

VALORACIÓ DEL PRONÒSTIC NEUROLÒGIC: BIOMARCADORS, PROVES COMPLEMENTÀRIES

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IV JORNADA D'ACTUALITZACIÓ

GRUP D'UNITATS DE CURES AGUDES CARDIOLÒGIQUES

Divendres, 22 de novembre



Bellvitge
Hospital

 Institut Català
de la Salut

PROTOCOL D'ACTUACIÓ EN PACIENTS EN COMA POST ATURADA CARDIORESPIRATÒTIA

De l'Hospital Universitari de Bellvitge
Març 2019



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FISIOPATOLOGIA DEL COMA ANÓXICO

Metabolismo anaerobio en el cerebro no supe la necesidades metabólicas a diferencia de otros otros tejidos: **5-10 s: pérdida de consciencia**

Se lesionan en el episodio agudo primero las áreas de vulnerabilidad neuronal selectiva:
sector CA-1 del hipocampo

Tálamo

Neocórtex

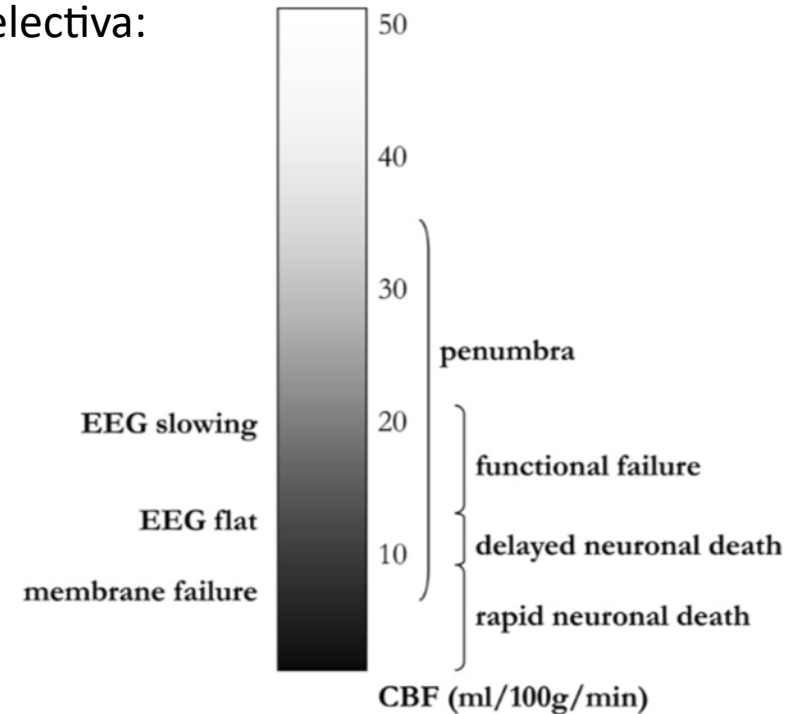
Células de Purkinje

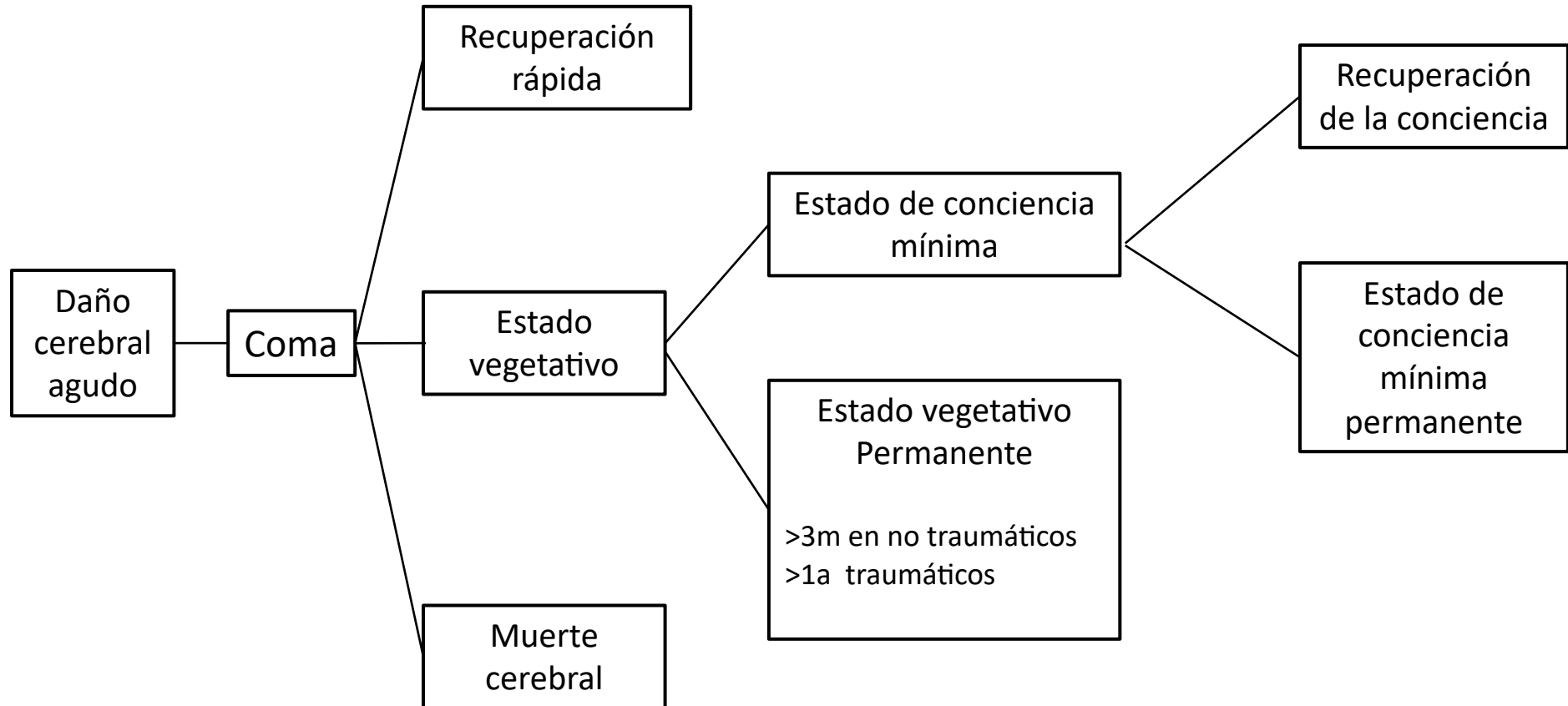
Estas áreas son más vulnerables por:

La presencia de receptores para neurotransmisores excitatorios

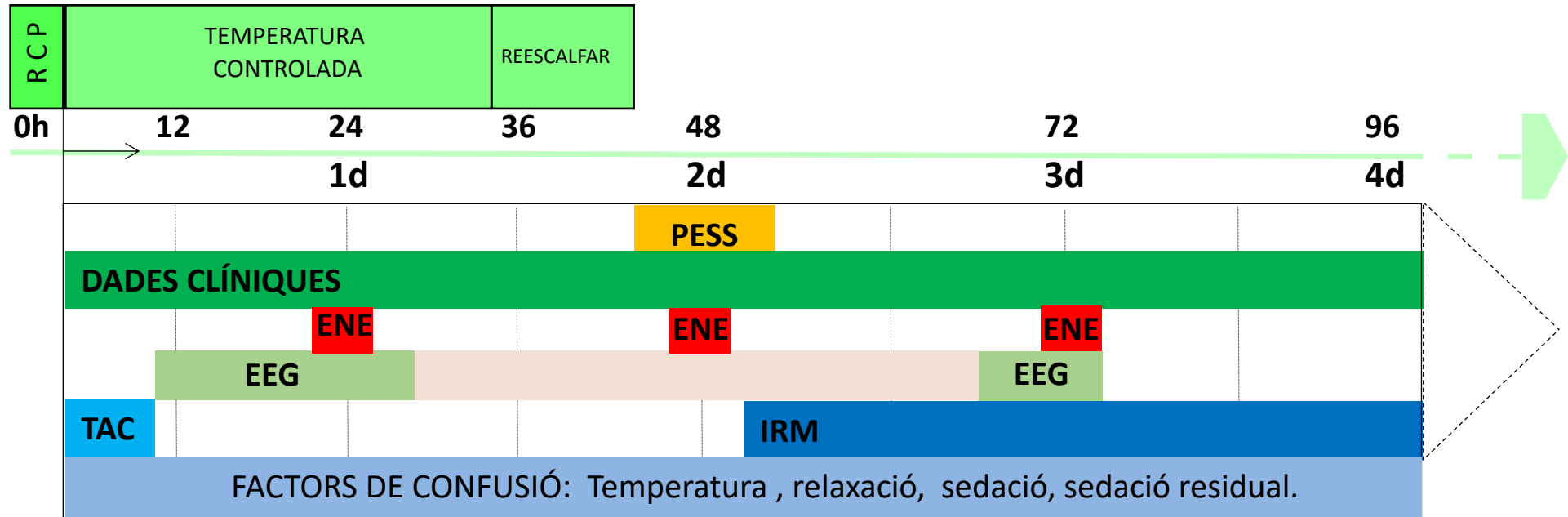
ó

Altas demandas metabólicas de oxígeno de estas neuronas





APROXIMACIÓ MULTIMODAL AL PRONÒSTIC DEL COMA ANÒXIC



DADES DE BON PRONÒSTIC:

EEG continu a les 12h
EEG reactiu
MMN present

DADES DE MAL PRONÒSTIC (sempre aproximació multimodal)

N20 absent bilateral als PESS

Absència de reflexes corneals i pupil·lars a les 72h

EEG S-S amb salves idèntiques. Passades 24h Supressió $<10 \mu\text{V}$ o S-S arreactiva.

ENE $> 79 \mu\text{g/L}$ a les 72h

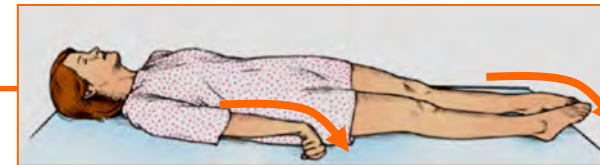
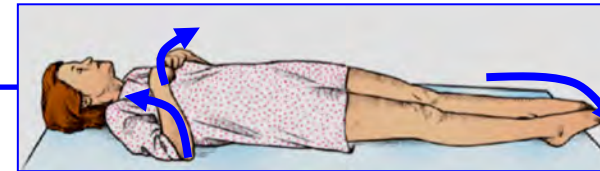
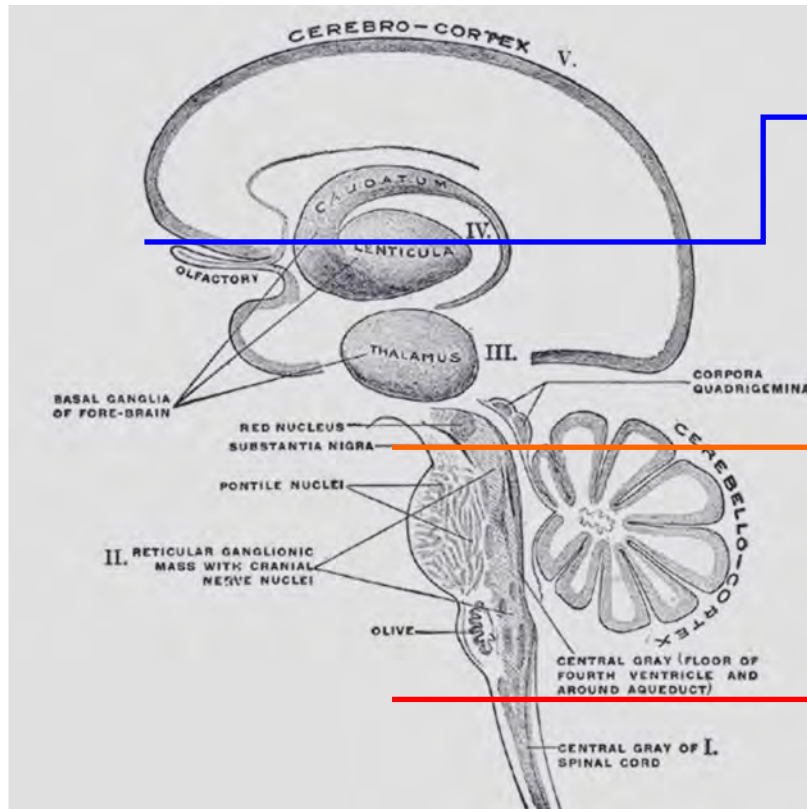
Estat mioclònic postanòxic que persisteix a les 72h amb tx correcta i amb EEG no reactiu i diferent de puntes a la línia mitja.

Tac inicial amb severa lesió anòxica difusa.

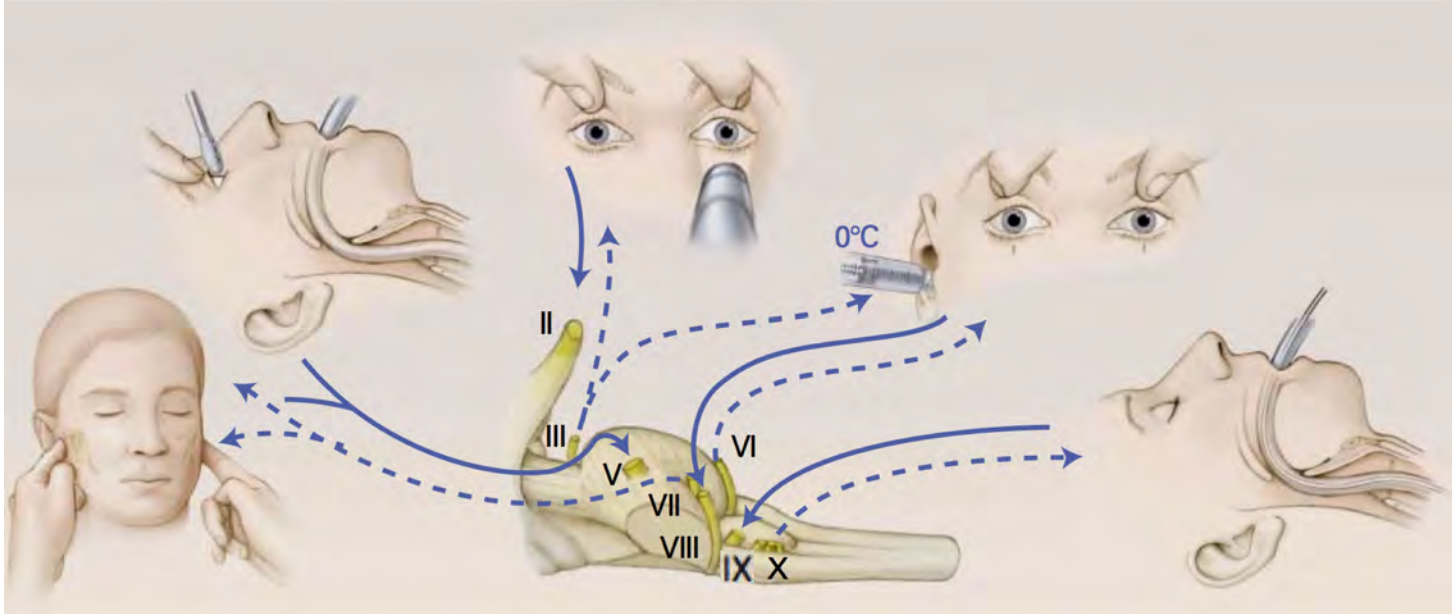
IRM amb severa lesió anòxica difusa.

Exploración clínica:

- Posturas o movimientos de **decorticación** o de **descerebración**

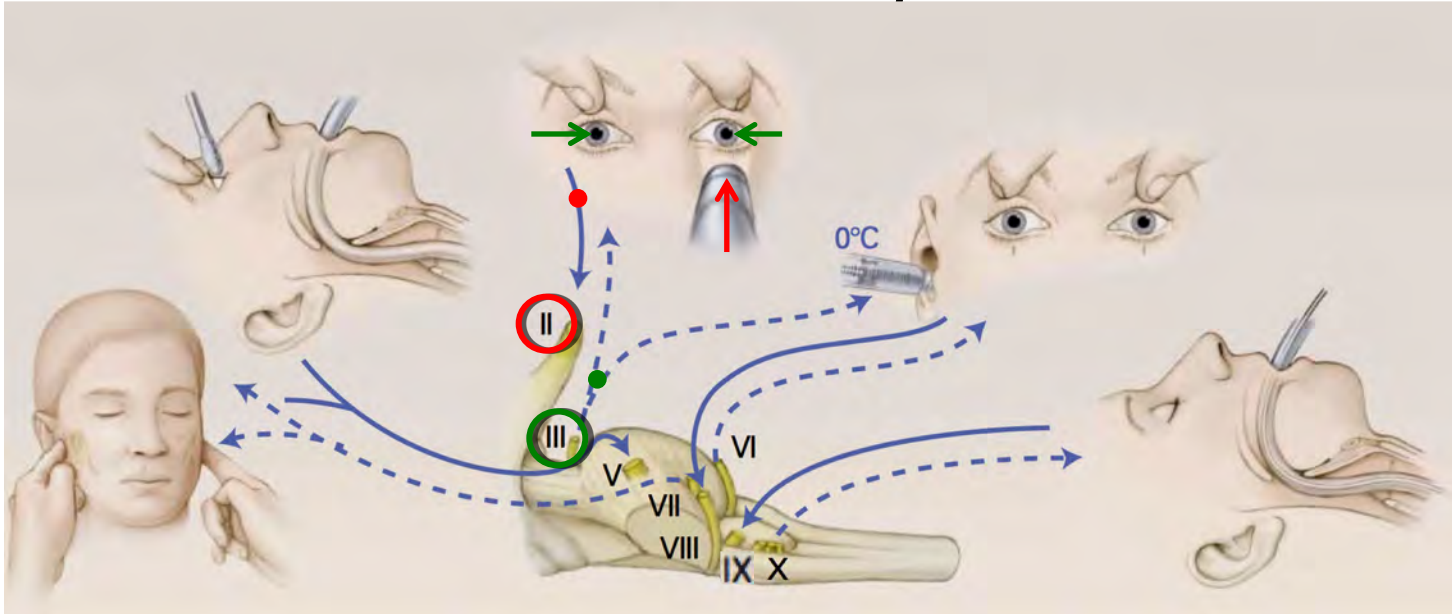


Exploración clínica: Reflejos de tronco



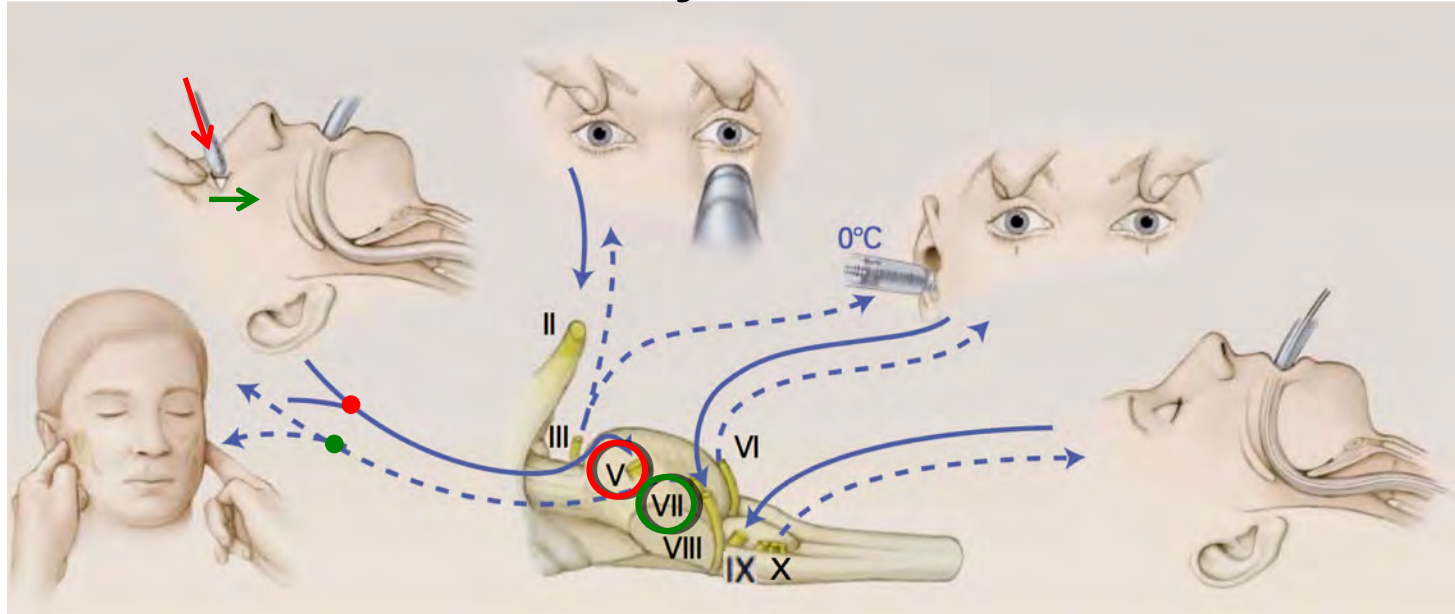
- Respuesta al dolor
- Reflejos corneales
- Reflejos fotomotores
- Reflejo oculovestibular
- Reflejo tusígeno

Exploración clínica: Reflejos



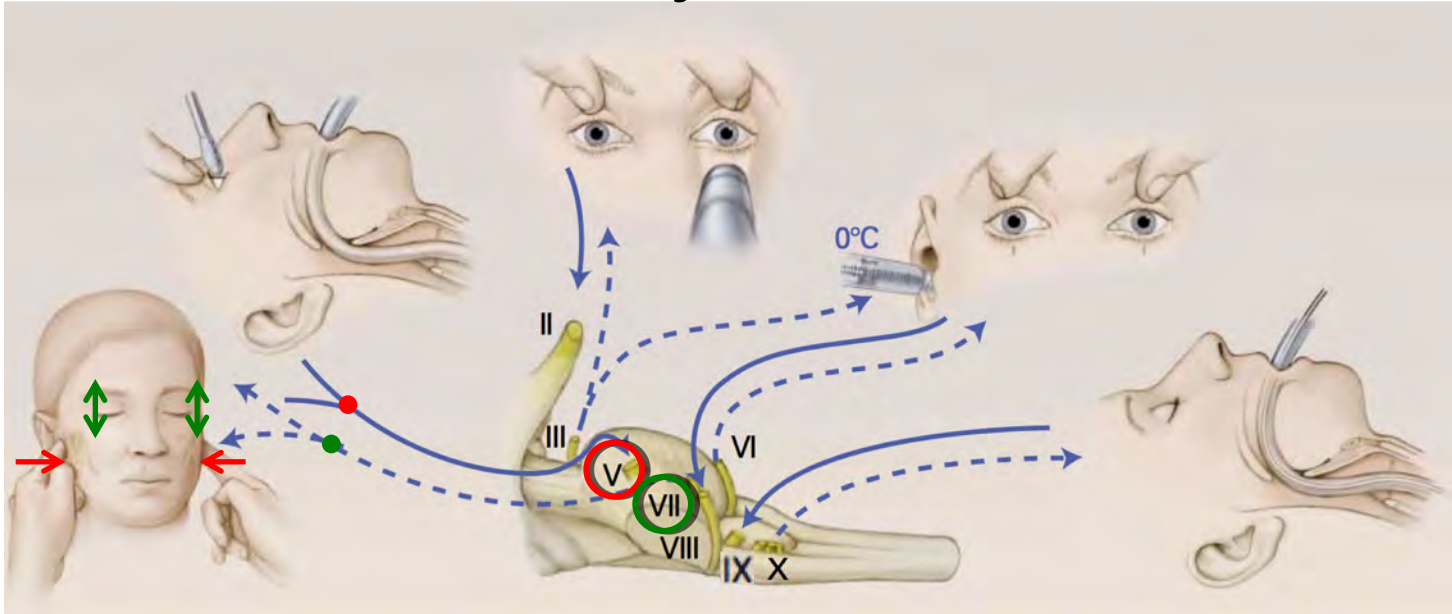
- Respuesta al dolor
 - Reflejos corneales
 - Reflejos fotomotores
 - Reflejo oculovestibular
 - Reflejo tusígeno
- Iluminación pupila
 - Miosis ipsilateral y consensuada
 - Aferencia II (visual)
 - Eferencia III (motor ocular común)

Exploración clínica: Reflejos de tronco



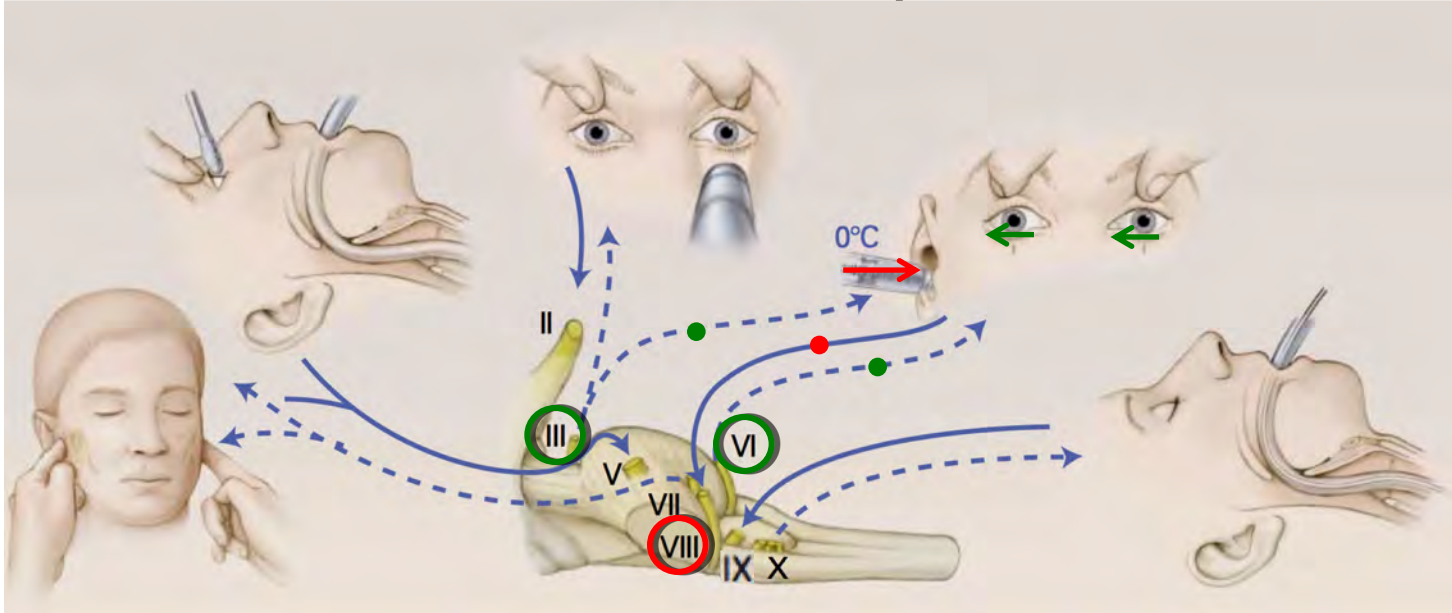
- Respuesta al dolor
 - Reflejos corneales
 - Reflejos fotomotores
 - Reflejo oculovestibular
 - Reflejo tusígeno
- Estímulo táctil corneal
 - Parpadeo/cierre ocular
 - Aferencia V (trigémino)
 - Eferencia VII (facial)

Exploración clínica: Reflejos de tronco



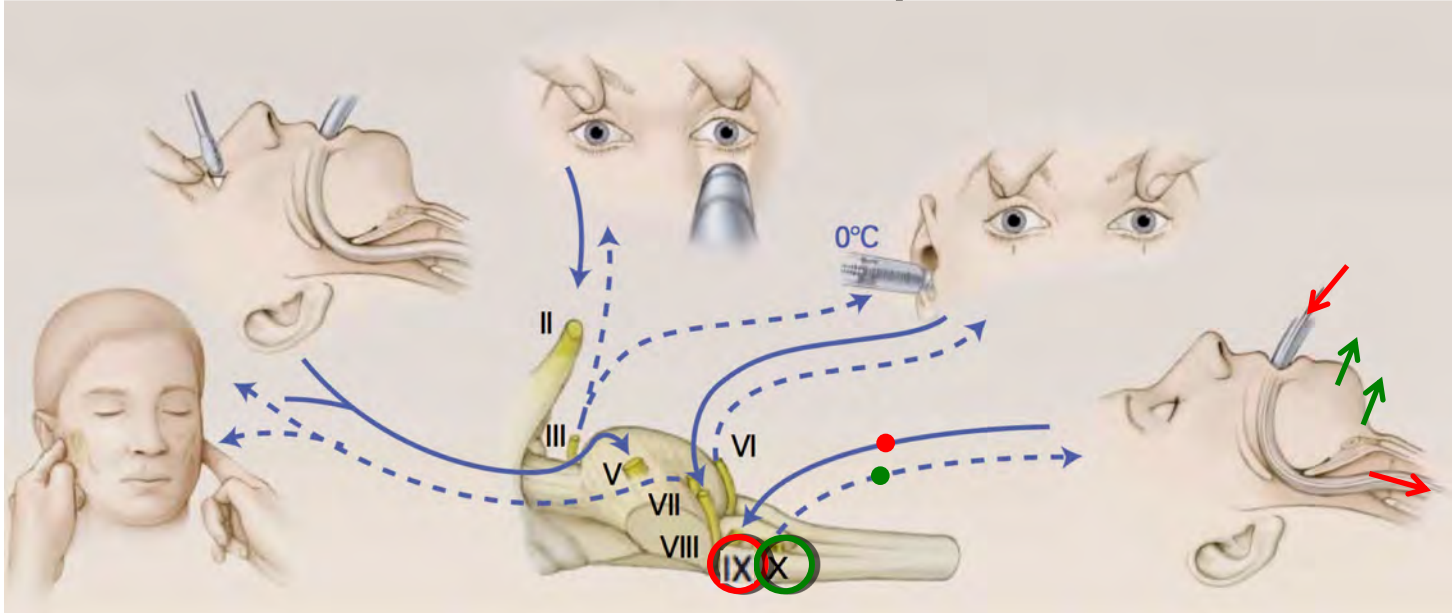
- Respuesta al dolor
 - Reflejos corneales
 - Reflejos fotomotores
 - Reflejo oculovestibular
 - Reflejo tusígeno
- Presión profunda cóndilo articulación temporomandibular
 - Mueca o apertura ocular
 - Aferencia V (trigémino)
 - Eferencia VII (facial)

Exploración clínica: Reflejos



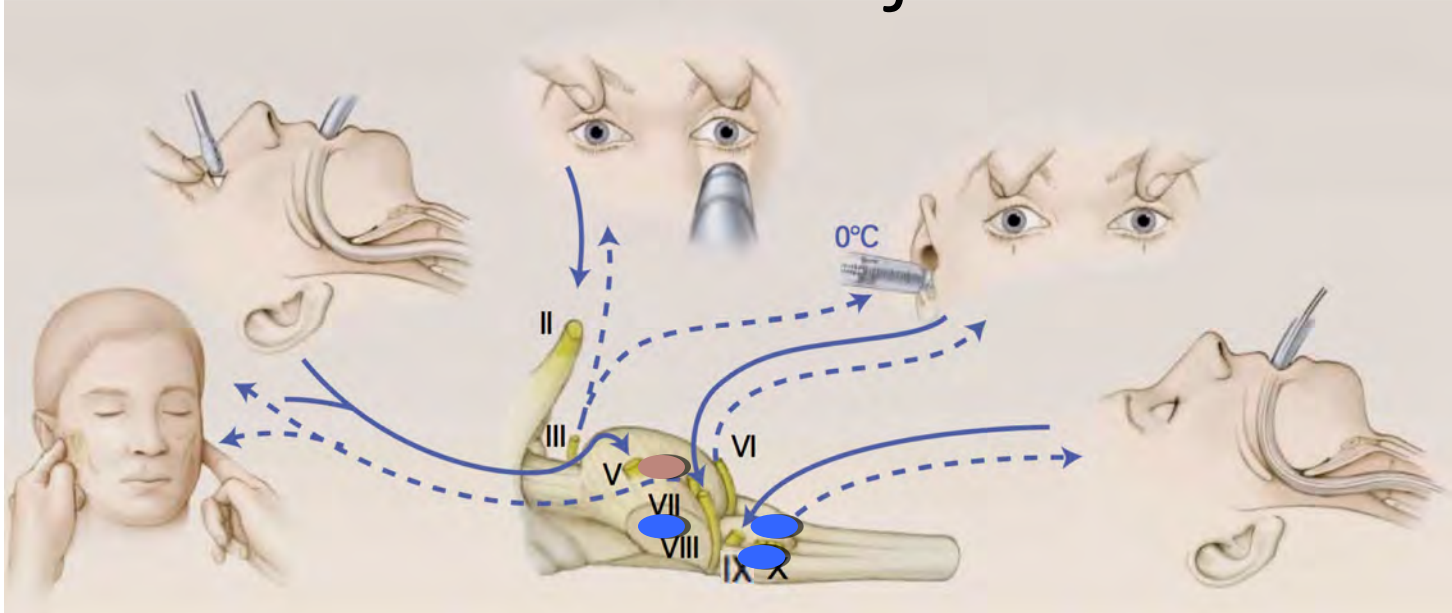
- Respuesta al dolor
 - Reflejos corneales
 - Reflejos fotomotores
 - Reflejo oculovestibular
 - Reflejo tusígeno
- Irrigación fría tímpano
 - Nistagmus / desviación mirada
 - Aferencia VIII (estatoacústico)
 - Eferencia III y VI

Exploración clínica: Reflejos



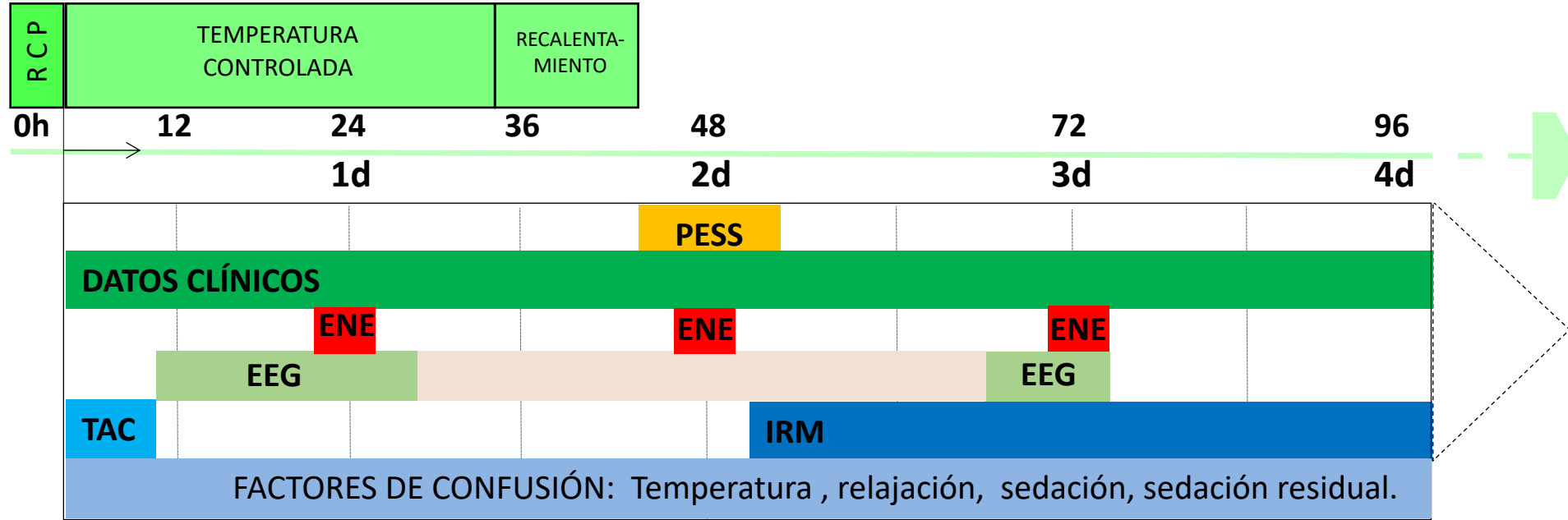
- Respuesta al dolor
 - Reflejos corneales
 - Reflejos fotomotores
 - Reflejo oculovestibular
 - Reflejo tusígeno
- Estimulación traqueal
 - Tos
 - Aferencia IX (glossofaríngeo)
 - Eferencia X (vago)

Exploración clínica: Reflejos



- Respuesta al dolor
- Reflejos corneales
- Reflejos fotomotores
- Reflejo oculovestibular
- Reflejo tusígeno
- Centro Respiratorio

APROXIMACIÓN MULTIMODAL AL PRONÓSTICO DEL COMA ANÓXIC



DATOS DE BUEN PRONÓSTICO:

EEG continuo a las 12h
EEG reactivo
MMN present

DATOS DE MAL PRONÓSTICO (siempre aproximación multimodal)

N20 ausente bilateral en los PESS

Ausencia de reflejos corneales y pupilares a las 72h

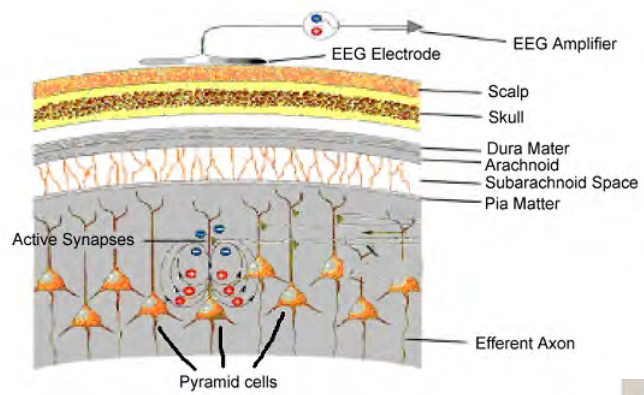
EEG S-S con salvas idénticas. Pasadas 24h Supresión $<10 \mu\text{V}$ o S-S arreactiva.

ENE $> 79 \mu\text{g/L}$ a las 72h

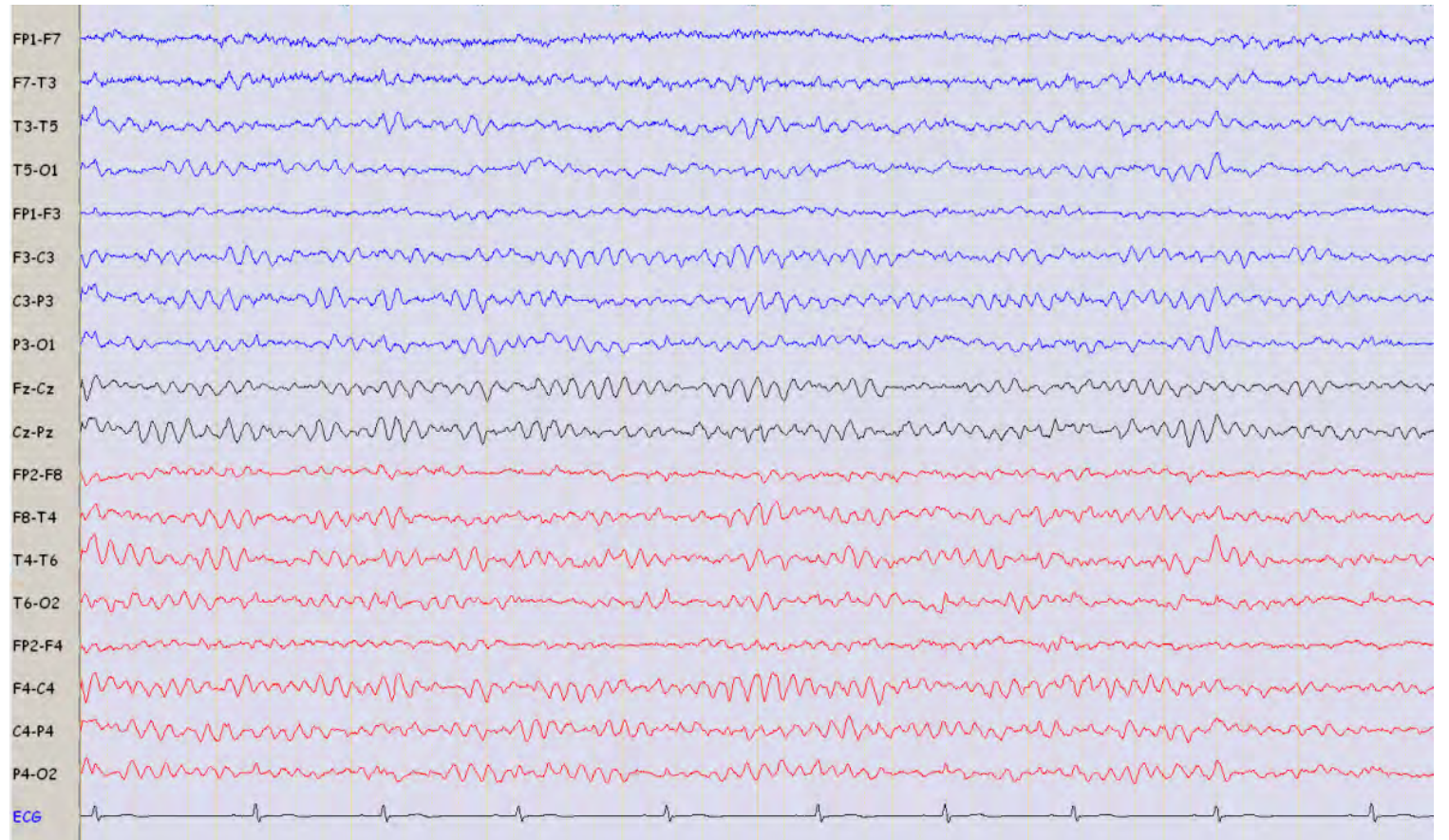
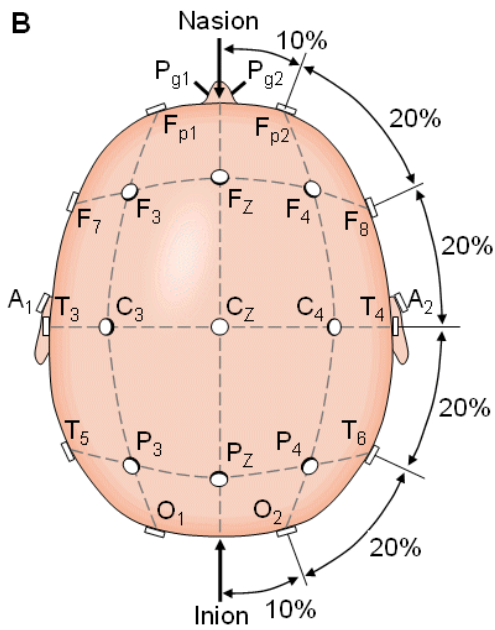
Estatus mioclónico postanóxico que persiste a las 72h con tx correcto y con EEG no reactivo y diferente de puntas en la línea media.

TAC inicial con severa lesión anóxica difusa.

IRM con severa lesión anóxica difusa.

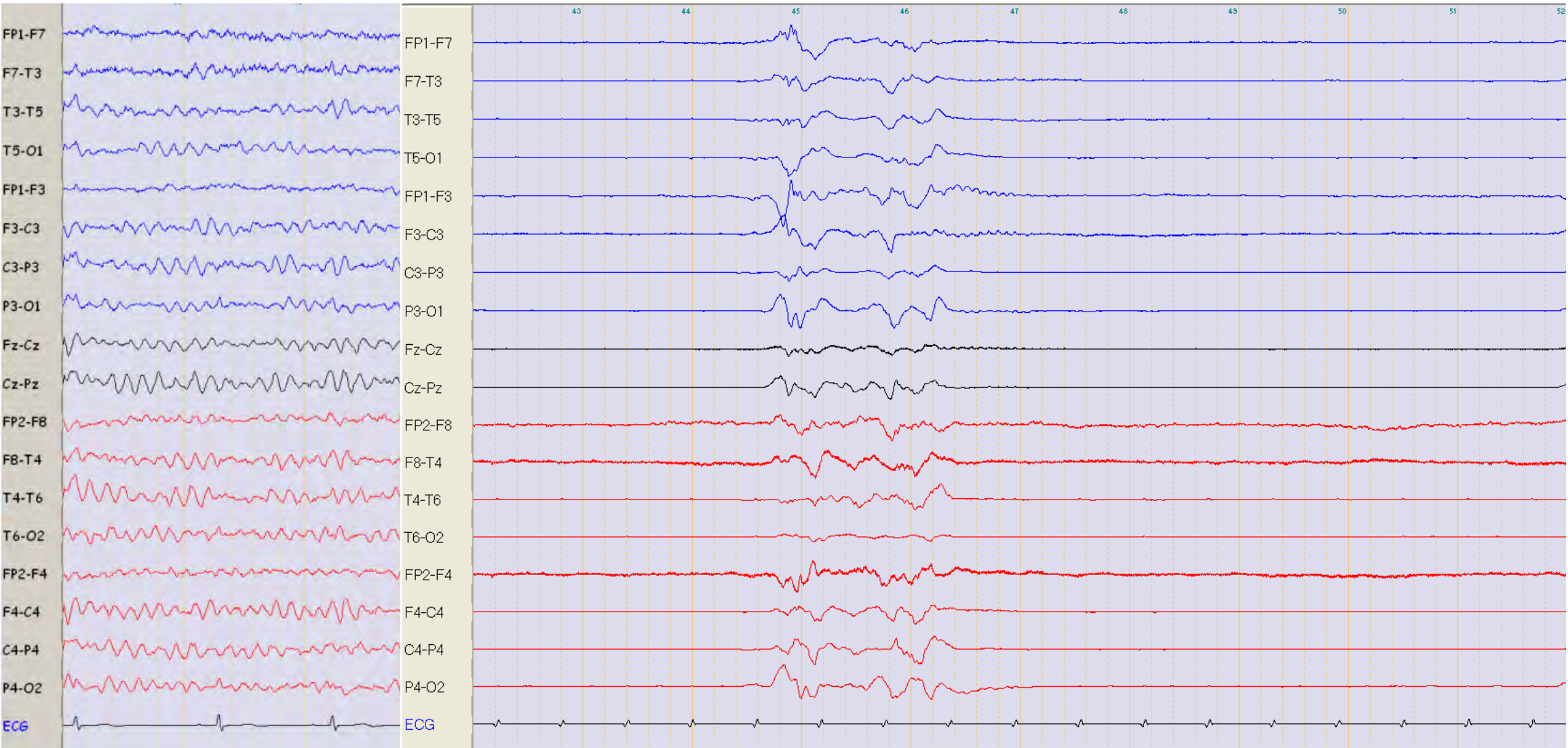


EEG



CONTINUOS

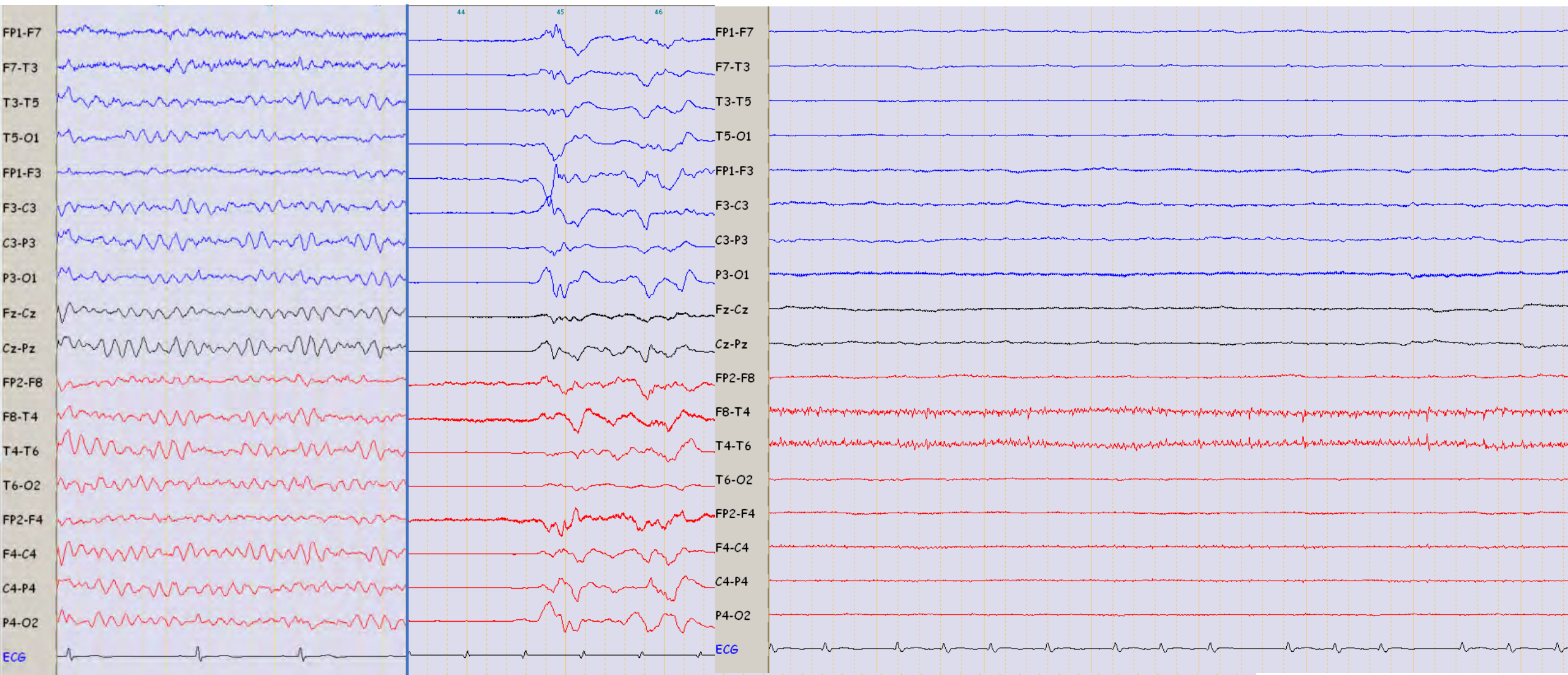
BURST- SUPPRESSION



CONTINUOS

BURST- SUPPRESSION

SUPPRESSION

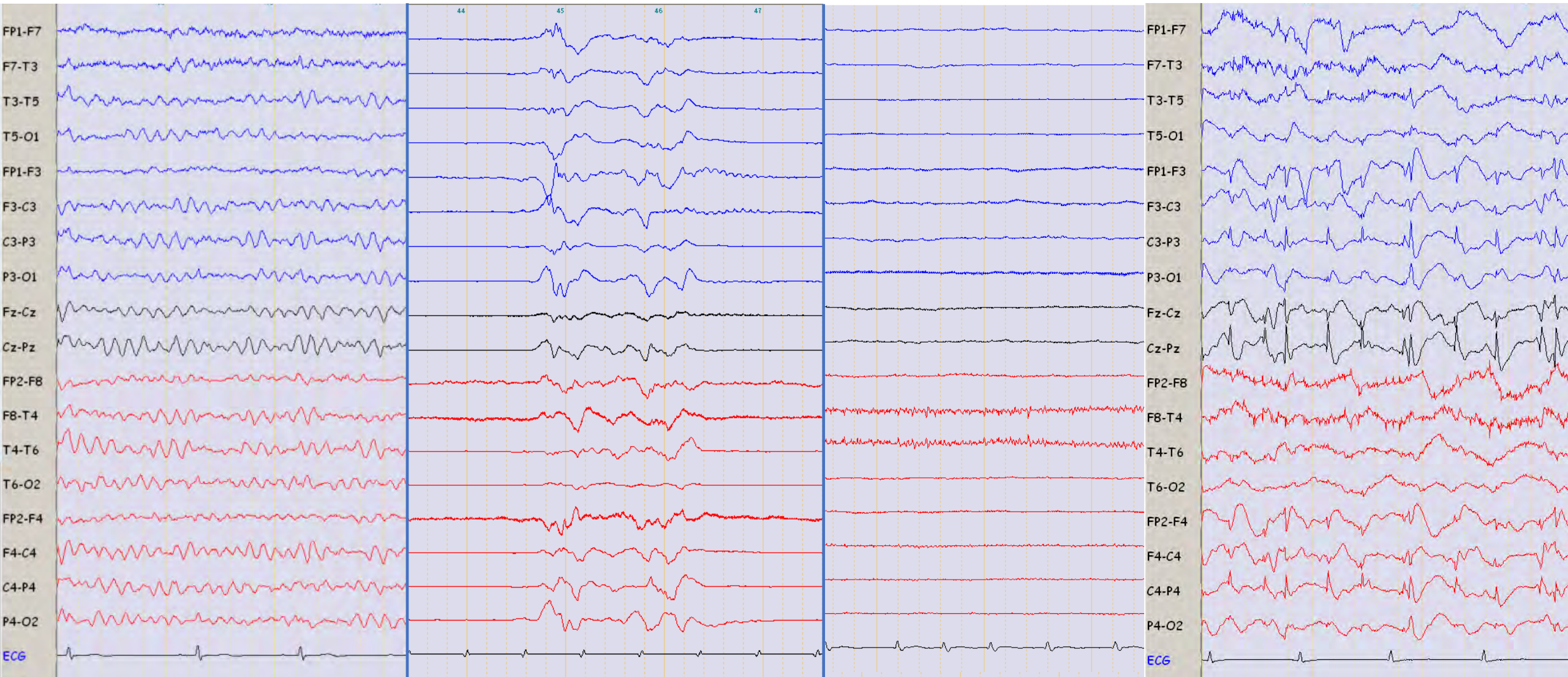


CONTINUOS

BURST- SUPPRESSION

SUPPRESSION

EPILEPTIFORM

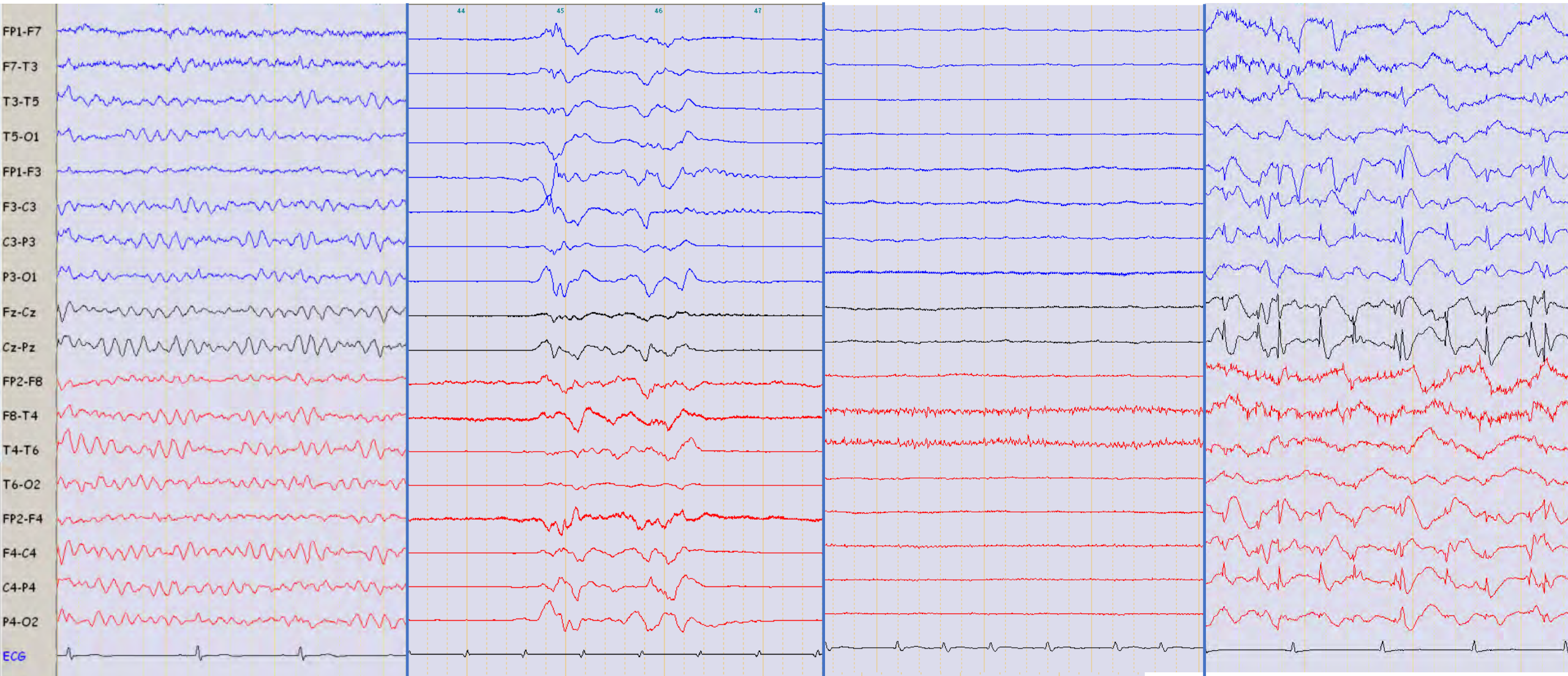


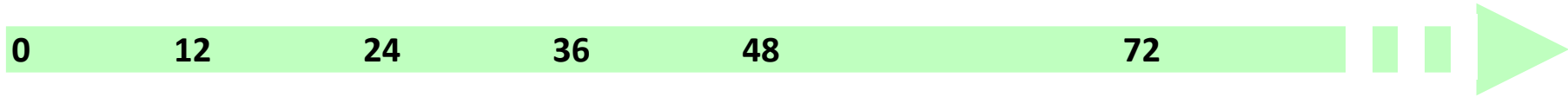
CONTINUOS

BURST- SUPPRESSION

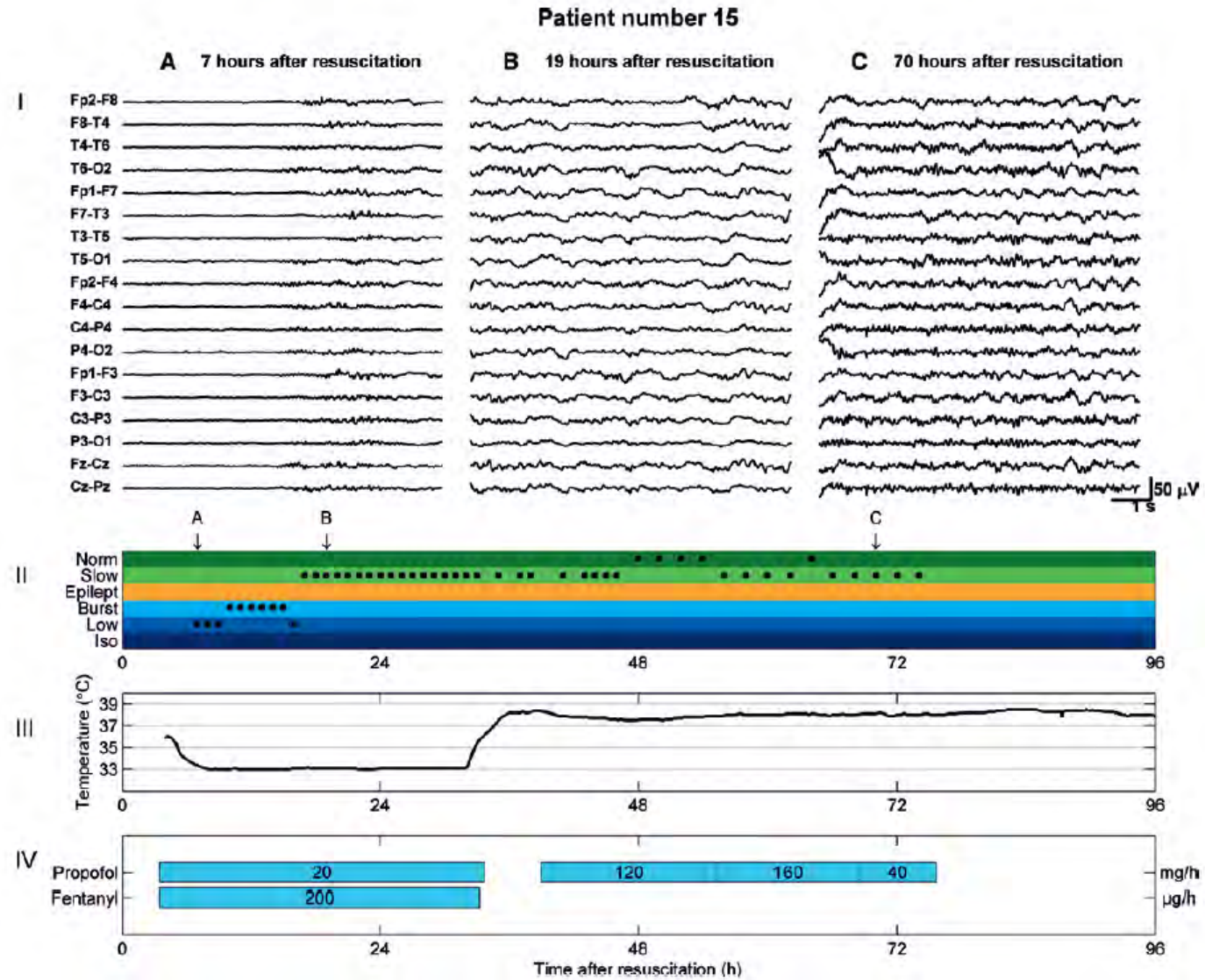
SUPPRESSION

EPILEPTIFORM

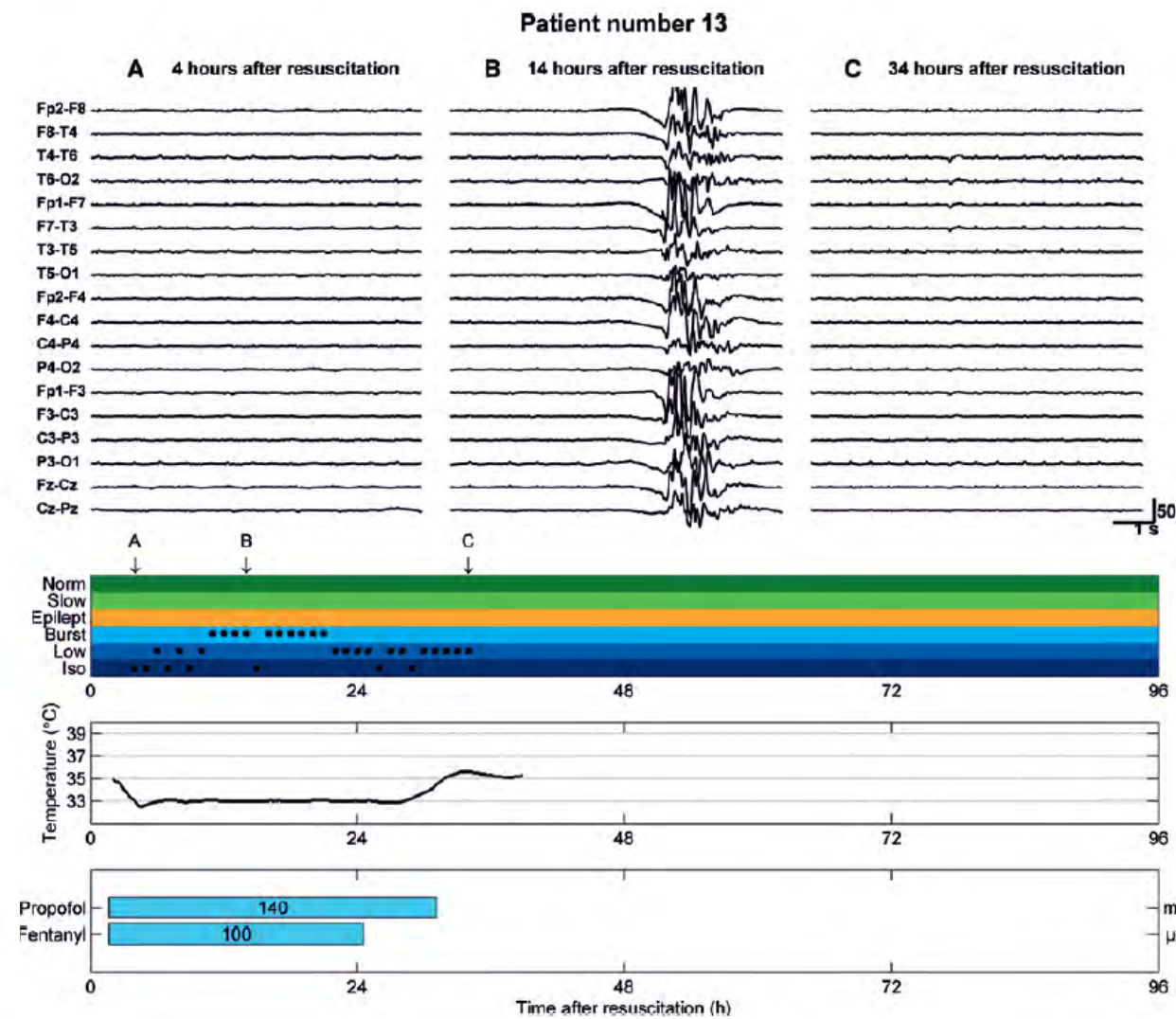
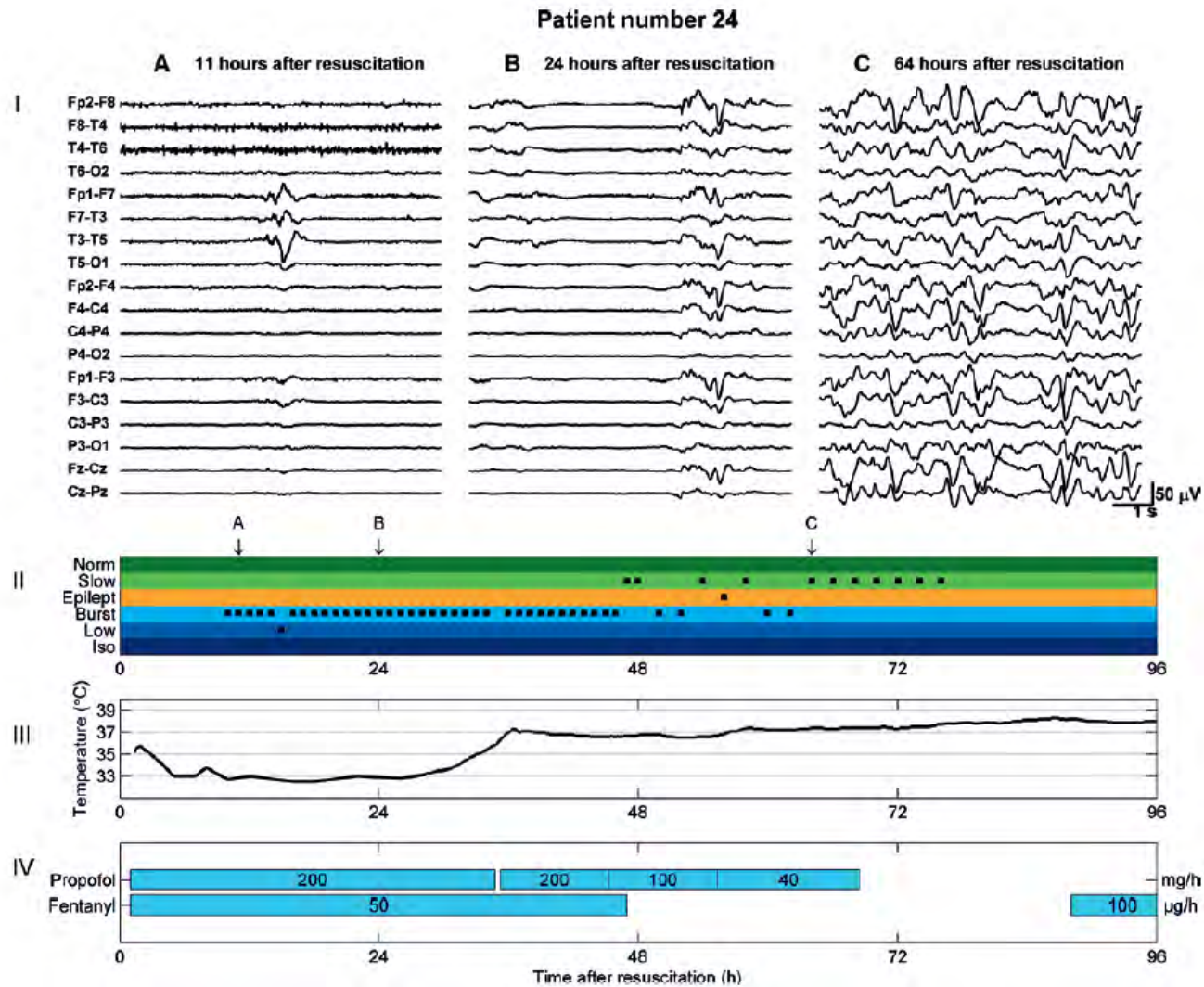


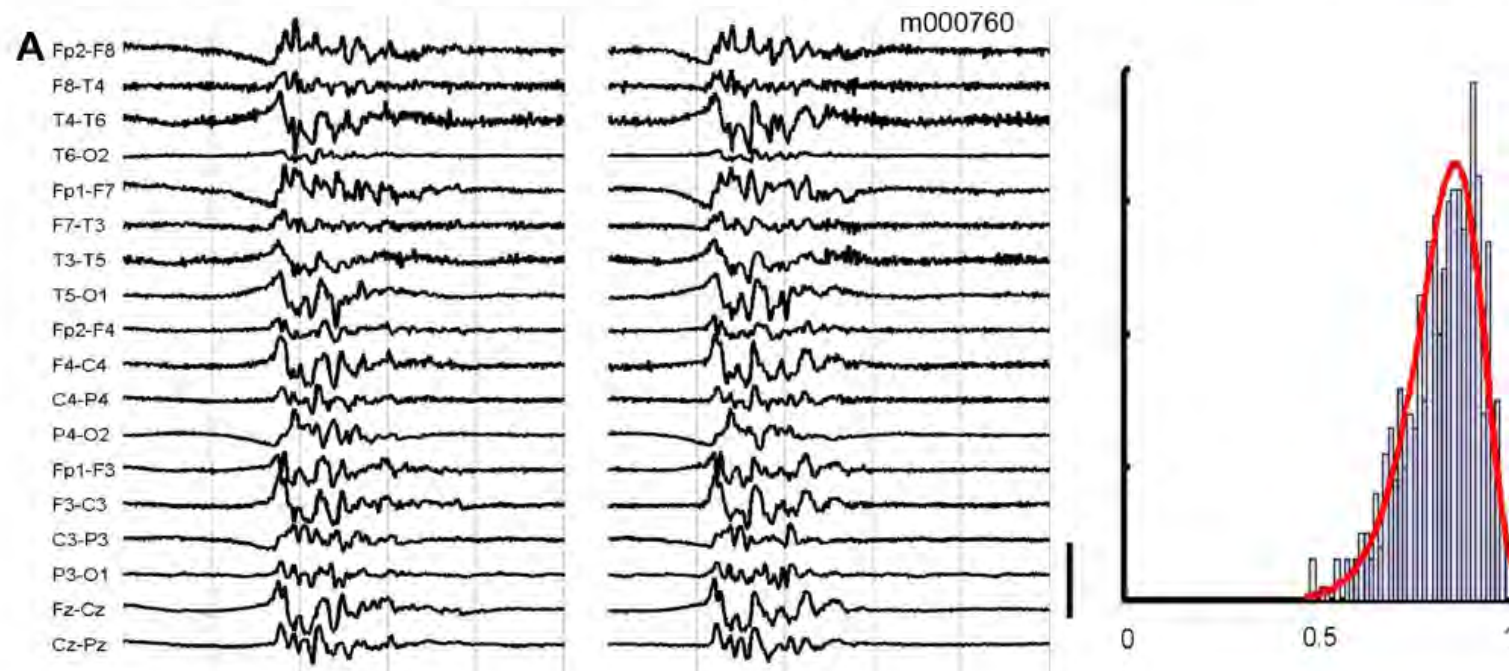
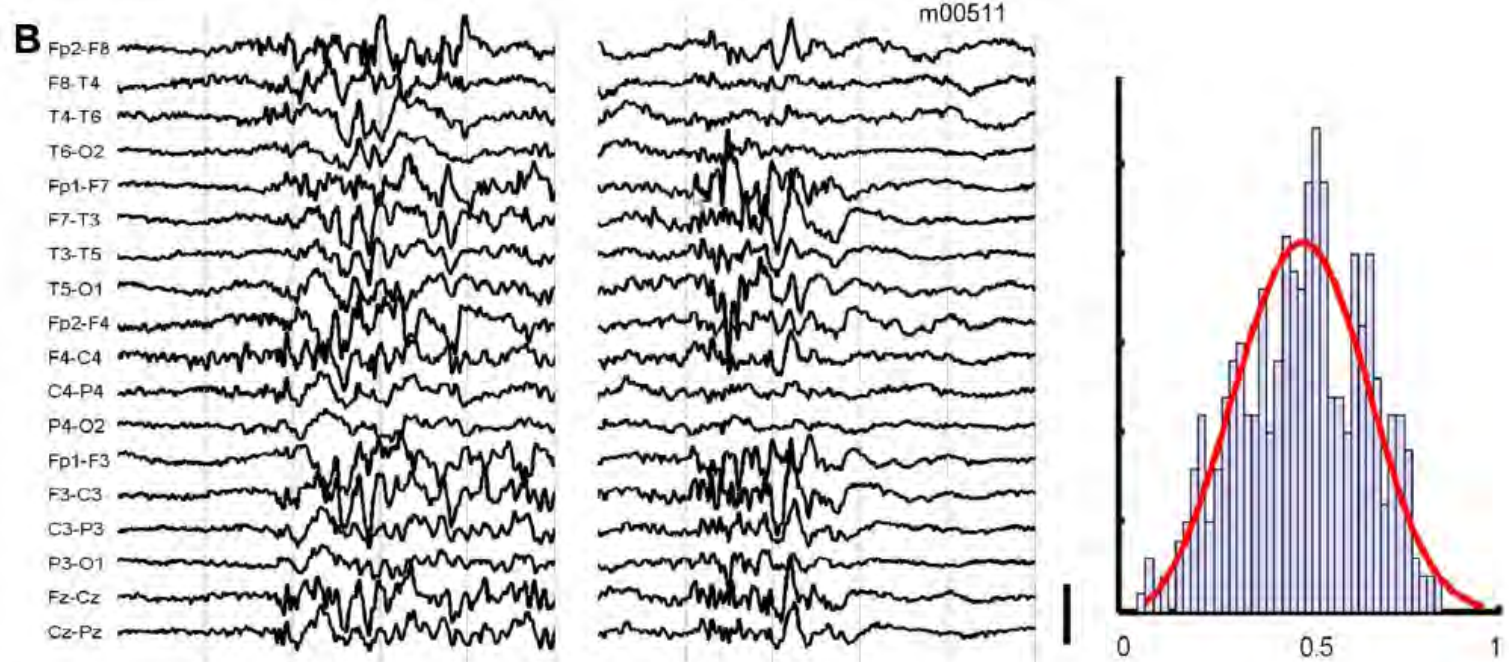


Good neurological outcome



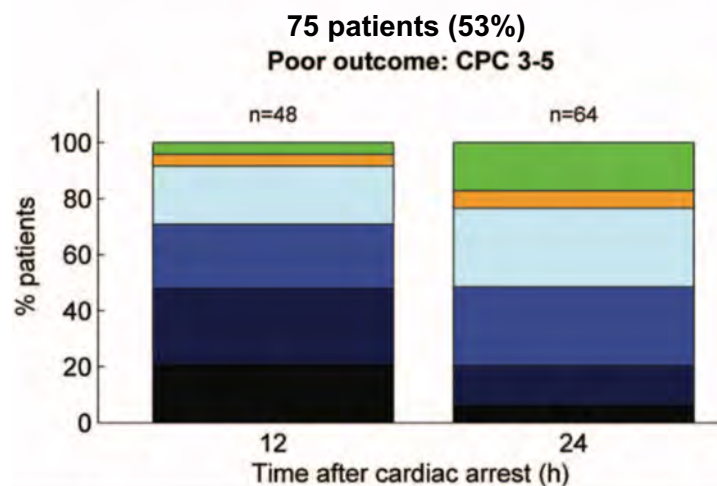
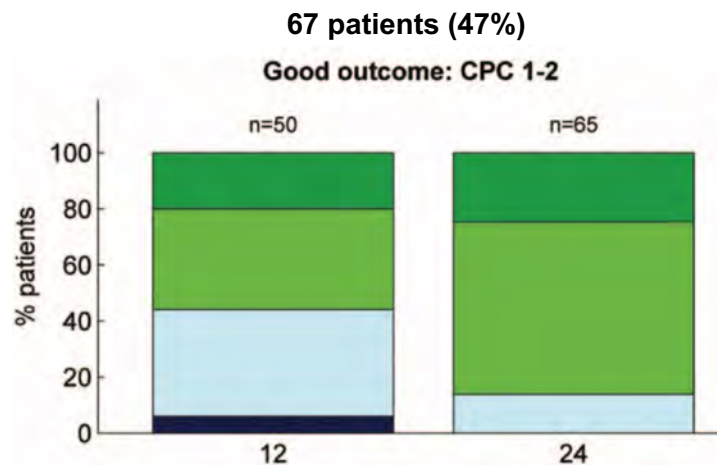
Poor neurological outcome





142 Patients (92 EEG 12h, 129 EEG 24h)

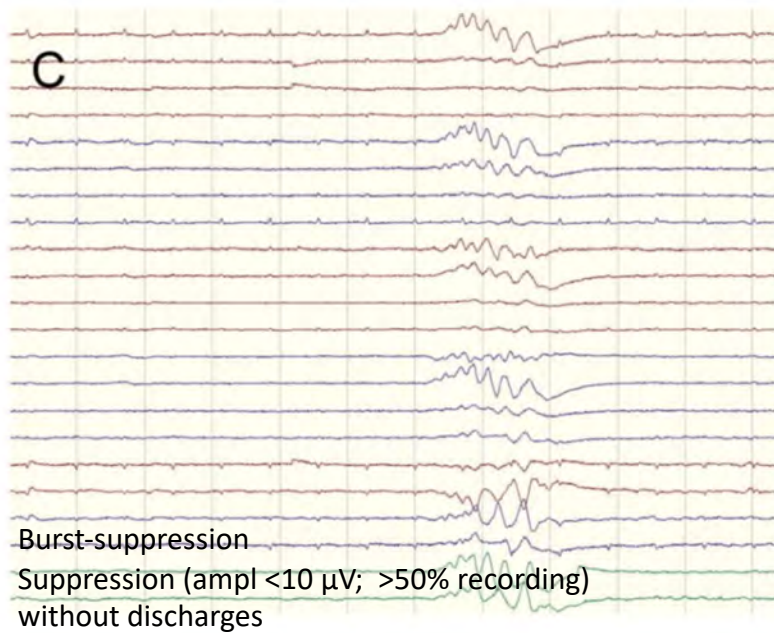
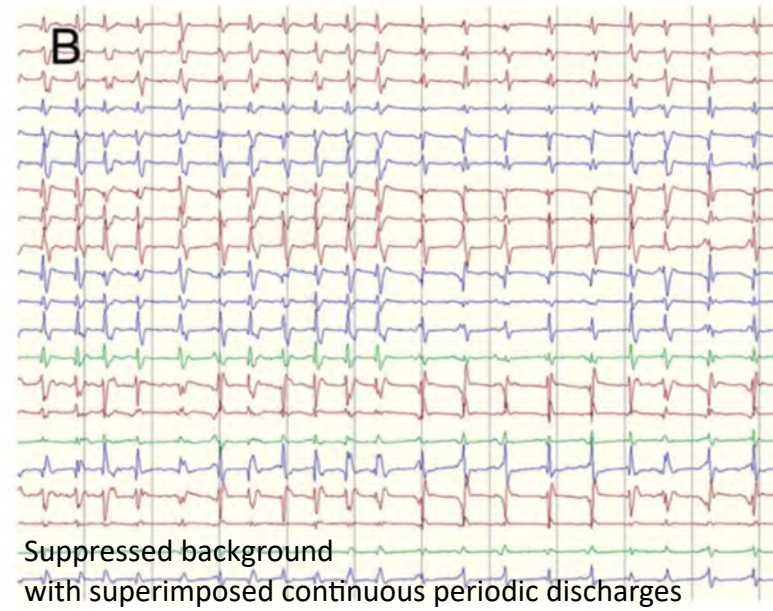
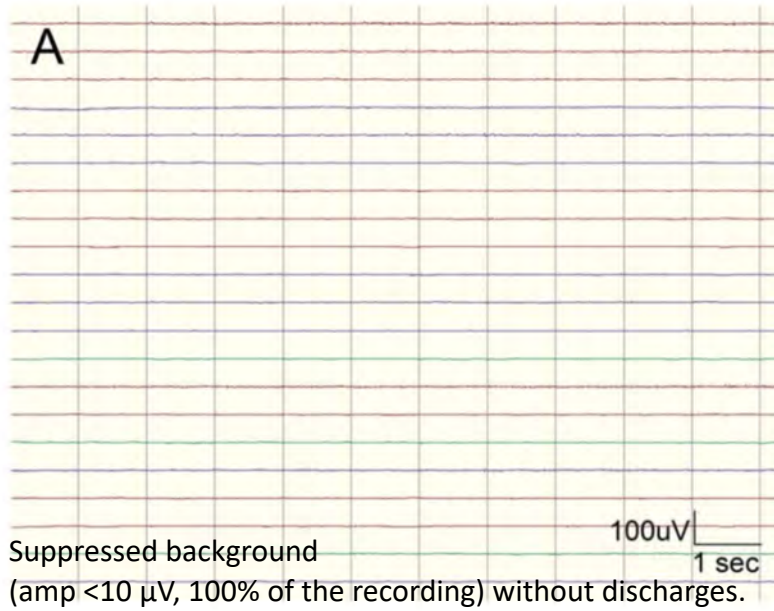
Best score within 6 months after cardiac arrest



- Normal : Dominant frequency $\geq 8\text{Hz}$, regardless reactivity and anterior-posterior differentiation
- Diffusely slowed : Dominant frequency $< 8\text{Hz}$
- Epileptiform : Seizures and GPDs, independent of background activity
- BS non identical : Non identical Bursts $> 20\mu\text{V}$ and $\geq 0,5\text{s}$; interbursts $> 1\text{s}$ and $< 10\mu\text{V}$
- BS identical : Identical Bursts $> 20\mu\text{V}$ and $\geq 0,5\text{s}$; interbursts $> 1\text{s}$ and $< 10\mu\text{V}$
- Low voltage : EEG activity $< 20\mu\text{V}$
- Iso-electric : No visible EEG activity

Variable	Time After Resuscitation (hr)	Predicting	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Electroencephalogram diffuse slowed or normal	12	Good outcome	56 (41-70)	96 (86-100)	93 (78-99)	68 (55-78)
Electroencephalogram isoelectric, low voltage, or burst-suppression with identical bursts	24	Poor outcome	48 (35-61)	100 (94-100)	100 (89-100)	66 (56-76)

Highly malignant EEG patterns



Highly malignant EEG patterns

Suppressed background

(amp <10 μ V, 100% of the recording)
without discharges.

Suppressed background

With **continuous periodic discharges**

Burst-suppression

Suppression (ampl <10 μ V; >50% recording)
without discharges

Burst-suppression with discharges.

Malignant EEG patterns

Periodic or rhythmic patterns:

Abundant Periodic Discharges (>50%)
Abundant Rhythmic SW (>50% of recording).
Unequivocal electrographic seizure.

Background EEG:

-Discontinuous background (suppression periods (<10 μ V; >10% of the recording).
-Low voltage background (<20 μ V).
-Reversed anterior-posterior gradient

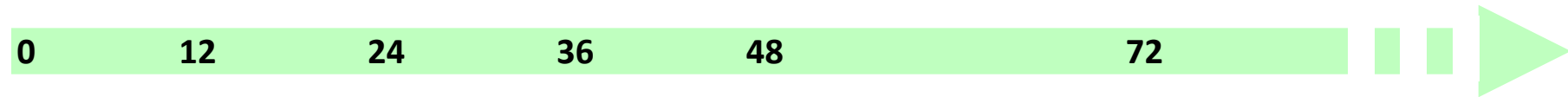
Reactivity:

Absence of background reactivity
or only SIRPIDs

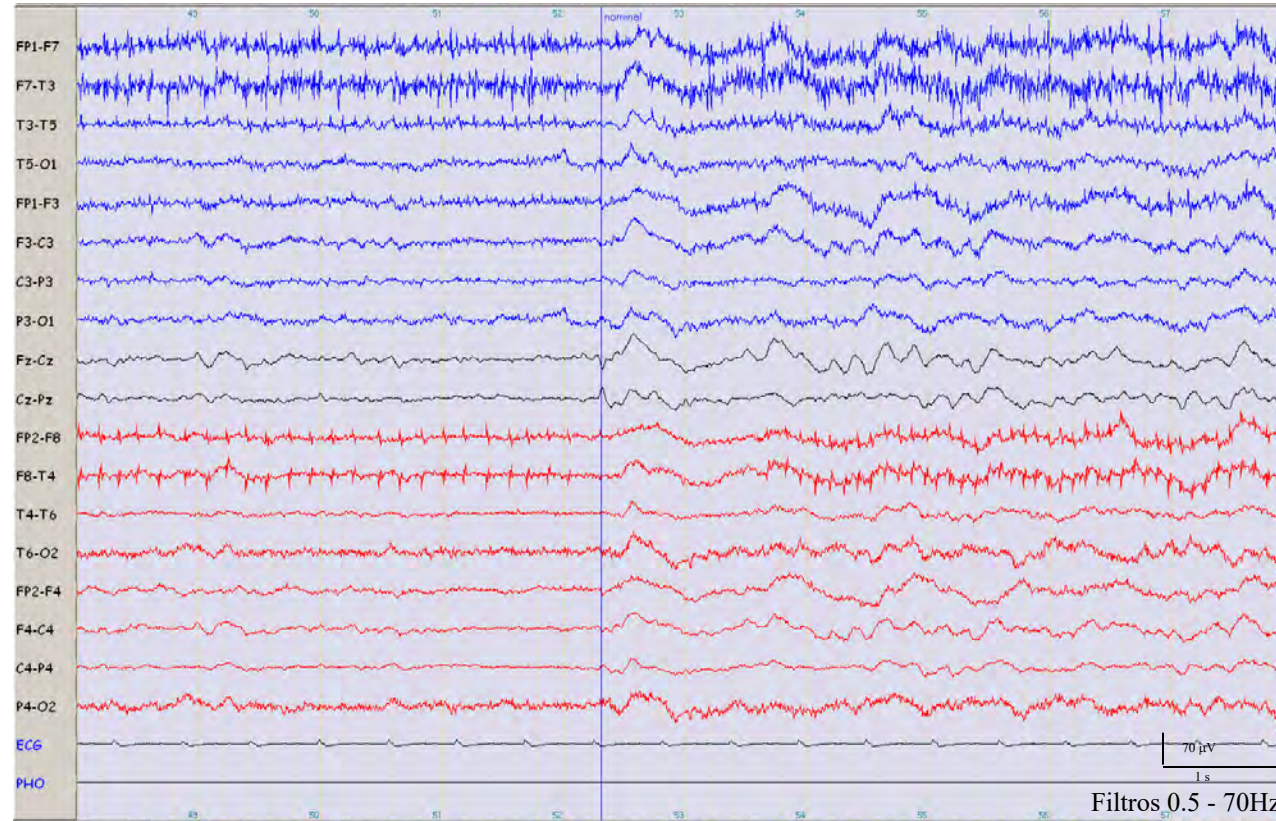
Benign EEG patterns

Absence of all malignant features stated above.

EEG REACTIVITY



Reactivity



184 patients

2 hospitals

EEG recorded during controlled normothermia

Favorable outcome	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
EEG-R	72% (66-79)	86% (78-93)	60% (50-69)	67% (58-76)	81% (72-90)
EMG-R	65% (58-72)	61% (51-71)	69% (60-78)	65% (55-76)	65% (56-74)
EEG- and/or EMG-R	73% (67-80)	94% (90-99)	53% (43-63)	66% (58-74)	91% (83-99)

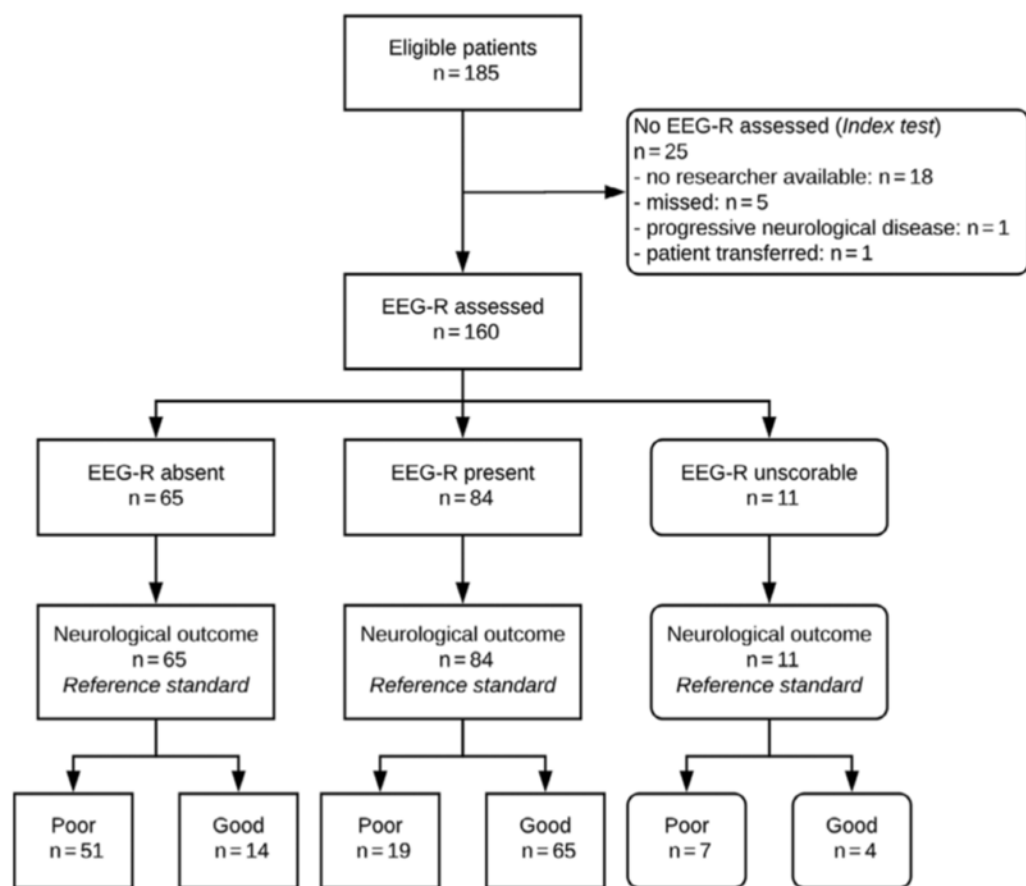


TABLE 3. Predictive Value of (Combinations of) Clinical and Neurophysiologic Measures

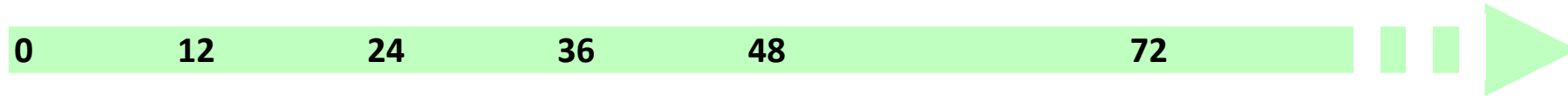
Measure	Available for Analysis, n	Predicted Outcome	Specificity (95% CI)	Sensitivity (95% CI)	PPV (95% CI)	NPV (95% CI)
EEG reactivity absent	149	Poor	82% (72–90)	73% (61–83)	79% (67–88)	77% (67–86)
EEG cat. A pattern at 24 h	141	Poor	97% (91–100)	46% (33–58)	94% (79–99)	67% (57–76)
Brainstem reflexes absent	149	Poor	100% (95–100)	27% (17–39)	100% (82–100)	61% (52–69)
SSEP N20 absent	38	Poor	100% (29–100)	31% (17–49)	100% (72–100)	11% (2–29)
Baseline: EEG cat. A pattern at 24 h OR brainstem reflexes absent OR SSEP N20 absent	149	Poor	98% (91–100)	54% (42–66)	95% (83–99)	71% (61–79)
Baseline AND EEG reactivity absent	149	Poor	99% (93–100)	51% (39–64)	97% (86–100)	70% (60–78)
EEG reactivity present	149	Good	73% (61–83)	82% (72–90)	77% (67–86)	79% (67–88)
EEG cat. C pattern at 12 h	66	Good	82% (63–94)	63% (46–78)	83% (64–94)	62% (45–78)
Brainstem reflexes present	149	Good	74% (62–84)	68% (57–78)	75% (63–85)	68% (56–78)
Baseline: EEG cat. C pattern at 12 h OR brainstem reflexes present	149	Good	70% (58–80)	79% (68–87)	75% (64–84)	74% (62–84)
Baseline AND EEG reactivity present	149	Good	89% (79–95)	66% (54–76)	87% (75–94)	70% (59–79)

Specificity, sensitivity, PPV, and NPV data are given as percentage (95% CI). For EEG, pattern classification, see Table 1. cat. = category; CI = confidence interval; EEG = electroencephalographic; NPV = negative predictive value; PPV = positive predictive value; SSEP = somatosensory evoked potential.

Post-hypoxic Myoclonus

EARLY

LATE

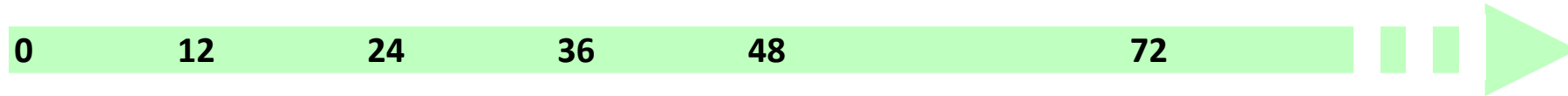


Post-hypoxic Myoclonus

Acute Post-hypoxic Myoclonus

Late Post-hypoxic Myoclonus

Lance Adams Syndrome



Post-anoxic Myoclonus

Myoclonus

Myoclonic Status

Status Myoclonus

Status Myoclonicus

Myoclonic Status Epilepticus

TABLE 1. Population Characteristics, Treatments, and Outcomes

	Overall Comatose Postarrest Cohort, n = 401	Clinical Myoclonus Cohort, n = 69
Characteristic		
Age, yr	58 ± 17	56 ± 16
Female	170 (41)	22 (32)
Out-of-hospital arrest	320 (77)	58 (84)
Shockable rhythm	118 (28)	17 (25)
Pittsburgh Cardiac Arrest Category		
2	83 (20)	10 (14)
3	49 (12)	3 (4)
4	224 (53)	47 (68)
Unknown	64 (15)	9 (13)
Survived	131 (31)	7 (10)
Favorable outcome ^a	70 (53)	4 (57)
Length of stay, days ^b		
Survivors	17 [12–26]	19 [10–29]
Nonsurvivors	4 [2–6]	4 [3–6]
Initial EEG findings		
Background		
Suppressed	89 (22)	5 (7)
Burst suppressed	140 (35)	52 (84)
Continuous	172 (43)	8 (12)
Superimposed patterns		
Ictal burst morphology		
Identical bursts	101 (25)	49 (71)
Nonidentical ictal bursts	7 (2)	2 (3)
Seizures	13 (3)	2 (3)
Periodic discharges {GPDs, LPDs}	16 (4)	2 (3)
Nonperiodic sharp waves	33 (8)	8 (12)
Nothing malignant	231 (58)	2 (3)
Antiepileptic drug use		
Propofol	239 (57)	55 (80)
Midazolam	190 (45)	60 (87)
Valproic acid	128 (30)	52 (75)
Levetiracetam	173 (41)	59 (86)
Phenytoin	77 (18)	29 (42)
Lacosamide	16 (4)	7 (10)
Phenobarbital	12 (3)	6 (7)
Total number of agents	2 ± 1	4 ± 1

Data are presented as means ± standard deviation or numbers with corresponding percentages, unless otherwise noted.

^aReported as percentage of survivors.

^bData presented as median with interquartile ranges.

EEG = electroencephalographic; GPD = generalized periodic discharge; LPD = lateralized periodic discharge.

TABLE 2. Incidence and Outcomes of Electroencephalographic Myoclonus Subtypes

Characteristic	Pattern			
	1	2	3	4
Description	Malignant PAMM	Possible precursor to Lance–Adams	Subcortical	Other
Background	Burst suppressed	Continuous, although may be suppressed early	Variable	Variable
Suppression ratio, median [IQR]	83 [53–97]	52 [38–82]	91 [89–94]	28 [8–60]
Discharges	Identical high-amplitude polyspike-wave bursts	Vertex spike-wave discharges	None	Variable, often periodic discharges or seizures
Treatment responsive?	No	Yes	N/A	No
Prevalence	48/69, 70% (57–80%)	8/69, 12% (5–22%)	2/69, 2% (0–10%)	7/69, 10% (4–20%)
Survival ^a	2/48, 3% (0–14%)	4/8, 50% (16–84%)	0/2, 0% (0–84%)	1/7, 14% (0–58%)
Favorable outcome ^{a,b}	0/2, 0% (0–8%)	4/4, 100% (40–100%)	0/0, N/A	0/1, 0% (0–98%)

^aFisher exact test, $p < 0.001$ across levels.

^bFavorable outcome is expressed as percentage of survivors.

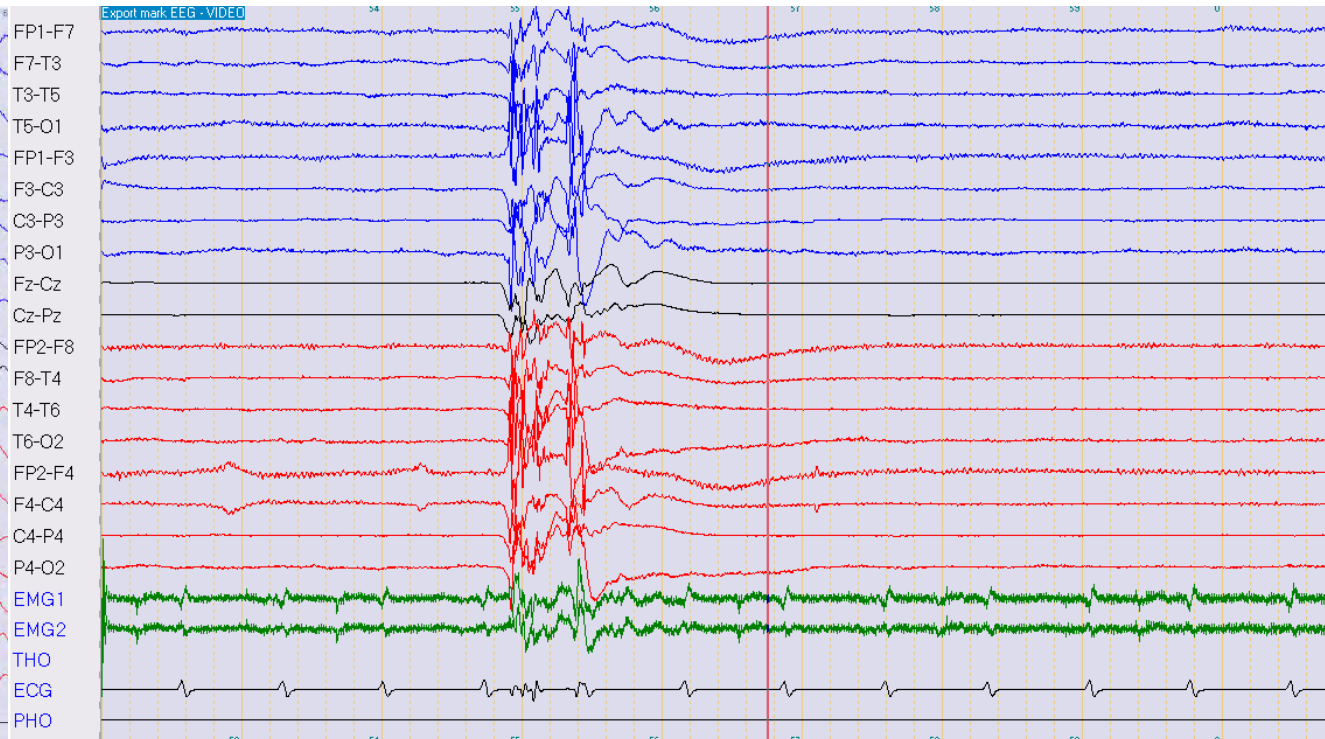
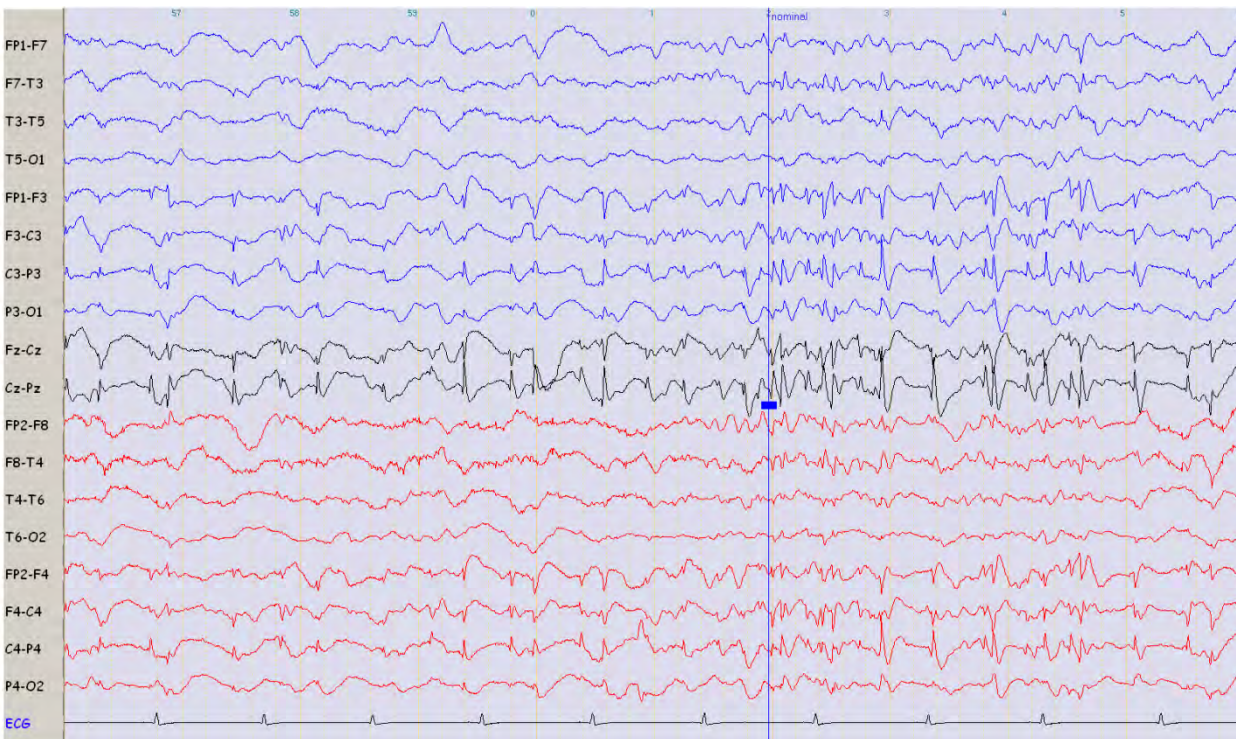
IQR = interquartile range; N/A = not applicable; PAMM = postanoxic multifocal myoclonus.

Table 1 Characteristics of the six comatose survivors of cardiac arrest (CA) treated with therapeutic hypothermia, improving beyond vegetative state despite postanoxic status epilepticus (PSE)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Total
Data collection	Retrospective	Retrospective	Retrospective	Prospective	Prospective	Prospective	
Age, y	60	61	55	53	68	58	53-68
Female	Yes	Yes	No	No	No	No	2/4
CA due to VF	Yes	Yes	No	Yes	Yes	Yes	5/6
Time to ROSC, min	32	45	17	20	20	21	17-45
Cardiac etiology	Yes	Yes	Yes	Yes	Yes	Yes	6/6*
Preserved BR	Yes	Yes	NA	Yes	Yes	Yes	5/5*
Absent MR	Yes	No	NA	No	No	Yes	2/5
SE diagnosis delay from CA, d	2	4	2	2	3	9	2-9
SE clinically (myoclonus)	Yes	No	Yes	Yes	No	No	3/6
EEG description	Repetitive diffuse sharp waves (1.5 Hz), bilateral	Repetitive diffuse sharp waves (2-3 Hz), bilateral	Repetitive diffuse sharp waves (2 Hz), bilateral	Sharp waves, spike-waves (2 Hz), L>R; SIRPID	Frontal evolving rhythmic sharp waves (3 Hz), bilateral	Frontal poly-spike-waves (2-3 Hz), R>L	
EEG reactivity	Yes	Yes	Yes	Yes	Yes	Yes	6/6*
PSE duration (d, on EEG)	3	2	2	2	5	3	2-5
Preserved N20 on SSEP	Yes	NA	Yes	Yes	Yes	Yes	5/5*
AEDs	PRO, VPA, CLZ	VPA, CLZ, LEV	PRO, PHT, LEV, CLZ	VPA, PHT, LEV, CLZ	PRO, VPA, LEV, CLZ	VPA, LEV, CLZ	
CPC outcome at 6 mo	3	2	2	1	3; death on day 18 (sepsis)	2	1-3
LA syndrome	Yes	No	No	Yes	No	No	2/6

*All or none of tested patients.

VF = ventricular fibrillation; ROSC = restoration of spontaneous cardiac rhythm; BR = brainstem reflexes (one or more); NA = not assessed; MR = motor response to painful stimuli; SE = status epilepticus; SIRPID = stimulus-induced rhythmic, periodic, or ictal discharges; SSEP = somatosensory evoked potentials; AED = antiepileptic drug; PRO = propofol; VPA = valproate; CLZ = clonazepam; LEV = levetiracetam; PHT = phenytoin; CPC = cerebral performance category; LA = Lance-Adams syndrome.

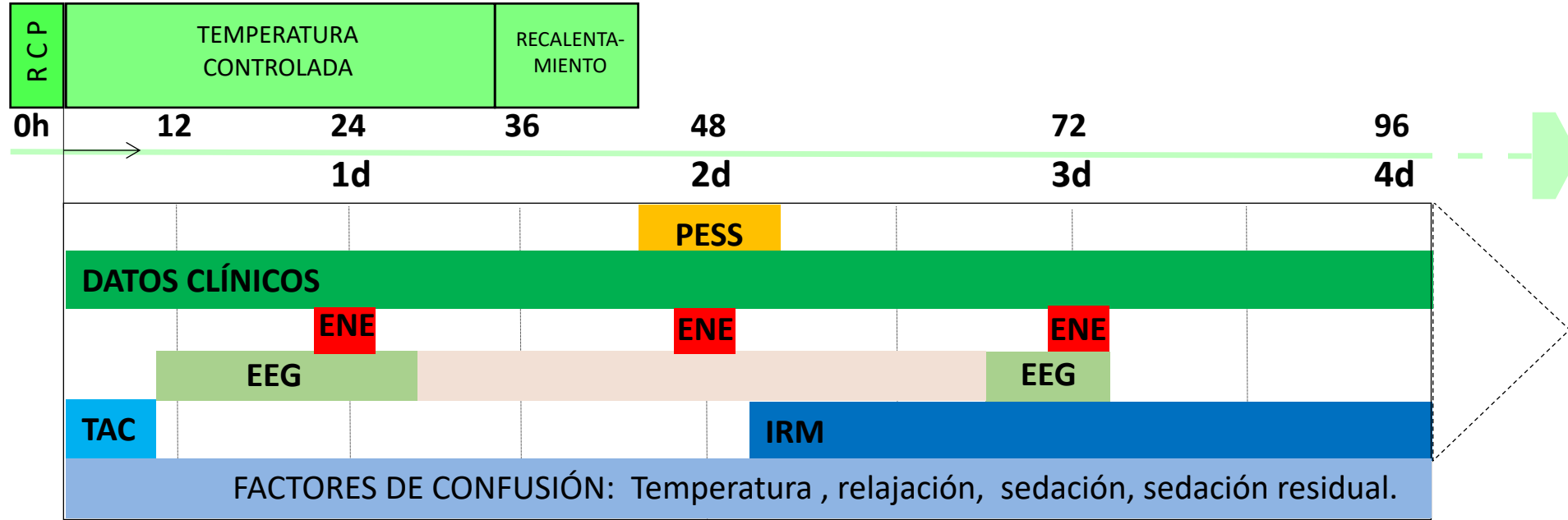


Mioclónicas de acción intencional (sd Lance-Adams)

Vive en su casa, puede andar con algunas caídas, precisa ayuda para actividades cotidianas

EXITUS

APROXIMACIÓN MULTIMODAL AL PRONÓSTICO DEL COMA ANÓXIC



DATOS DE BUEN PRONÓSTICO:

EEG continuo a las 12h
EEG reactivo
MMN present

DATOS DE MAL PRONÓSTICO (siempre aproximación multimodal)

N20 ausente bilateral en los PESS

Ausencia de reflejos corneales y pupilares a las 72h

EEG S-S con salvas idénticas. Pasadas 24h Supresión $<10 \mu\text{V}$ o S-S arreactiva.

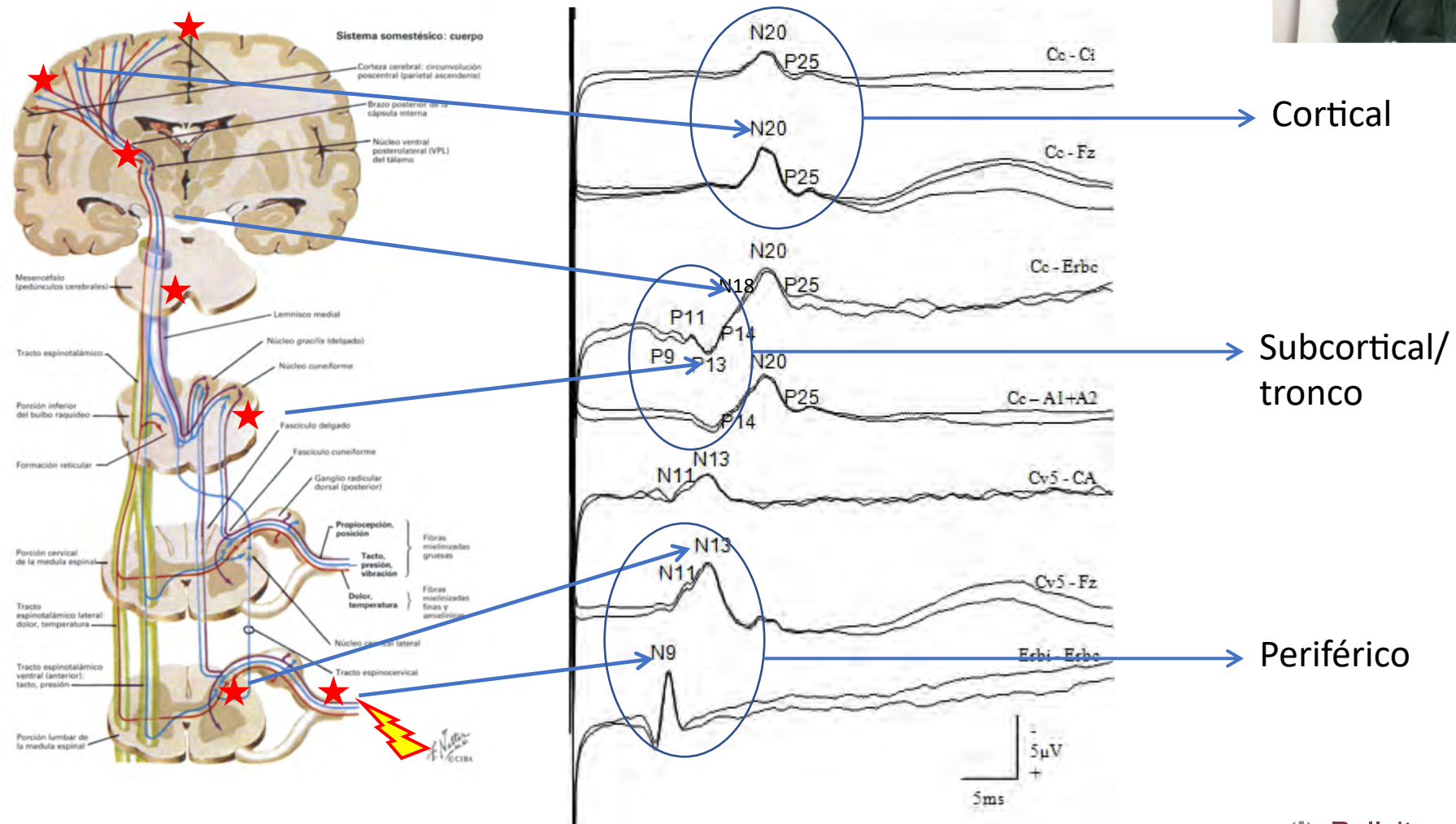
ENE $> 79 \mu\text{g/L}$ a las 72h

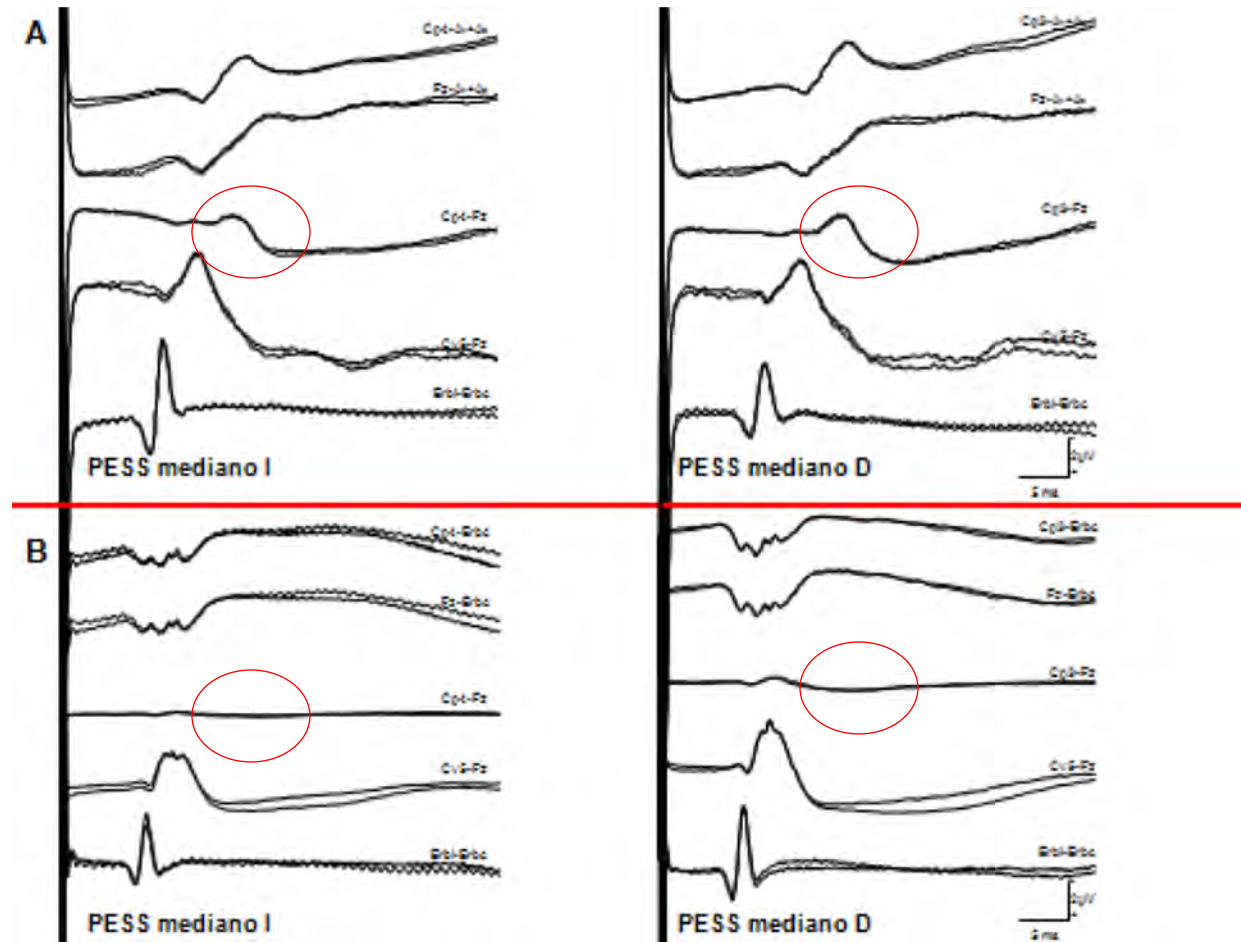
Estatus mioclónico postanóxico que persiste a las 72h con tx correcto y con EEG no reactivo y diferente de puntas en la línea media.

TAC inicial con severa lesión anóxica difusa.

IRM con severa lesión anóxica difusa.

Potenciales evocados somatosensoriales





FPR of 0[0–3]%

Sandroni 2014

Ejemplo de 2 pacientes en coma de etiología anóxica.

A: paciente con **N20 presente** en los potenciales evocados somatosensoriales y por tanto desde el punto de vista de los potenciales con **pronóstico indeterminado**.

B: paciente con **N20 ausente** y por tanto desde el punto de vista de los potenciales evocados con **mal pronóstico**.

ENOLASA NEURONAL ESPECÍFICA (ENE)

És un gamma isòmer de l'enolasa que es localitza a les neurones i cèl·lules neuroectodèrmiques.

Augmenta en dany cerebral: ictus, traumatismes cranials, **aturada cardiorespiratoria ...**

També augmenta en algunes malalties neoplàsiques (carcinoma bronquial, neuroblastoma, apudoma, seminoma, glioma, meningioma, neurofibroma i neurinoma) i afeccions pulmonars benignes.

Com a factor de mal pronòstic neurològic a les 72 hores de l'aturada cardíaca:

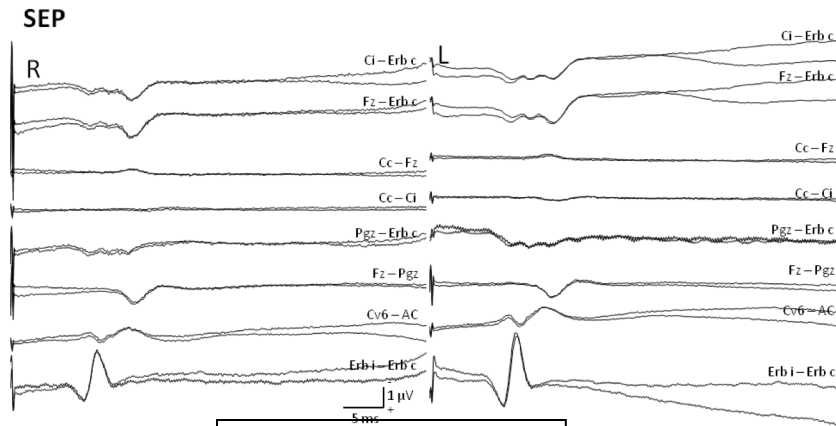
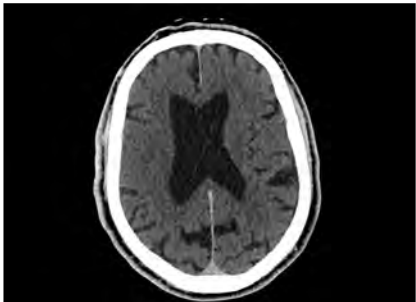
>27 µg/L en pacients no sotmesos a hipotèrmia

>79 µg/L en pacients sotmesos a hipotèrmia

Stammet P, Collignon O, Hassager C, Wise MP, Hovdenes J, Åneman A, Horn J, Devaux Y, Erlinge D, Kjaergaard J, Gasche Y, Wanscher M, Cronberg T, Friberg H, Wetterslev J, Pellis T, Kuiper M, Gilson G, Nielsen N; TTM-Trial Investigators. Neuron-Specific Enolase as a Predictor of Death or Poor Neurological Outcome After Out-of-Hospital Cardiac Arrest and Targeted Temperature Management at 33° C and 36° C. *J Am Coll Cardiol.* 2015;19;65(19):2104-14.

Steffen IG, Hasper D, Ploner CJ, Schefold JC, Dietz E, Martens F, Nee J, Krueger A, Jörres A, Storm C. Mild therapeutic hypothermia alters neuron specific enolase as an outcome predictor after resuscitation: 97 prospective hypothermia patients compared to 133 historical non-hypothermia patients. *Crit Care.* 2010;14(2):R69.

Chung-Esaki HM, Mui G, Mlynash M, Eyngorn I, Catabay K, Hirsch KG. The neuron specific enolase (NSE) ratio offers benefits over absolute value thresholds in post- cardiac arrest coma prognosis. *J Clin Neurosci.* 2018;57:99-104.



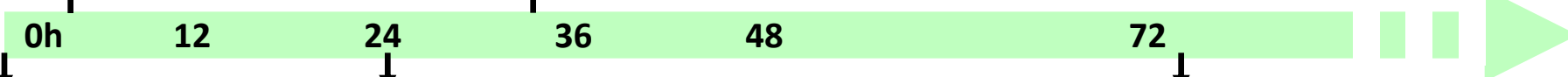
Ph 7,23
Lactato 5,85

Mioclónicas

PE:
N20 ausente bilateral

Reflejos de tronco alterados
Ausencia de respuestas motoras al dolor

EXITUS 5d



0h

♂ 75a. 30min RCP
PCR extrahospitalario
FV (desfibrilable)

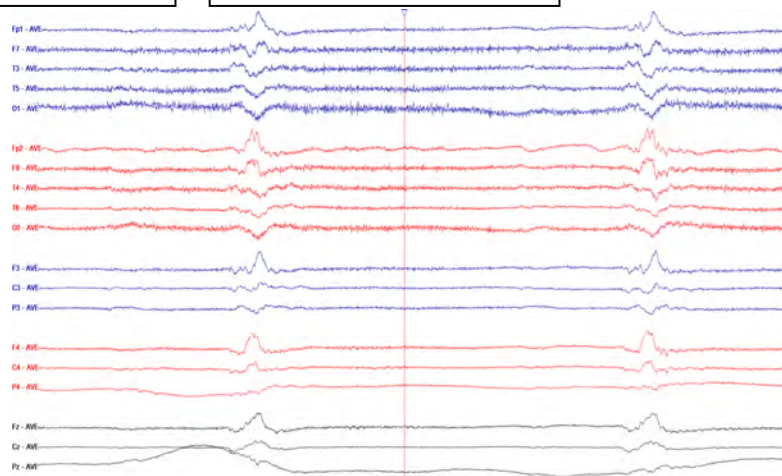
24h

EEG: Salva –supresión
Arreactivo
Salvas idénticas

72h

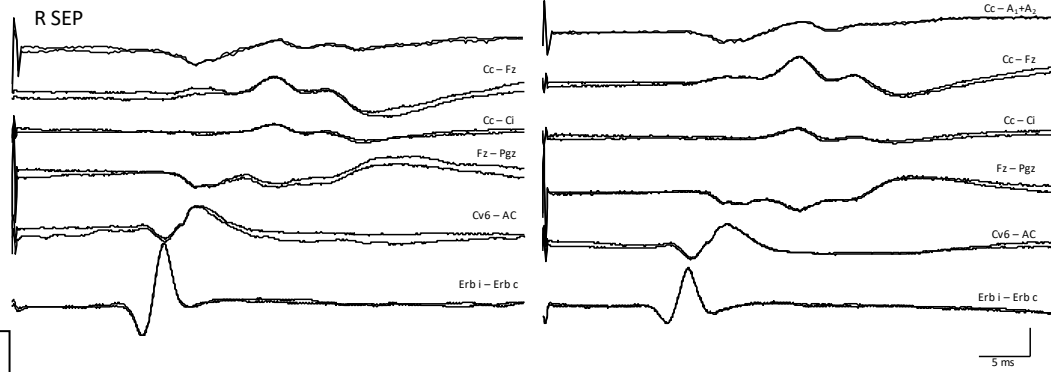
ENE: 507 μg/L

Ventilación espontánea
Reflejos de tronco alterados
(pupilas arreactivas a la luz,
corneales y ROC ausentes)
Ausencia de respuestas motoras al dolor.





Ph 7,13
Lactato 6,36mmol/L



Mioclónicas?

PE:
N20 presente bilateral

ALTA 21d
sin secuelas neurológicas

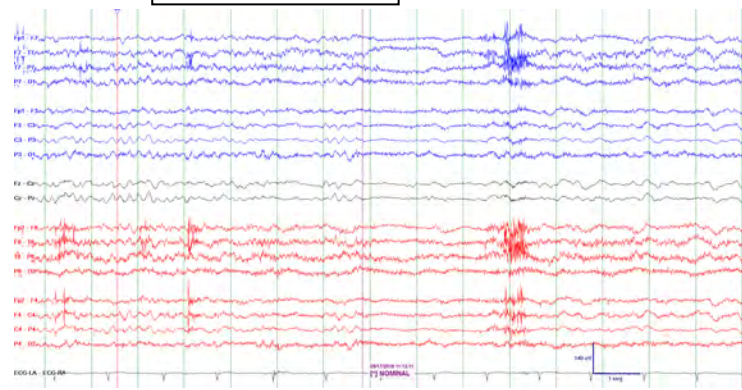
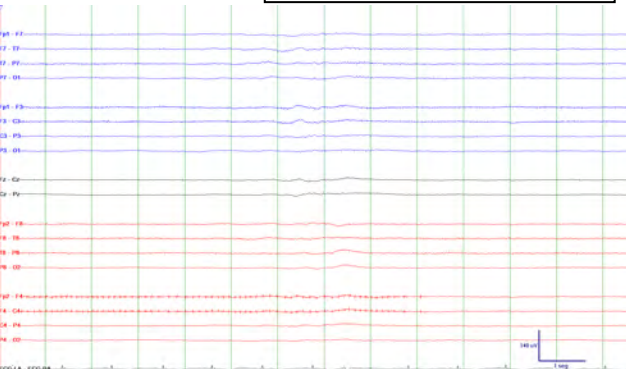


♂ 42a. 35min RCP
PCR extrahospitalario
Asistolia (no desfibrilable)

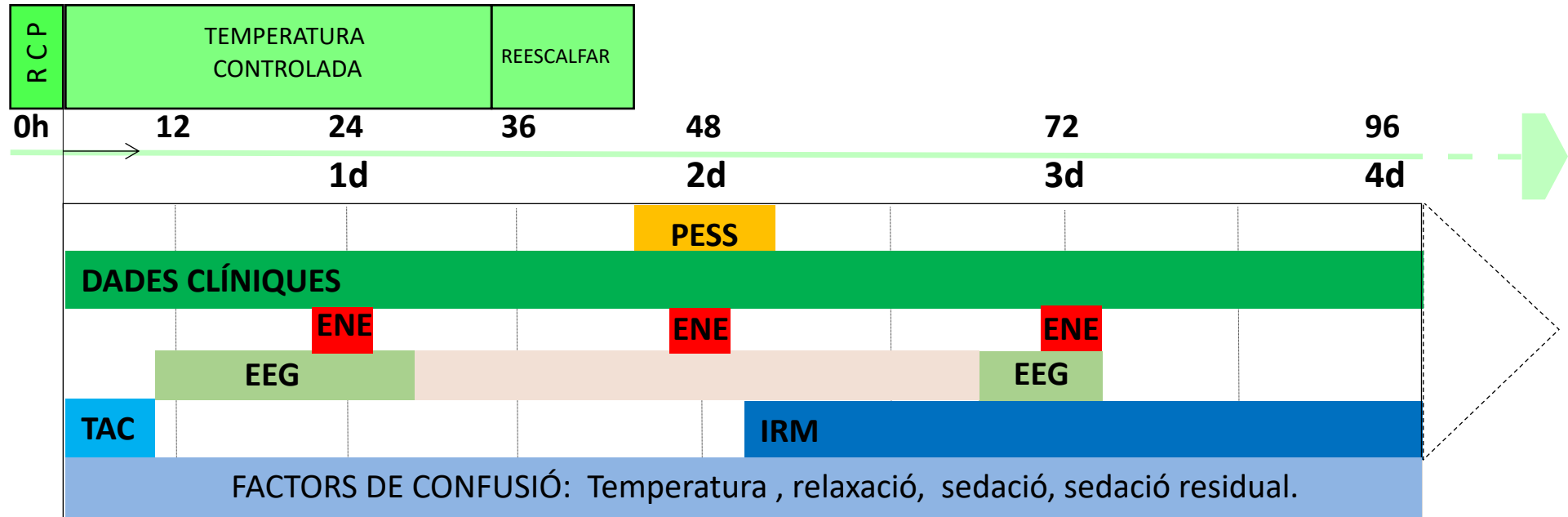
EEG: Salva -supresión
10h Arreactivo

EEG: Continuo
32h Reactivo

ENE: 14,9 µg/L



APROXIMACIÓ **MULTIMODAL** AL PRONÒSTIC DEL COMA ANÒXIC



DADES DE BON PRONÒSTIC:

EEG continu a les 12h
EEG reactiu
MMN present

DADES DE MAL PRONÒSTIC (sempre aproximació multimodal)

N20 absent bilateral als PESS

Absència de reflexes corneals i pupil·lars a les 72h

EEG S-S amb salves idèntiques. Passades 24h Supressió $<10 \mu\text{V}$ o S-S arreactiva.

ENE $> 79 \mu\text{g/L}$ a les 72h

Estat mioclònic postanòxic que persisteix a les 72h amb tx correcta i amb EEG no reactiu i diferent de puntes a la línia mitja.

Tac inicial amb severa lesió anòxica difusa.

IRM amb severa lesió anòxica difusa.

Part 8: Post-Cardiac Arrest Care

2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

Clifton W. Callaway, Chair; Michael W. Donnino; Ericka L. Fink; Romergryko G. Geocadin;
Eyal Golan; Karl B. Kern; Marion Leary; William J. Meurer; Mary Ann Peberdy;
Trevonne M. Thompson; Janice L. Zimmerman

Circulation. 2015;132[suppl 1]:S465–S482.

Resuscitation 95 (2015) 202–222



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Resuscitation

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European Resuscitation Council and European Society of Intensive Care Medicine Guidelines for Post-resuscitation Care 2015
Section 5 of the European Resuscitation Council Guidelines for Resuscitation 2015[☆]

Jerry P. Nolan^{a,b,*}, Jasmeet Soar^c, Alain Cariou^d, Tobias Cronberg^e,
Véronique R.M. Moulaert^f, Charles D. Deakin^g, Bernd W. Bottiger^h, Hans Fribergⁱ,
Kjetil Sunde^j, Claudio Sandroni^k

Resuscitation 85 (2014) 1779–1789



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journal homepage: www.elsevier.com/locate/resuscitation

Prognostication in comatose survivors of cardiac arrest: An advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine[☆]

Claudio Sandroni^{a,*}, Alain Cariou^b, Fabio Cavallaro^a, Tobias Cronberg^c, Hans Friberg^d,
Cornelia Hoedemaekers^e, Janneke Horn^f, Jerry P. Nolan^g, Andrea O. Rossetti^h,
Jasmeet Soarⁱ