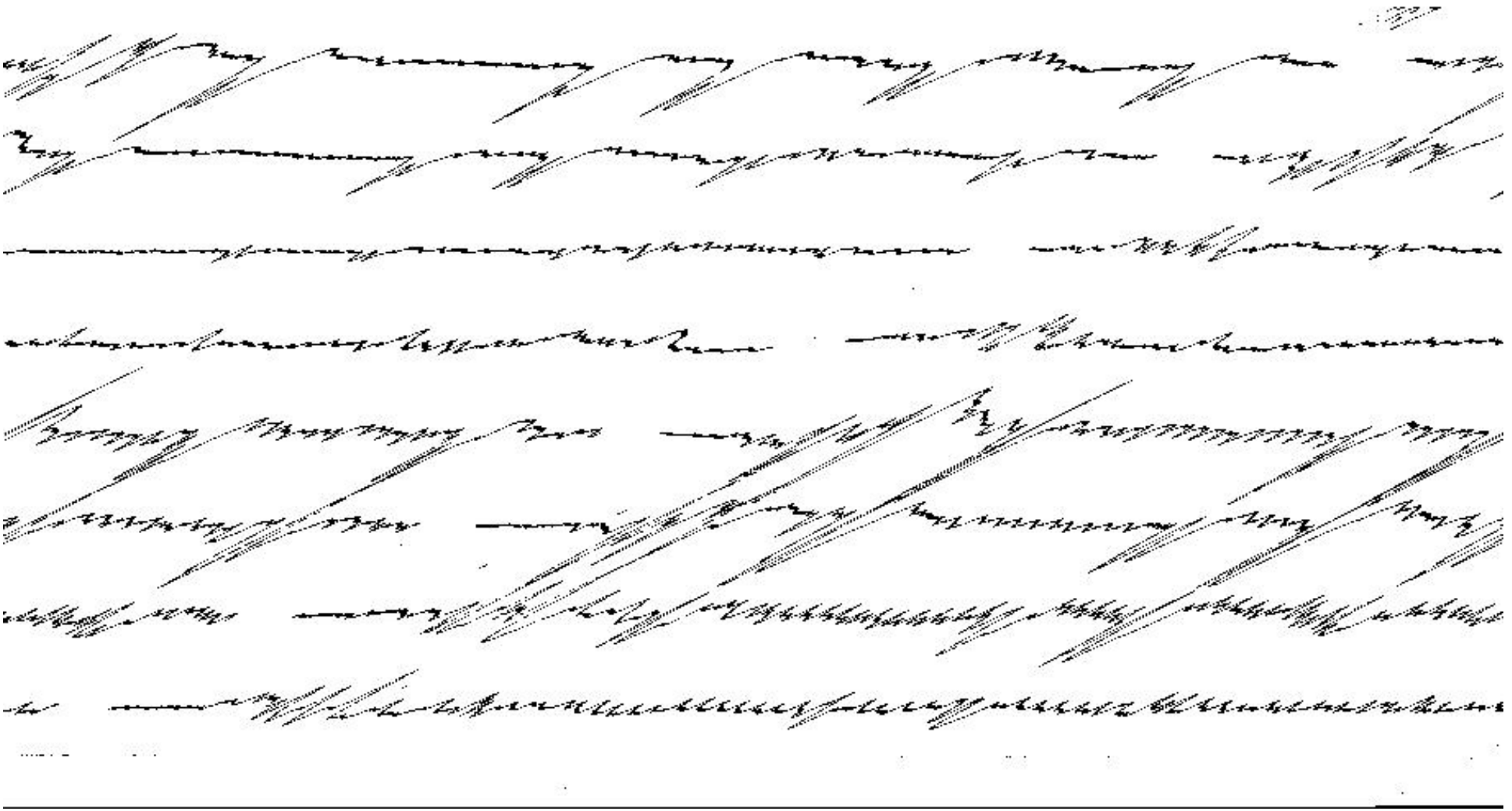

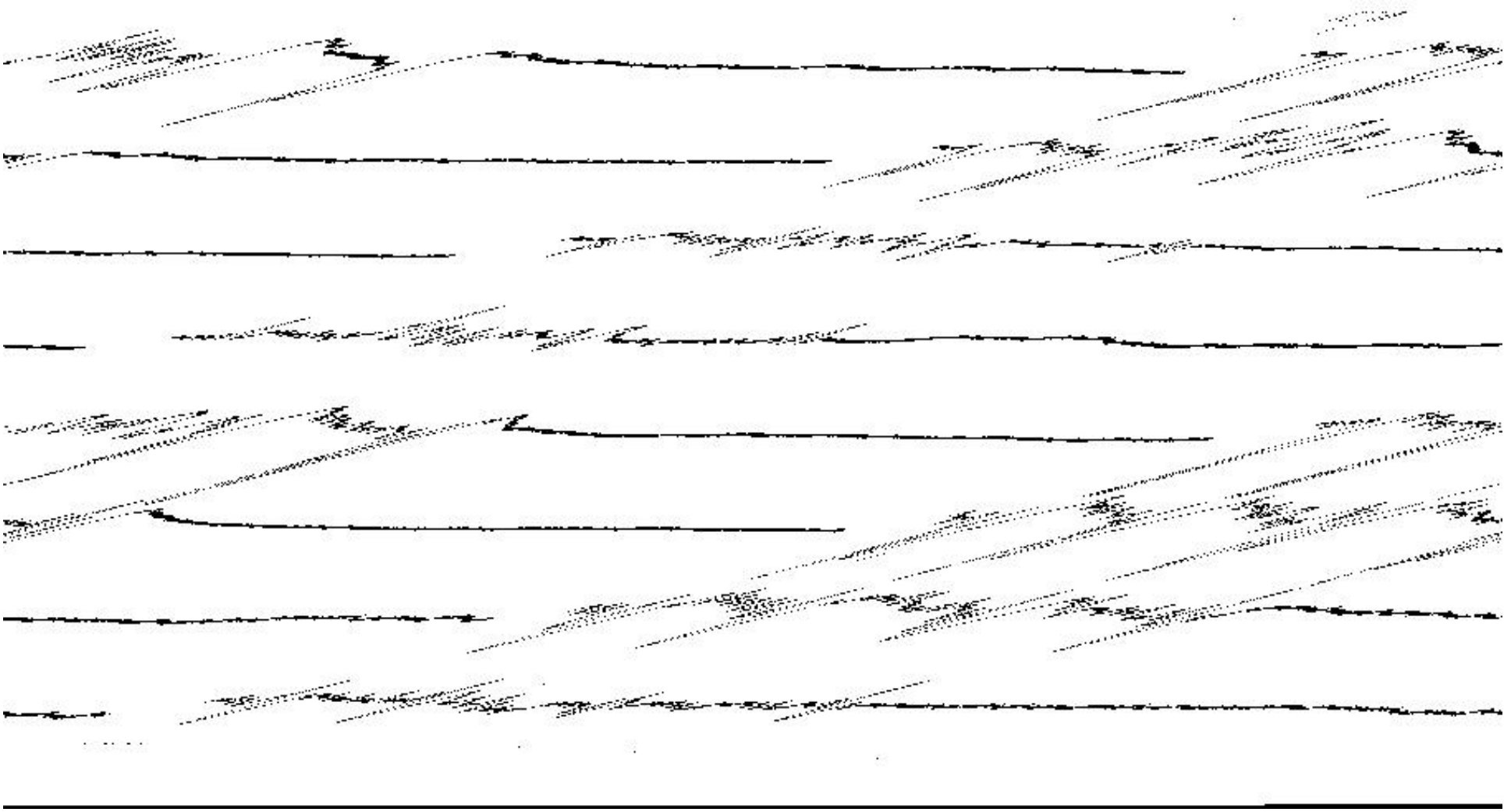

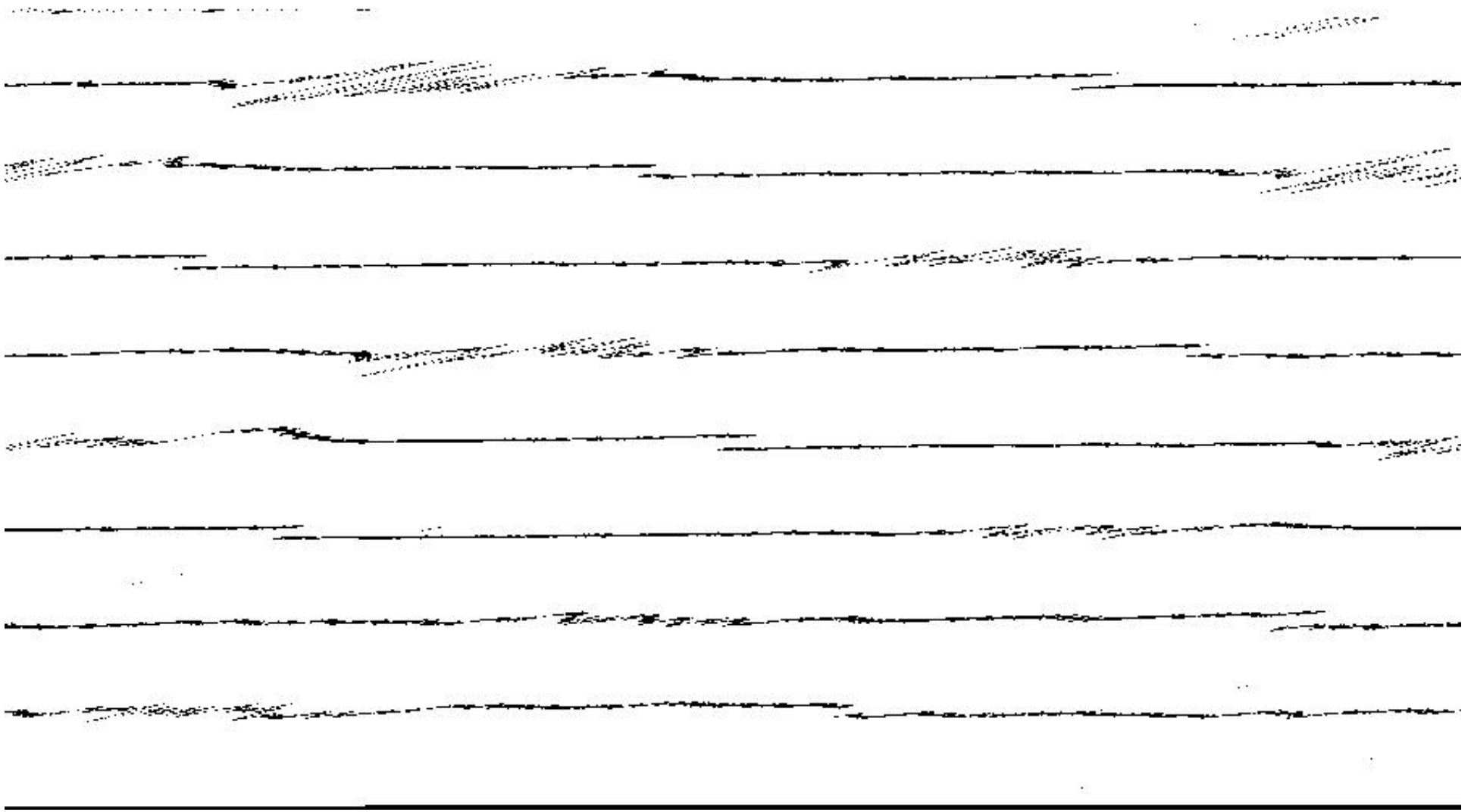

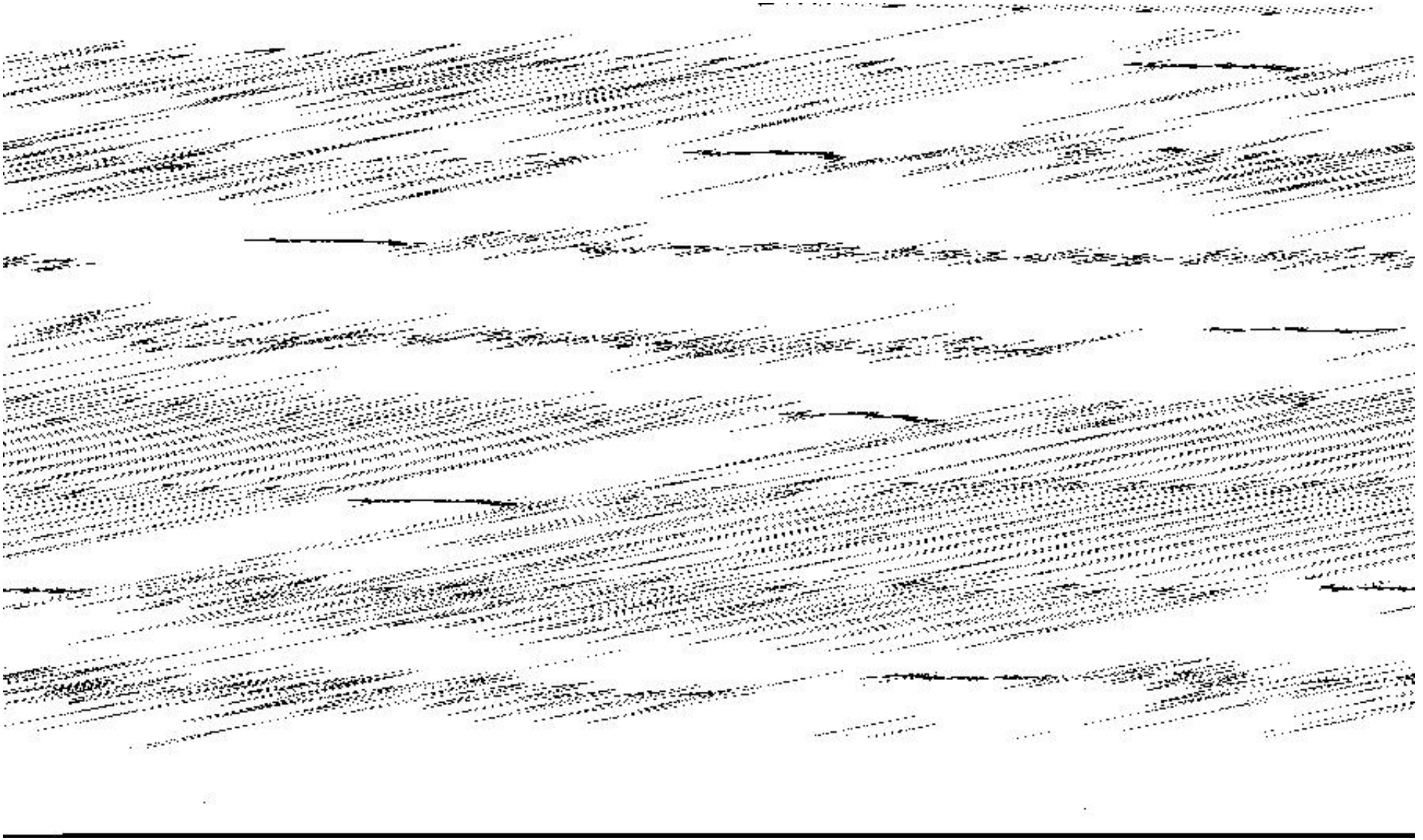

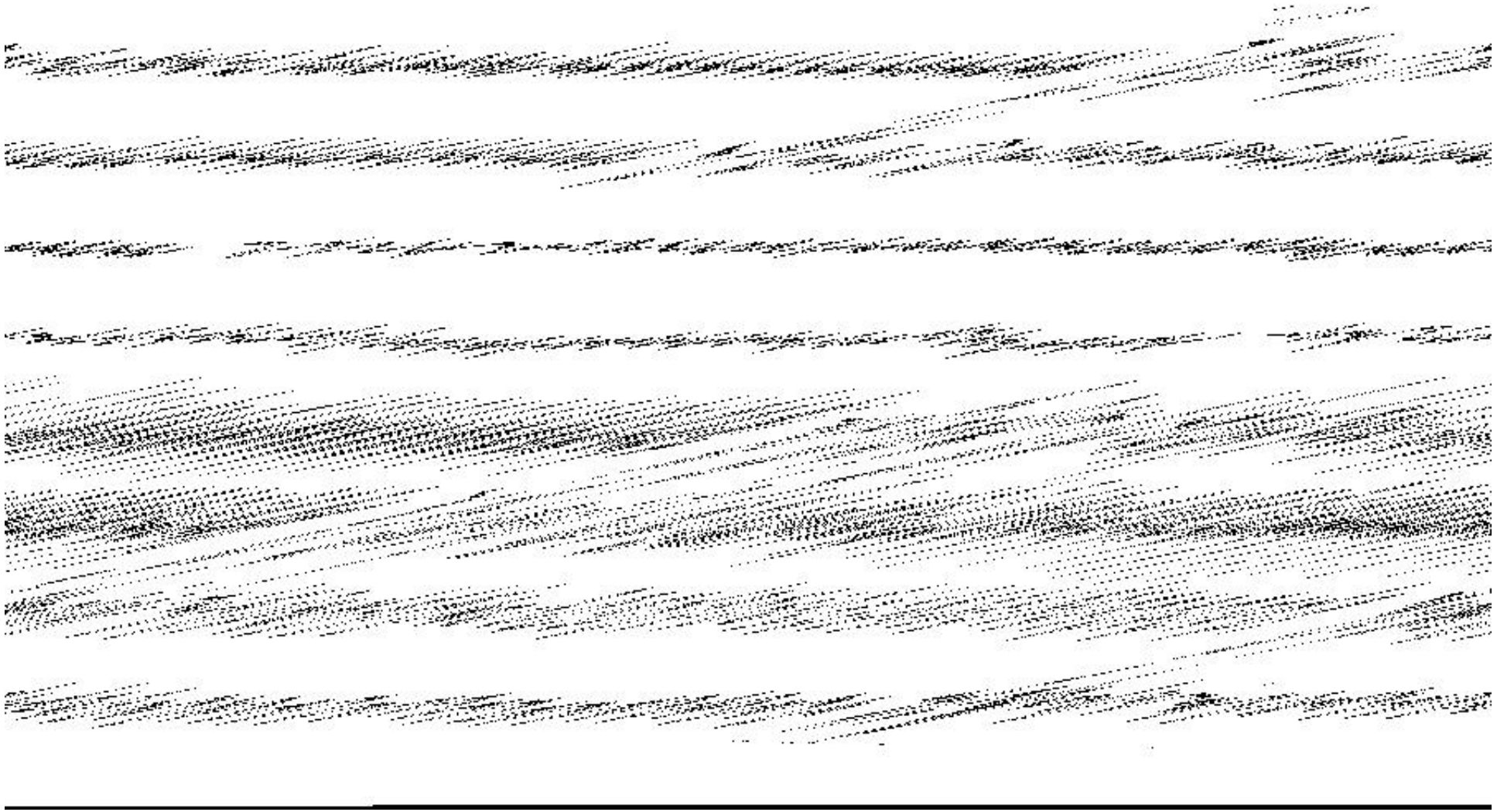

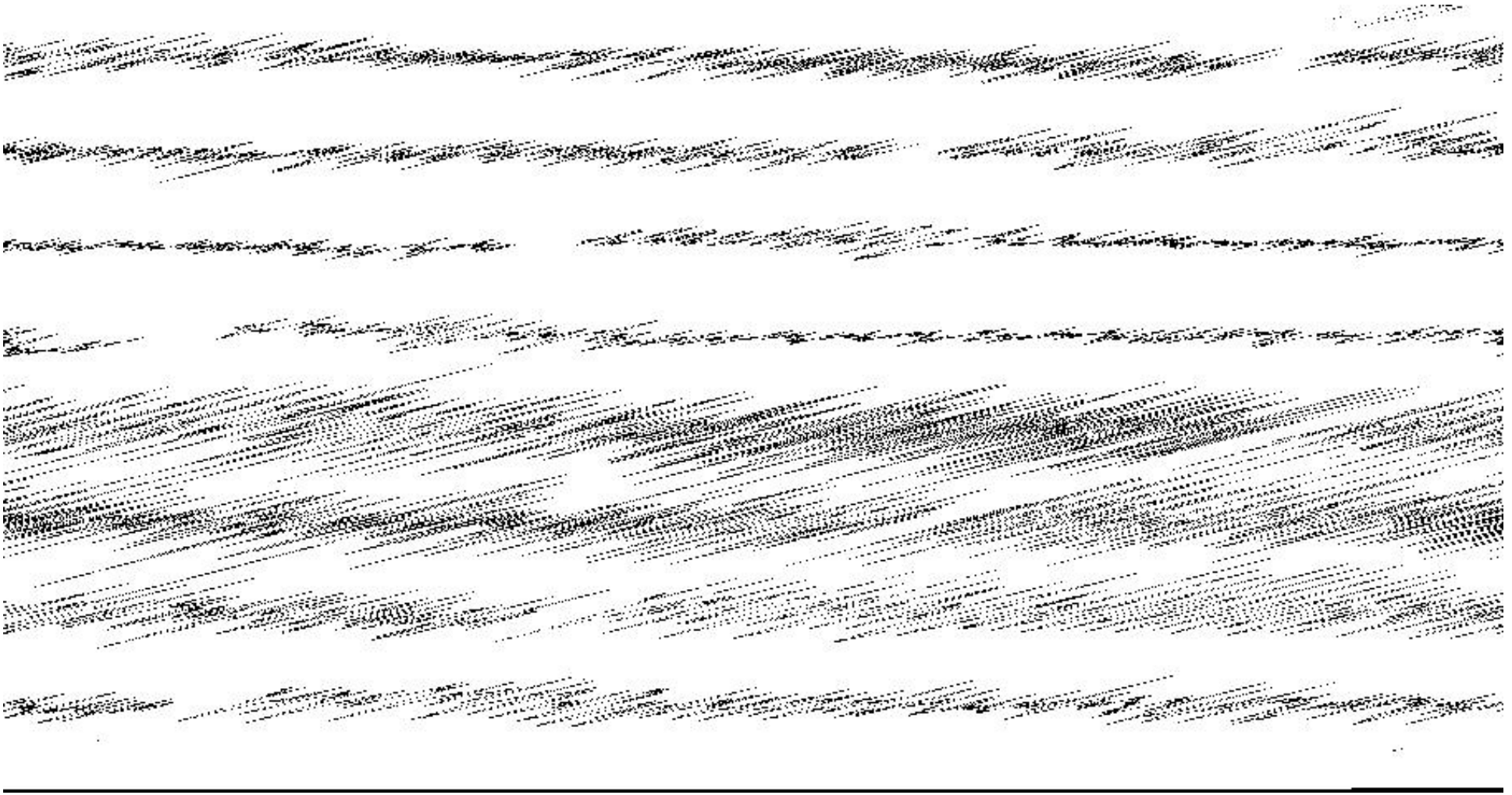

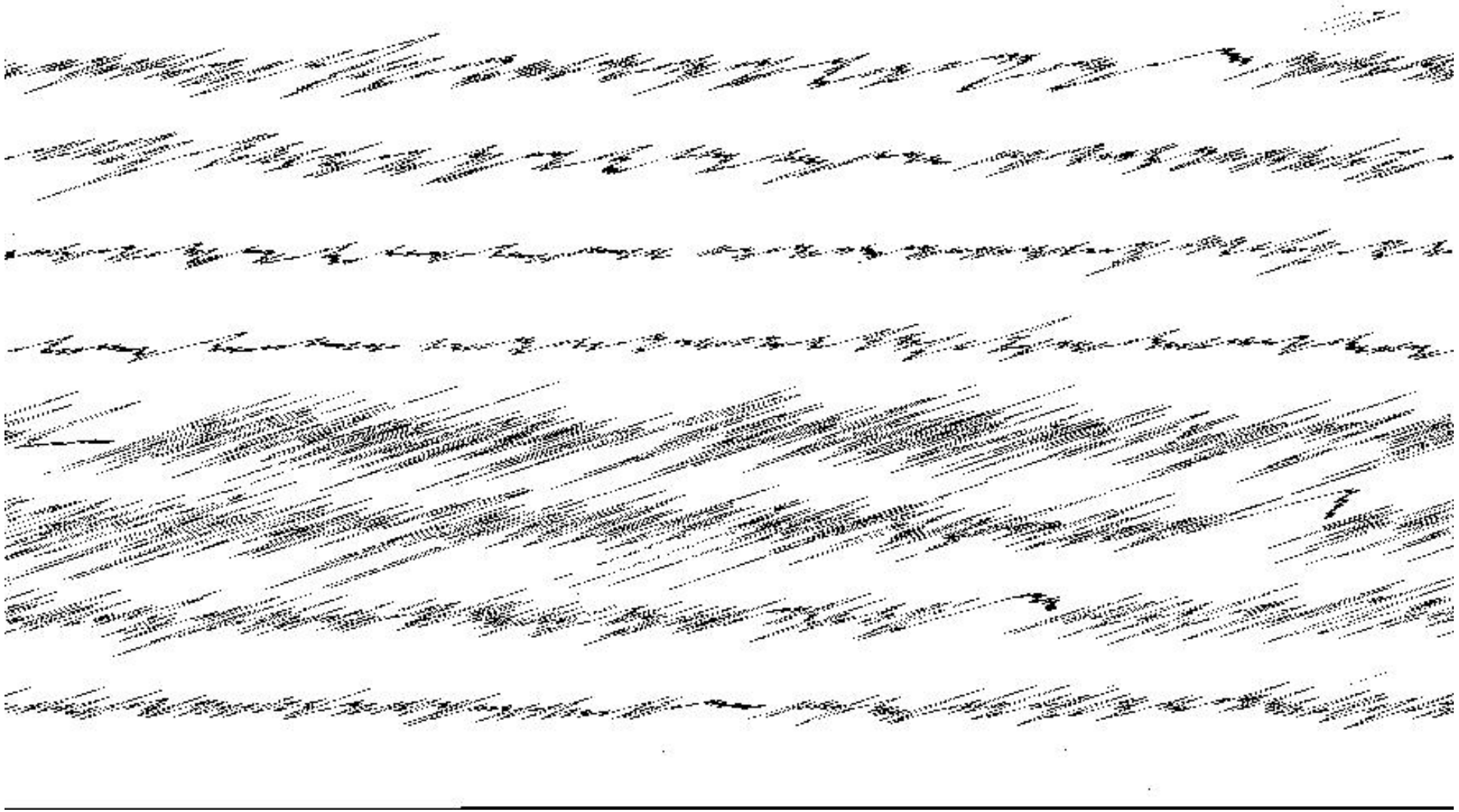

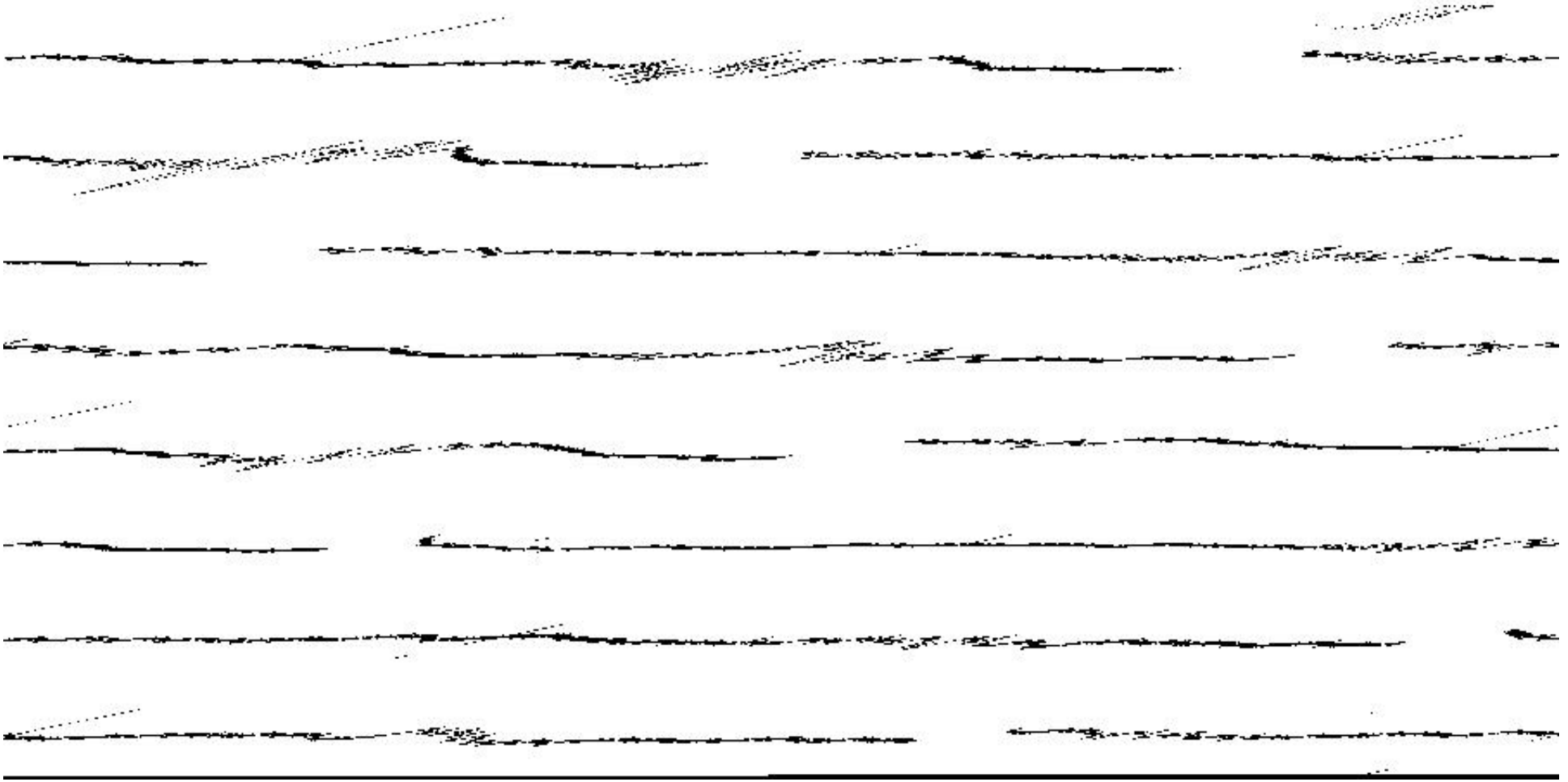

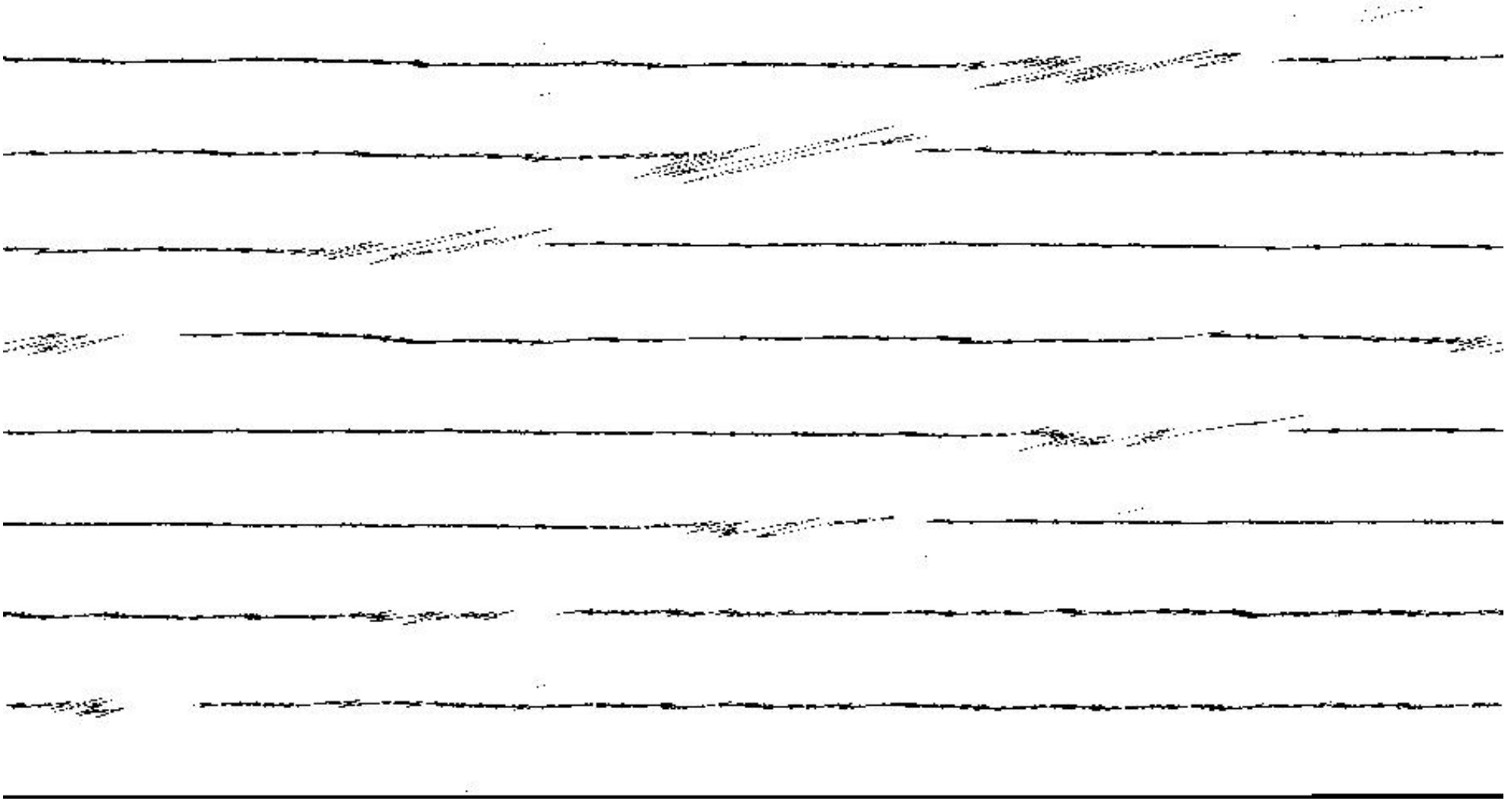

Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus

- Retrospective review of 40 patients with RSE treated with pentobarbital
- 5 died during treatment
- survival correlated best with the etiology of SE

Krishnamurthy and Drislane Epilepsia 1999;40:759-762

Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus

EEG pattern	Slow	S-B	Flat
N	3	12	20
SE duration	6h	16h	14h
PB duration	26h	72h	14h
survival	3 (100%)	3 (25%)	12 (60%)

median durations

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doi:10.1093/brain/aws091 Brain 2012: Page 1 of 15 | 1

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy

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In a previous paper, we reviewed the range of therapies available for the treatment of super-refractory status epilepticus. Here we report a review of the outcome of therapies in refractory and super-refractory status epilepticus. Patients ($n = 1168$) are reported who had therapy with: thiopental, pentobarbital, midazolam, propofol, ketamine, inhalational anaesthetics (isoflurane, desflurane), antiepileptic drugs (topiramate, lacosamide, pregabalin, levetiracetam), hypothermia, magnesium, pyridoxine, immunotherapy, ketogenic diet, emergency neurosurgery, electroconvulsive therapy, cerebrospinal fluid drainage, vagal nerve stimulation and deep brain stimulation. The outcome parameters reported include control of status epilepticus, relapse on withdrawal, breakthrough seizures and mortality. Where reported (596 cases), the long-term outcome was found to be death (35%), severe neurological deficit (13%), mild neurological deficit (13%), undefined deficit (4%) and recovery to baseline (35%). The quality of reported outcome data is generally poor and the number of cases reported for all non-anaesthetic therapies is low. Outcome assessment is complicated by changes in co-medication, delay in response and publication bias. Given these deficits, only broad recommendations can be made regarding optimal therapy. An approach to therapy, divided into first-line, second-line and third-line therapy, is suggested on the basis of this outcome evaluation. The importance of treatments directed at the cause of the status epilepticus, and of supportive ITU care is also emphasized.

Therapy	Number of published papers reporting outcome data	Number of published cases in which outcome data are provided
Pentobarbital/thiopental	23	192
Propofol	24	143
Midazolam	20	585
Ketamine	7	17
Inhalational anaesthetics	7	27
Hypothermia	4	9
Magnesium	2	3
Pyridoxine	2	2
Immunotherapy	8	21
Ketogenic diet	4	14
Vagal nerve stimulation	4	4
Deep brain stimulation	1	1
ECT	6	8
Emergency neurosurgery	15	36
CSF drainage	1	2
Topiramate	10	60
Levetiracetam	8	35
Pregabalin	1	2
Lacosamide	2	10

Outcome	Thiopental/pentobarbital (*n* = 192)	Midazolam (*n* = 585)	Propofol (*n* = 143)
Control	64% (123/192)	78% (458/585)	68% (97/143)
No control ever achieved[a]	5% (9/192)	16% (93/585)	11% (16/143)
Breakthrough seizures	0% (0/192)	3% (19/585)	1% (2/143)
Withdrawal seizures	9% (18/192)	<1% (2/585)	6% (8/143)
Therapy failure because of side-effects	3% (5/192)	<1% (1/585)	6% (8/143)
Death during therapy	19% (37/192)	2% (12/585)	8% (12/143)

Table 3 Long-term outcome

Outcome[a]	*n* = 596
Deaths	207 (35%)
Severe neurological deficit	79 (13%)
Mild neurological deficit	80 (13%)
Undefined neurological deficit	22 (4%)
Recovery to baseline	208 (35%)

[a]In the reports of 596 cases (51% of the total of 1168), the long-term outcome was recorded. In the other 575 cases, no long-term outcome data were provided.

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