Neurocritical Care and Prognostication after Cardiac Arrest

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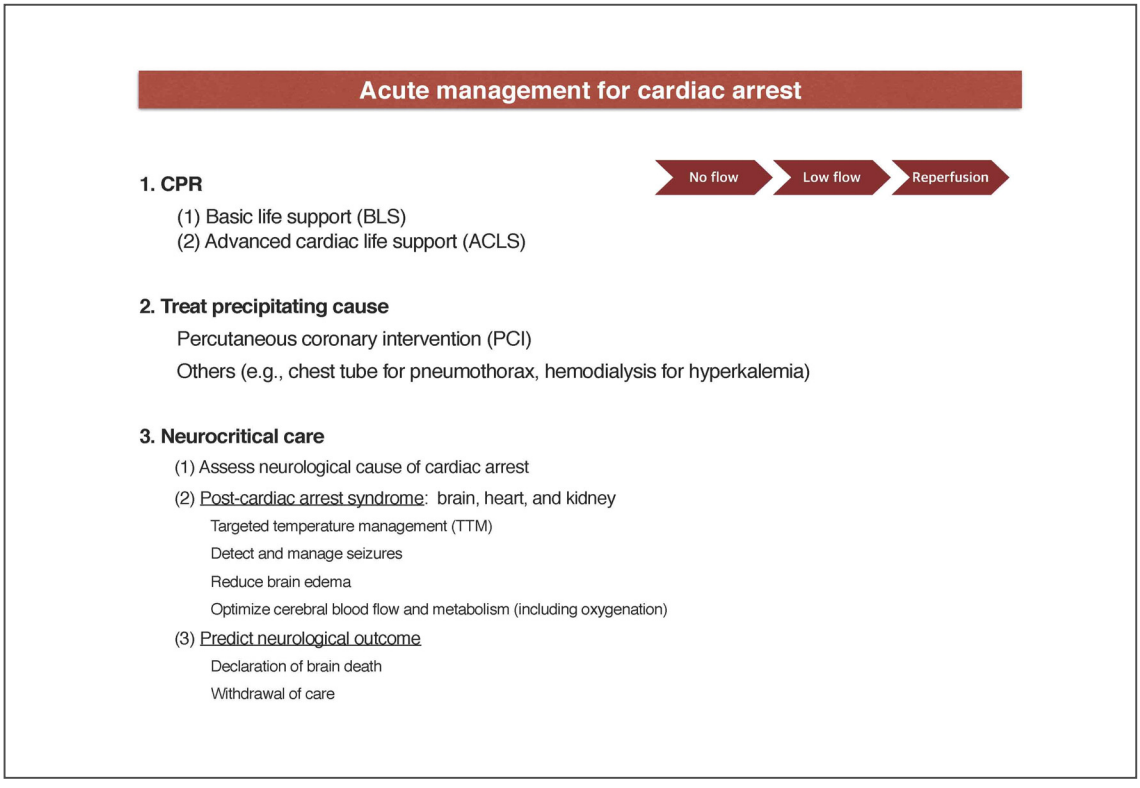
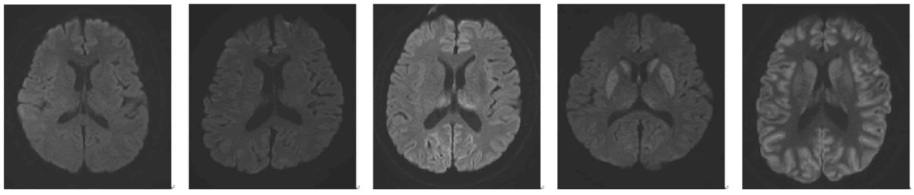
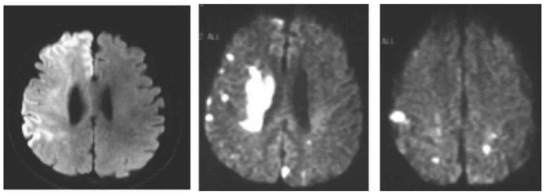


Two types of ischemia

Global ischemia



Focal ischemia



Global ischemia

- Compromised blood flow to the brain: severity & duration
- Damage limited to the neurons
  - Cerebral neocortex: Pyramidal neurons in layer 3, 5, 6
  - Hippocampus: Pyramidal neurons in CA1
  - Cerebellum: Purkinje cells
  - Striatum: Medium spiny neurons

Focal ischemia

- Ischemic stroke
- Destroying multiple cell types

Hypoxic-Ischemic Encephalopathy

Biochemical

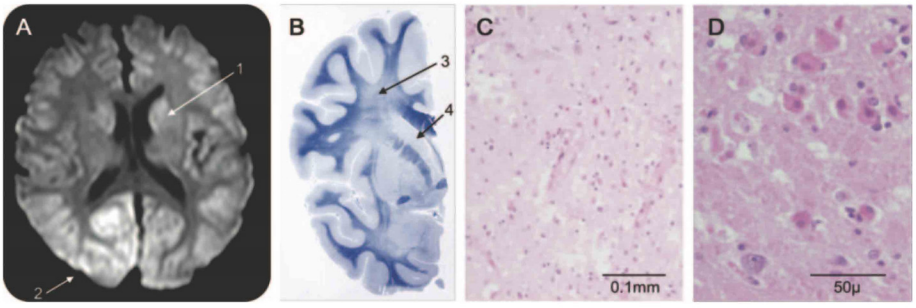
- Anoxic depolarization
- ATP depletion
- Glutamate release
- Free radical formation
- Nitric oxide production

Functional

- Mitochondrial damage
- Cytoskeletal damage
- Glutamate R activation

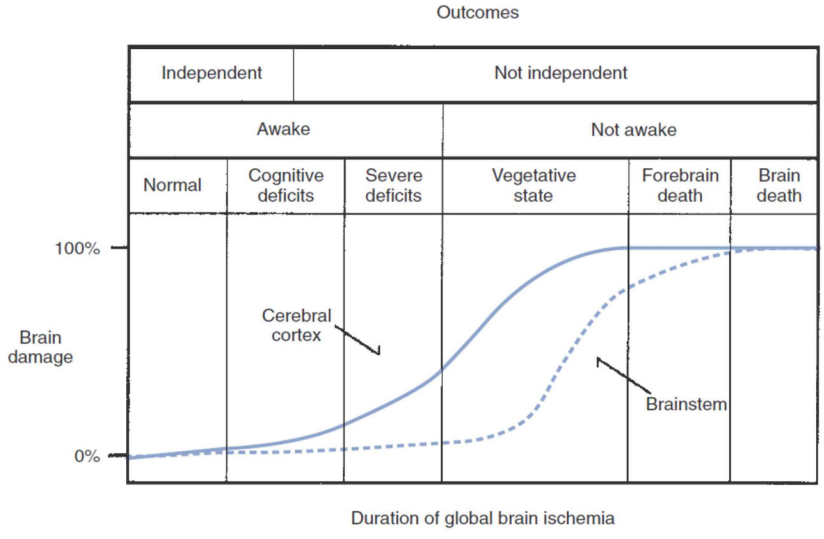
Neuropathological

- Necrosis
- Apoptosis
- Autophagocytosis



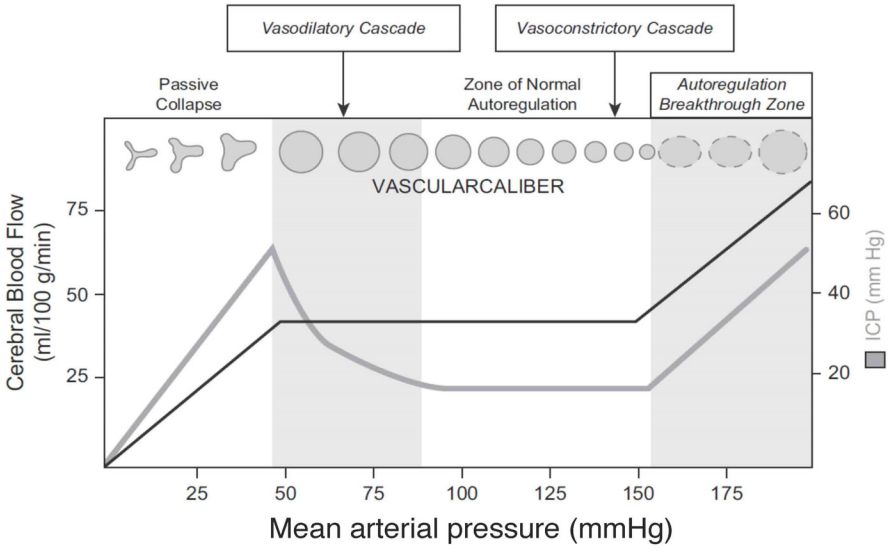
Cronberg T, Neurology 2011 ; Busl KM, NeuroRehabilitation 2010

Rostral-caudal deterioration



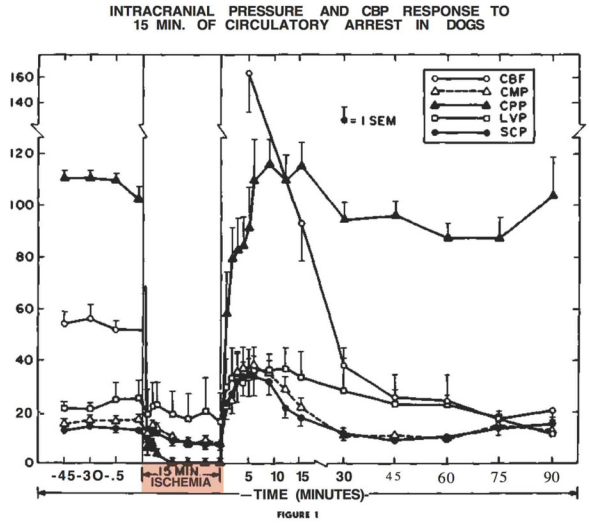
Longstreth WT, 2008

Altered autoregulation



Wartenberg KE, Crit Care Clin 2007

Dynamic process

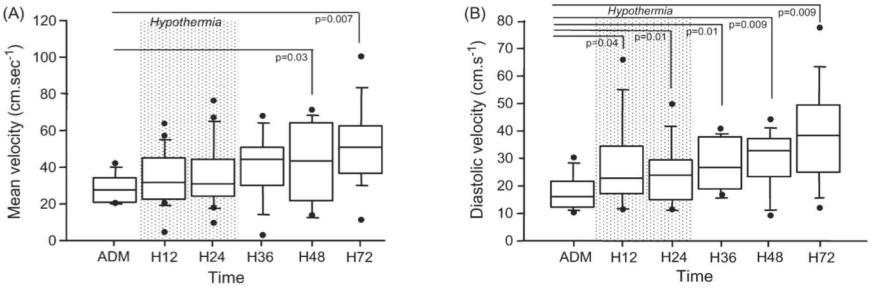


Twelve dogs subjected to 15 minutes of total systemic circulatory arrest by aortic and venae cavae occlusion. CBF = cerebral blood flow (cc/100 gm per minute); CMP = cisterna magna pressure (mm Hg); CPP = cerebral perfusion pressure {mm Hg); LVP = lateral ventricular pressure (mm Hg); SCP = supracortical pressure (mm Hg).

hyperflow

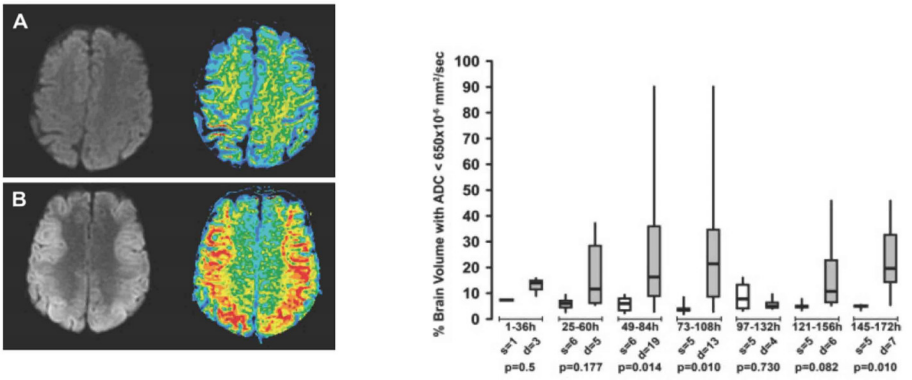
no-reflow phenomenon

Snyder JV, Stroke 1975

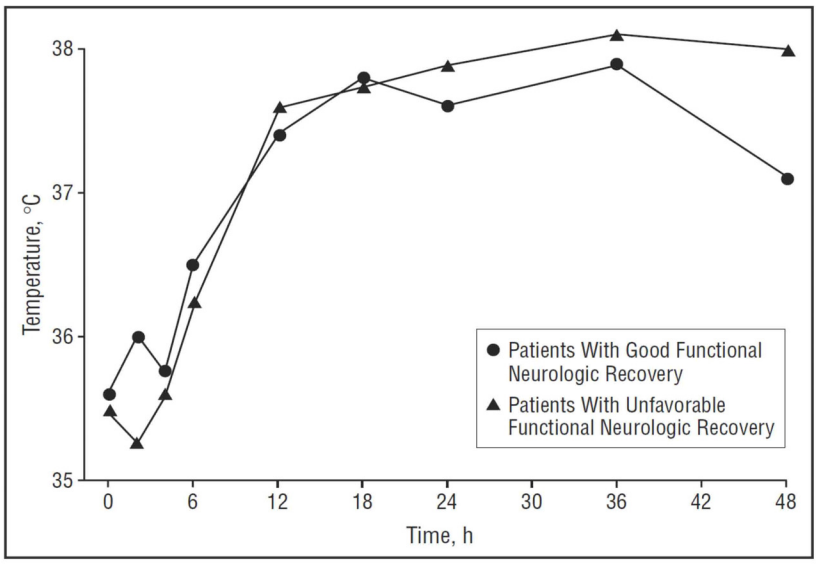


Poiseuille-Hagen law: $Q = \frac{dV}{dt} = \frac{\Delta p \pi r 4}{8 \eta L}$

Lemiale V- Resuscitation 2008



Wijman CA, Ann Neurol 2009



Zeiner A, Arch Int Med 2001

Classification: clinical perspective

Cardiac arrest

The cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation

- Cardiac origin vs. noncardiac origin
- Adult vs. pediatric
- Shockable rhythm vs. non-shockable rhythm
- **Out-of-hospital cardiac arrest (OHCA)** vs. **in-hospital cardiac arrest (IHCA)**

Mozaffarian D, Circulation 2015

Targeted temperature management (TTM)

Part 8: Post–Cardiac Arrest Care

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

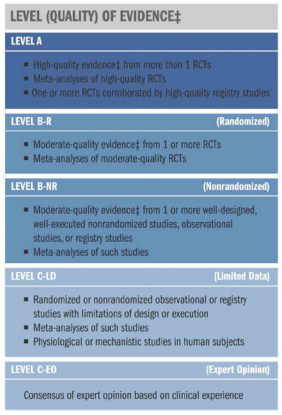
New recommendations

We recommend that **comatose** (ie, **lack of meaningful response to verbal commands**) adult patients with ROSC after cardiac arrest have TTM (Class I, LOE B-R for VF/pVT OHCA; Class I, LOE C-EO for non-VF/pVT and IHCA)

We recommend selecting and maintaining a constant temperature between 32 °C and 36 °C during TTM (Class I, LOE B-R)

It is reasonable that TTM be maintained for at least 24 hours after achieving target temperature (Class IIa, LOE C-EO)

It may be reasonable to actively prevent fever in comatose patients after TTM (Class IIb, LOE C-LD)



Callaway CW, Circulation 2015

Part 4: Advanced Life Support

2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

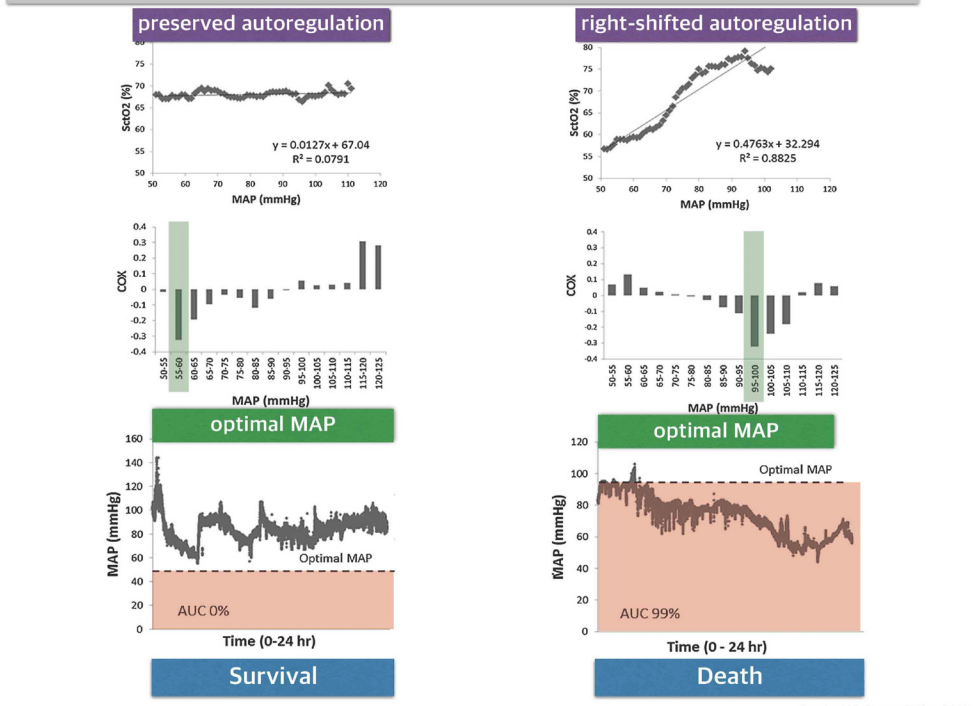
We recommend TTM as opposed to no TTM for adults with OHCA with an initial shockable rhythm who remain unresponsive after ROSC

We suggest TTM as opposed to no TTM for adults with OHCA with an initial nonshockable rhythm who remain unresponsive after ROSC

We suggest TTM as opposed to no TTM for adults with in-hospital cardiac arrest with any initial rhythm who remain unresponsive after ROSC

Callaway CW, Circulation 2015

Blood pressure



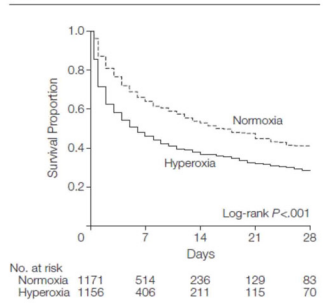
Ameloot K, Resuscitation 2015

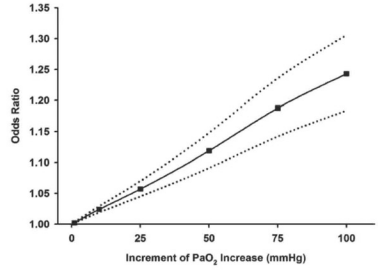
O_2

Association Between Arterial Hyperoxia Following Resuscitation From Cardiac Arrest and In-Hospital Mortality

JAMA. 2010;303(21):2165-2171

Figure. In-Hospital Death Between Hyperoxia and Normoxia

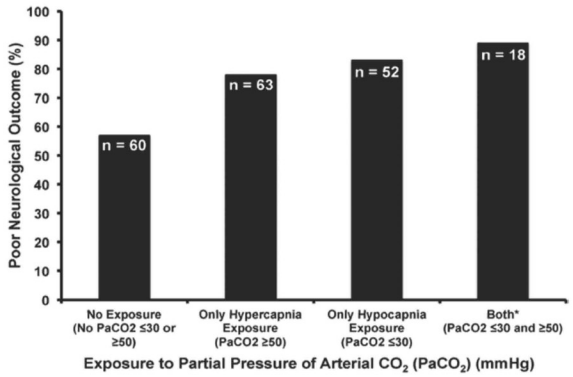




Kilgannon JH, Circulation 2011

CO_2

Poor neurological outcome (CPC score 3—5)

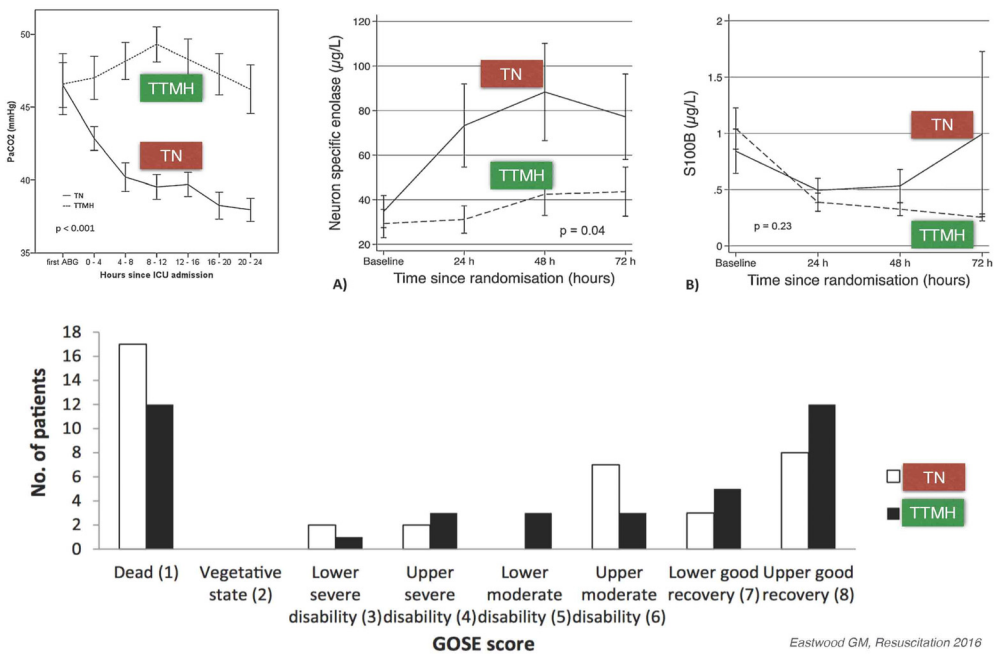


Roberts BW, Circulation 2013

targeted normocapnia (TN) ($PaCO_2$ 35–45 mmHg)

therapeutic mild hypercapnia (TTMH) ($PaCO_2$ 50–55 mmHg)

Phase II multi-center RCT (n = 86)



Eastwood GM, Resuscitation 2016

Scale for outcome measurement

Table 1. Cerebral Performance Category (CPC) Scale*

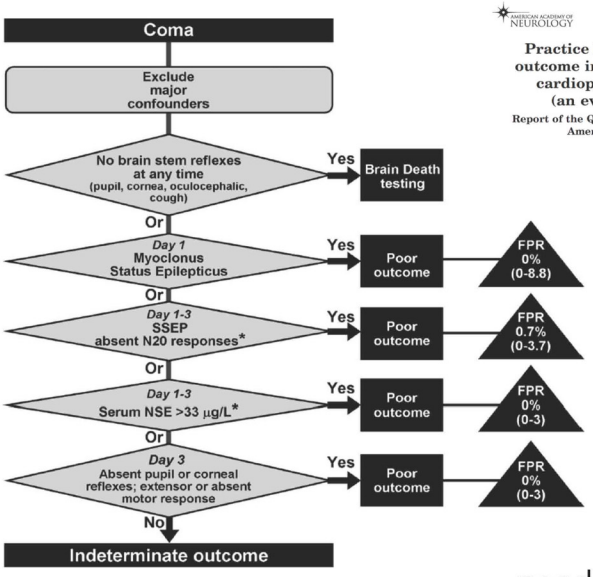
Good outcome	**CPC 1**	Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.
	CPC 2	Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
Poor outcome	**CPC 3**	Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
	CPC 4	Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
	CPC 5	Brain death: apnea, areflexia, EEG silence, etc.

* If the patient is anesthetized, paralyzed, or intubated, use "as is" clinical condition to calculate score.

From Safar P. Resuscitation after Brain Ischemia, in Grenvik A and Safar P Eds: Brain Failure and Resuscitation, Churchill Livingstone, New York, 1981; 155-184.

Holzer M, N Engl J Med 2010;363:1256-64

Guidelines



2006 Neurology

Practice Parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

need to be updated…

Neurological examination

The earliest time to prognosticate a poor neurologic outcome using clinical examination

In patients treated with TTM

☞ **72 hours** after return to normothermia

In patients not treated with TTM

☞ **72 hours** after cardiac arrest

This time until prognostication can be even longer than 72 hours after cardiac arrest if the residual effect of **sedation or paralysis** confounds the clinical examination

Callaway CW, Circulation 2015

Pupillary light reflexes

Bilateral absence of pupillary light reflexes
(FPR 0.5% [95% CI 0—2])

Corneal reflexes

Absence of corneal reflexes (FPR 5% [0—25])

Motor responses

Absent or extensor response to pain (FPR 24% [6—48])

Motor responses are less reliable in patients undergoing TTM than in those not receiving TTM

Myoclonus

Generalized status myoclonus (multifocal spontaneous twitches lasting for more than 30 min) (FPR 0% [0–3])

Brief myoclonic jerks mostly restricted to the face or trunk, controllable with sedatives, and accompanied with a more benign (ie, continuous and reactive) EEG, do not suggest an invariably poor outcome (up to 11% [3–26])

Rossetti AO, Lancet Neurol 2016; Callaway CW, Circulation 2015

EEG

Background activity

Low voltage (<20 μV) background at 24 hr (FPR 0% [95% CI 0—17])

Burst suppression at any time (FPR 0% [0–11])

Burst suppression with identical bursts (FPR 0% [0—17])

Spontaneously discontinuous background during TTM (FPR 7% [0—24])

Alpha coma pattern

➢ Good outcome

Continuous background activity as soon as 12 hr (PPV 92% [80—98])

Normal voltage background at 24 hr (PPV 72% [53—86])

Background reactivity

Absence of reactivity to external stimuli at 72 hr (FPR 7% [1—15])

Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPID) (FPR 2% [0—11])

Epileptiform features

Sharp waves, spikes, poly-spikes, and waves in repetitive patterns (FPR, 9% [2–21])

Rossetti AO, Lancet Neurol 2016; Callaway CW, Circulation 2015

Timing

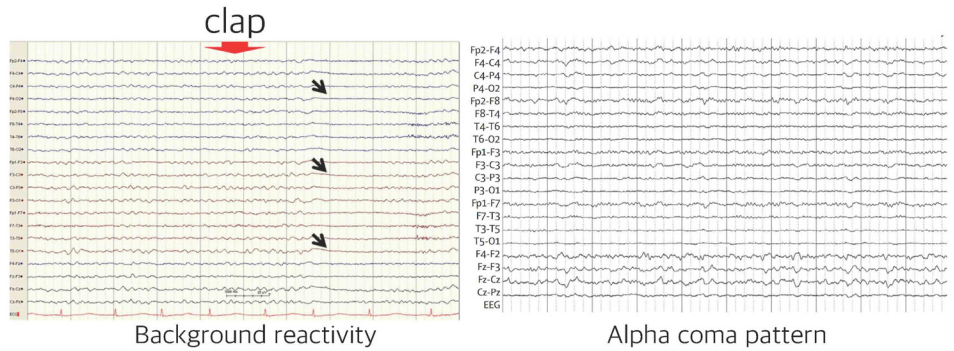
Recordings done too early (<12 hr) could overestimate the degree of brain injury

Repeated assessment

Two standard EEG recordings within 48 h are as informative as continuous EEG

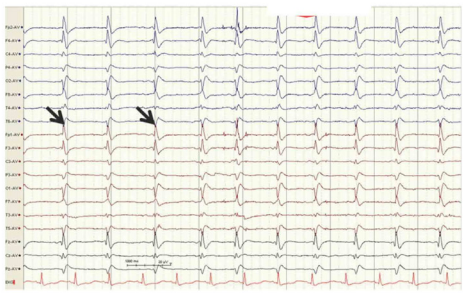
Repeated assessments during the first 72 h

Rossetti AO, Lancet Neurol 2016; Callaway CW, Circulation 2015; Alvarez V , Crit Care 2013

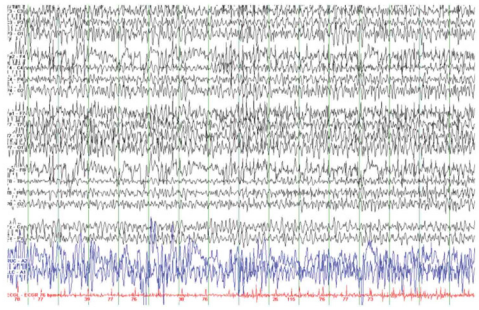


Background reactivity

Alpha coma pattern

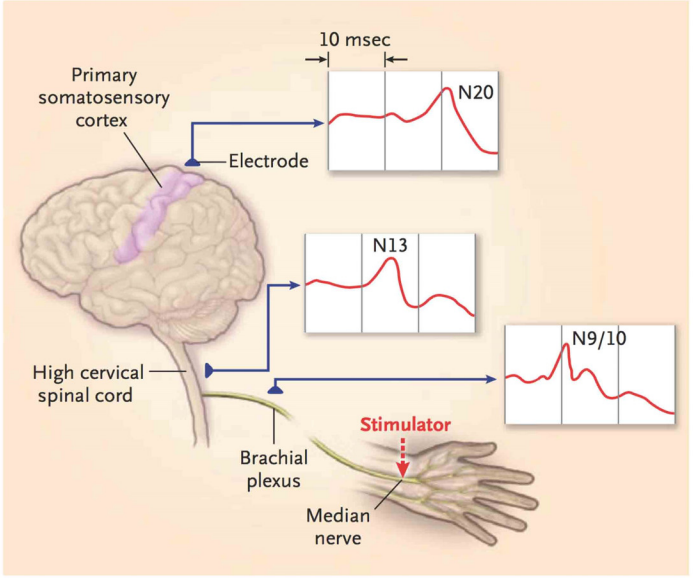


Burst suppression with identical bursts

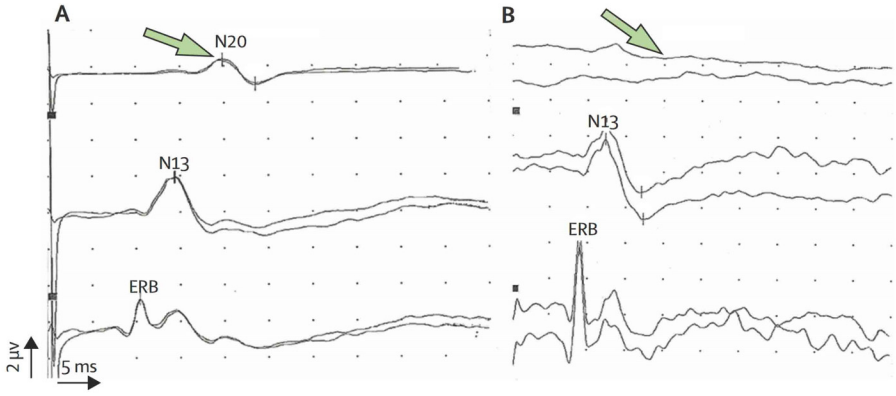


Seizure

Somato-sensory evoked potential



Young GB, NEJM 2009; Rossetti AO, Lancet Neurol 2016



Young GB, NEJM 2009; Rossetti AO, Lancet Neurol 2016

Biochemical markers

NSE

Neuronal damage

As high as 120 μg/L at 48 h; and 50 μg/L at 72 h

Concentrations of < 33 μg/L are inconsistently related to good outcome (PPV 63% [52–73])

S-100 β

Astrocyte damage

Given the possibility of high FPRs, blood levels of NSE and S-100B **should not** be used alone to predict a poor neurologic outcome.

Rossetti AO, Lancet Neurol 2016; Callaway CW, Circulation 2015

Neuroimaging study

CT

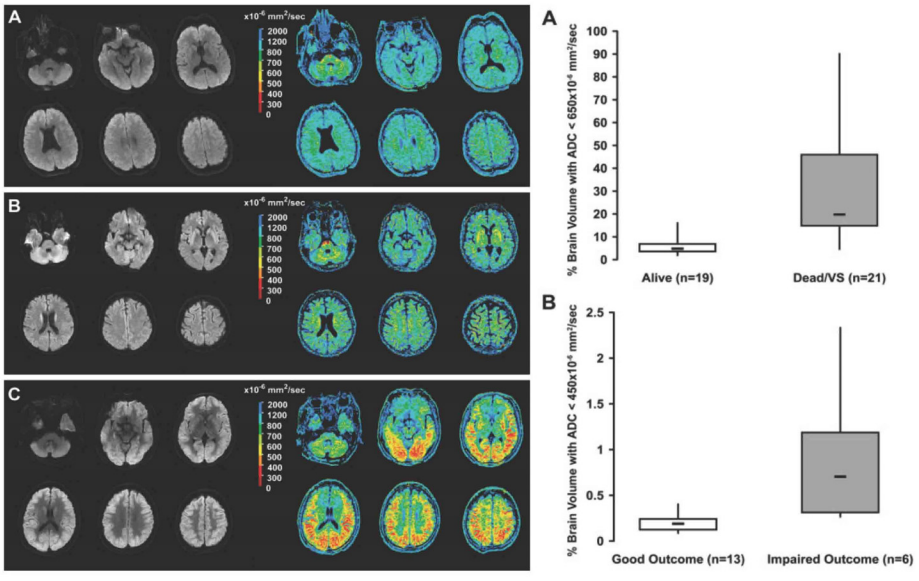
Reduced grey-white matter discrimination within 2 hr

MRI

Extensive restriction of diffusion on MRI at 2—6 days

Absence of diffusion changes does not consistently predict a good outcome (PPV 73% [45–92])

Rossetti AO, Lancet Neurol 2016; Callaway CW, Circulation 2015



Wijman CA, Ann Neurol 2009

	Feature related to good outcome	PPV (95% CI)	Feature related to poor outcome	FPR (95% CI)
Clinical examination				
Pupillary light reflex	Bilaterally present at >72 h	61% (50–71)	Bilaterally absent at >72 h	0·5% (0–2)
Corneal reflex	Bilaterally present at >72 h	62% (51–72)	Bilaterally absent at >72 h	5% (0–25)
Early myoclonus	NA	NA	Present at <48 h with epileptiform EEG (status myoclonus)	0% (0–3)
Early myoclonus	NA	NA	Present at <48 h with continuous reactive EEG	5–11% (3–26)
Motor reaction to pain	Flexion or better at >72 h	81% (66–91)	Absent or extension posturing at >72 h	10–24% (6–48)
EEG				
Background	Continuous at 12–24 h	92% (80–98)	Diffuse suppression or low voltage at 24 h	0% (0–17)
	Normal voltage at 24 h	72% (53–86)	Burst suppression at 24 h	0% (0–11)
Reactivity to stimuli	Present during hypothermia Present after return of normothermia	86% (76–92) 78% (64–88)	Absent during hypothermia Absent after return of normothermia	2% (0–9) 7% (1–15)
SIRPIDs	NA	NA	Present at any time	2% (0–11)
Repetitive epileptiform transients	NA	NA	Present during hypothermia	0% (0–30)
			Present after return of normothermia	9% (2–21)
SSEP				
SSEP recording	Bilaterally present	58% (49–68)	Bilaterally absent after return of normothermia	0·5% (0–2)
NSE				
Serum NSE concentration	<33 µg/L at 48 h	63% (52–83)	>120 µg/L at 48 h	0% (0–1)
	..	..	>68 µg/L at 48 h	1% (1–3)
Imaging				
Brain CT	Normal grey–white matter at 2–48 h	37% (9–75)	Reduced grey–white matter ratio at 2–48 h	0% (0–12)
Brain MRI	Absence of reduced diffusion at 24 h to 7 days	73% (45–92)	Reduced diffusion at 24 h Reduced diffusion at 7 days	0% (0–22) 54% (26–80)

Rossetti AO, Lancet Neurol 2016

	Strengths	Weaknesses
Clinical examination	Very low FPR for poor prognosis (especially pupillary light reflex); can identify early signs of awareness	Motor response might have high FPR (up to 25%) for poor prognosis; reliability might be reduced by residual sedation, organ failure, and hypothermia; myoclonus not invariably correlating with poor prognosis (needs to be integrated into EEG)
Electroencephalography	Low FPR for poor prognosis (especially absence of continuous background and reactivity); good accuracy in predicting favourable prognosis (especially presence of background and reactivity); allows detection and management of seizures	Absence of standardisation for stimulus application (reactivity); needs expert interpretation
Early somatosensory evoked potentials	Very low FPR for poor prognosis	Low accuracy in predicting favourable prognosis; has lower sensitivity than EEG for predicting poor prognosis; needs expert interpretation; not available everywhere
Biomarkers	Additional method to substantiate poor prognosis	Cannot reliably identify favourable prognosis; needs experienced laboratory staff and expert interpretation
Brain imaging	Additional method to substantiate poor prognosis	Cannot reliably identify favourable prognosis; needs high-volume centres and expert interpretation

FPR=false-positive rate.

Table 2: **Strengths and weaknesses of main prognostic methods**

Rossetti AO, Lancet Neurol 2016