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Case Report

A major miss in prognostication after cardiac arrest: Burst suppression and brain healing

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ABSTRACT

We report a case with therapeutic hypothermia after cardiac arrest where meaningful recovery far exceeded anticipated negative endpoints following cardiac arrest with loss of brainstem reflexes and subsequent status epilepticus. This man survived and recovered after an out-of-hospital cardiac arrest followed by a 6-week coma with absent motor responses and 5 weeks of burst suppression. Standard criteria suggested no chance of recovery. His recovery may relate to the effect of burst-suppression on EEG to rescue neurons near neuronal cell death. Further research to understand the mechanisms of therapeutic hypothermia and late restoration of neuronal functional capacity may improve prediction and aid end-of-life decisions after cardiac arrest.

1. Case report

A 71-year-old man with coronary artery disease, status postcoronary bypass 30 years prior, hypertension, diabetes, and atrial fibrillation presented after cardiac arrest, underwent therapeutic hypothermia, and upon rewarming, developed status epilepticus (SE). The SE was followed by generalized periodic discharges to maintain ACNS teminology (GPDs) and burst-suppression on EEG for 5 weeks, followed by a meaningful neurological recovery.

The patient was initially found at the bottom of a pool, pulseless, 10 min into a morning swim. Cardiopulmonary resuscitation (CPR) was initiated, and the automated external defibrillator confirmed a shockable rhythm. One shock was delivered, with return of a pulse within 10 min. He was intubated by EMS. In the emergency department, he initially withdrew all extremities to pain. Brainstem function was not documented. After sedation and paralysis, he had midline gaze with 2-mm unreactive pupils, absent corneals, absent gag, increased tone, and triple flexion in lower extremities, and pain induced no withdrawal in the upper extremities. The hypothermia protocol was initiated. Cardiac catheterization showed chronic severe three-vessel disease but no acute injury. Head CT scan showed minimal loss of gray-white differentiation. During rewarming, continuous electroencephalogram (EEG) recording revealed SE (Fig. 1A), and occasional brief 20-second episodes of left pectoral muscle contractions were observed. Levetiracetam and lorazepam were continued, and valproic acid and propofol were started, and seizures improved. The patient's score on the Glasgow coma scale remained at 3, without vestibulo-ocular, gag, and corneal reflexes. He recovered left pupil reactivity at 48 h. While electrographic seizures stopped three days after cardiac arrest, abundant GPDs persisted every few seconds (Fig. 1B).

Propofol was increased, and burst-suppression on EEG was achieved on day 5 post-arrest. Despite an increased burst-suppression ratio up to 1:30 with 1-second bursts of moderate amplitude sharply contoured theta and delta slowing followed by 30 s of very low amplitude/voltage diffuse delta slowing, there were still runs of high amplitude GPDs (Fig. 2). On day 9, phenobarbital was loaded. By day 13, both lorazepam and propofol were weaned off, but he remained in burst-suppression. During this time, the neurological team suggested withdrawal of care based on American Academy of Neurology practice parameters that absent brainstem reflexes at 72 h predict poor outcome with high specificity [3]. The absence of corneal reflexes 19 days after a cardiopulmonary arrest was viewed as incompatible with any meaningful recovery. Further, absence of motor response at 7 days is considered an absolute cutoff [4]. The family declined withdrawal of care.

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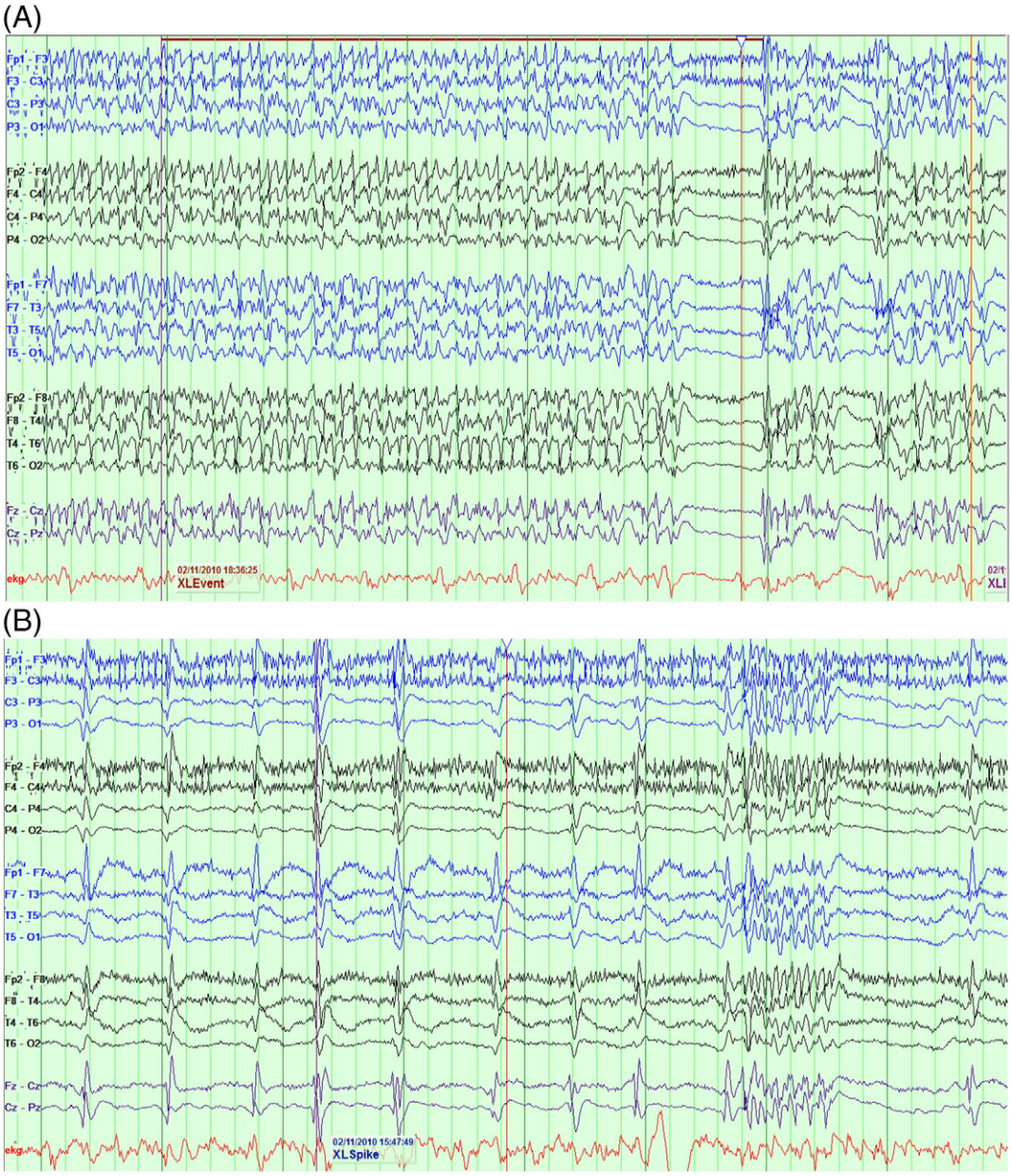

Fig. 1. EEG patterns during initial coma: (A) electrographic SE; (B) generalized periodic discharges.

Over the next week, phenobarbital was weaned off, and the patient's EEG pattern remained in a continuum between burst-suppression and a discontinuous diffusely slow background on EEG. The burst-suppression ratio ranged from 1:1 to 1:2 with 1-second bursts of moderate amplitude delta and theta slowing followed by 1–2 s of very diffuse low amplitude delta slowing. The discontinuous background was several seconds of moderate amplitude slowing with occasional one-second bursts of diffuse low voltage activity (Fig. 3). He remained in a deep coma, had return of corneal reflexes, but had no oculocephalic response, no tracking, no spontaneous eye opening, no limb movement to noxious stimuli, and no autonomic response to nailbed pressure. The family again declined withdrawal of care.

He showed trace pupil and corneal reflexes on day 20. By day 30, there were small movements noted in his face and hand, and by day 37 post-arrest, he was more alert, opening his eyes spontaneously but not following commands. The alternating EEG pattern continued until day 37 postcardiac arrest. Subsequent milestones included the following; opening eyes to name, smiling to various stimuli, and purposeful movement of the right arm and legs spontaneously (45 days), speaking intelligible words and command following (50 days), speaking in short sentences (day 55), and interacting and answering questions appropriately and following 1-step commands consistently (day 60). The patient was discharged to an acute rehabilitation facility on day 79 and was interacting well, moving all extremities, and following simple commands. A graphic display to illustrates the improvement of cognitive status over time is depicted in Fig. 4. He has residual impairments in sustained attention, executive function, naming of low frequency items, and mild short-term memory. However, he can speak extemporaneously in public forums, travel internationally on family vacations, and participate in diverse physical and social activities.

His EEG improved throughout, becoming more continuous after day 40 with isolated generalized bursts of spike-and-wave discharges every 2–8 s. His last inpatient EEG on day 73 showed disorganized background with a posterior-dominant rhythm of 6 Hz without normal sleep patterns. Six months after discharge, normal sleep transients

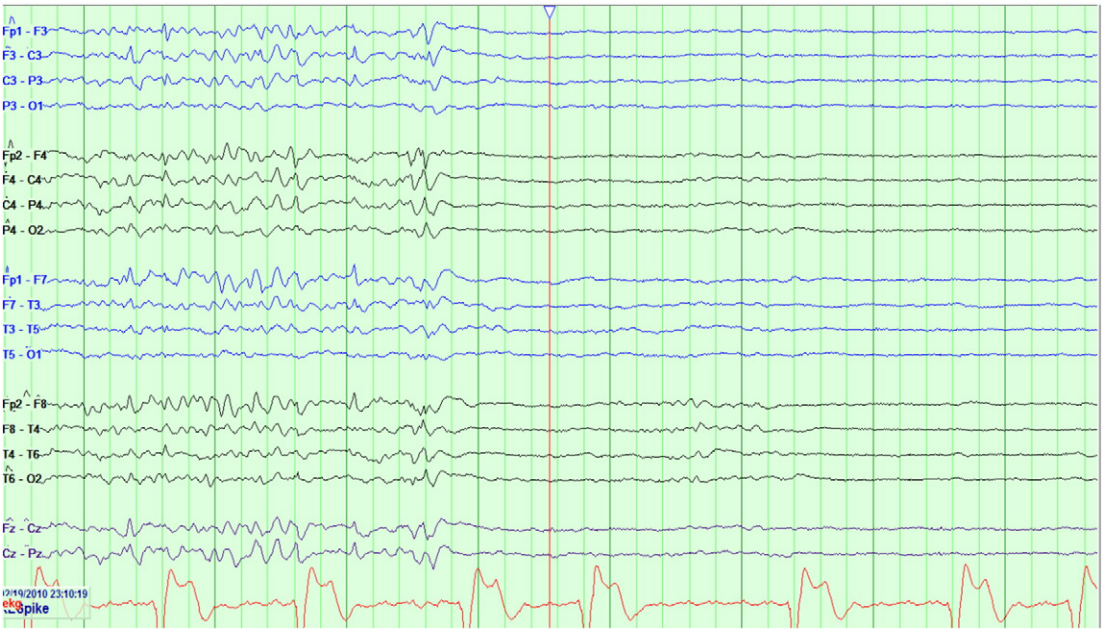

Fig. 2. EEG pattern of burst suppression on day 10.

reappeared with an organized background, mild generalized slowing of the background activity, and bilateral, independent and bisynchronous, frontotemporal epileptiform discharges. Over the next year, the background organization improved with the return of a normal posterior-dominant rhythm with epileptiform activity becoming less frequent. He remains on levetiracetam and valproate.

2. Discussion

This case illustrates the unprecedented finding of recovery of consciousness, fluent speech, ambulation, wide range of executive functions, and anterograde memory after over 6 weeks of coma following an out-of-hospital cardiac arrest treated with hypothermia but with prolonged and severe seizure activity that would predict futility by current dogma. Predictors of poor neurological outcome at 24, 48, and 72 h after cardiac arrest had previously guided prognosis [1,2] and recommendation by the neurological team to withdraw care. However, the family declined, and he later developed EEG burst-suppression. On day 30, he started to spontaneously awaken and went on to make a remarkable recovery.

The American Academy of Neurology practice parameters conclude that absent brainstem reflexes or absent extensor motor response at 72 h predicts poor outcome with high specificity [3]. However, these predictors are less reliable with therapeutic hypothermia, and current guidance suggests caution in forming prognostic statements after therapeutic hypothermia [2]. As in our case, patients without pupillary, oculocephalic, or corneal reflexes between 36 and 72 h or with EEG burst-suppression pattern with generalized epileptiform activity have

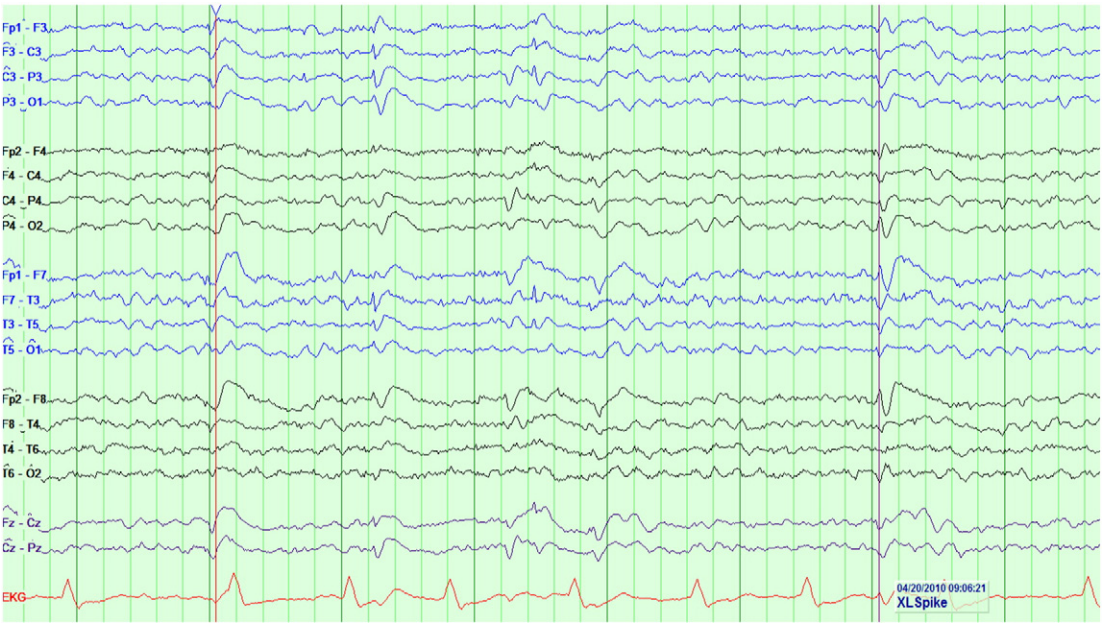

Fig. 3. EEG pattern on day 72 showed improved, continuous, background and intermittent left frontotemporal spikes.

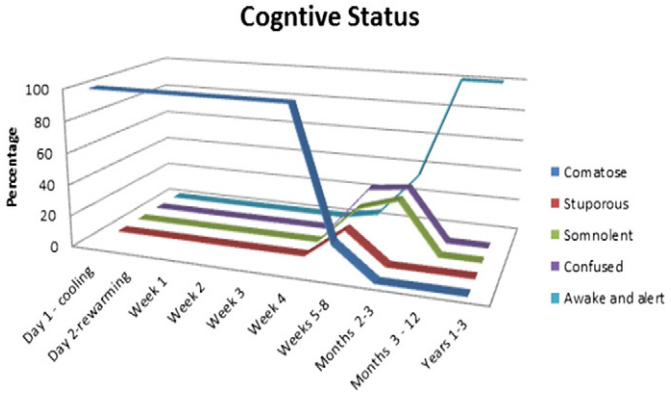

Fig. 4. Changes in level of consciousness and alertness over the course of recovery.

variable recovery [5–7]. Pupillary reflexes are spared in a barbiturate or benzodiazepine coma supporting that loss of pupillary responses early into cooling results from anoxic injury [8]. Hypothermia has changed the prognostic outlook, and irreversible management decisions should be delayed for several days. However, the absence of corneal and pupillary light reflexes 19 days after a cardiopulmonary arrest in a 71-year-old is still frequently viewed as incompatible with meaningful recovery. Despite late recovery of motor response 6 days after hypothermia [2], absence of motor response at 7 days has been considered an absolute cutoff with no examples of recovery in large population studies; [4] thus, recovery of motor response after 6 weeks of coma is an extreme outlier against prior observations. Currently, for our patient, standard medical care would withdraw therapy; thus illustrating the limits of prognostic guidelines.

Our patient's EEG was initially reactive which supports brain functional integrity [7]. We postulate that continuation of burst-suppression after withdrawal of sedative treatment may provide a clue regarding the underlying mechanism of late recovery. Modeling studies [9] of burst-suppression on EEG suggest that ATP-gated potassium channel activation stabilizes cell membranes, leading to alternating periods of activity and suppression with diminished ATP and neuronal firing. Such conditions occur with severe deafferentation, markedly decreased metabolic rates (i.e., general anesthesia), or alterations in subcellular energy produced by hypoxic effects on mitochondria. Burst-suppression may reflect an intrinsic mechanism used to rescue neurons from cell death, and therapeutic hypothermia may extend its effects, facilitating recovery of neurons on the edge of programmed cell death where clinical criteria [1] predict their demise. In hypoxic/ischemic injury, diffuse injury impairs metabolic regulation, leading to a recovery of basal dynamics at the neuronal circuit level caused by transient increases in energy [7,10]. Burst-suppression correlates with reduced extracellular calcium, which may prevent synaptic transmission [11]. Downstream subcellular consequences are unknown but “stunning” and hibernating of excitable cardiac tissue after hypothermia can occur [12]. Our patient's clinical course and electrophysiological findings suggest a role of cellular energy reserve in slow recovery of brain function after severe brain injuries (Fig. 5). Is burst suppression an adaptive response that facilitates brain healing? Future research is needed to define the mechanisms that underlie brain resilience and recovery.

3. Conclusion

This case far exceeds all existing known endpoints for patterns of recovery following cardiac arrest and highlights the need for prolonged monitoring periods [13]. Similar recoveries arise in traumatic brain injuries and can be measured at the population level 2 to 5 years after injury [14]. New prognostic frameworks are needed that can accommodate evolving data about the course of recovery following therapeutic hypothermia and how to recalibrate decisions to withhold or withdraw life-sustaining therapies based on preexisting criteria [1], which may no longer be valid and prone to misinterpretation. Patients who formerly would have died or remained permanently vegetative are a new cohort that the acute care system is not currently prepared for, and this single case warrants careful consideration of its possible generalizability [15]. These observations demonstrate an urgency to establish a mechanistic understanding of the impact of hypothermia on recovery of neuronal function after anoxic injury to guide rational decision-making in postcardiac arrest care.

Separate out the Ethical statement from the manuscript's conclusion. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Contributorship statement

Danielle A. Becker, MD, MS — data analysis, writing, and editing.
Nicholas D. Schiff, MD — clinical care, data analysis, writing, and editing.
Lance B. Becker, MD — data analysis, writing, and editing.
Manisha G Holmes, MD — data analysis.
Joseph J. Fins, MD — writing and editing.
James M. Horowitz, MD — writing and editing.
Orrin Devinsky, MD — clinical care, data analysis, writing, and editing.

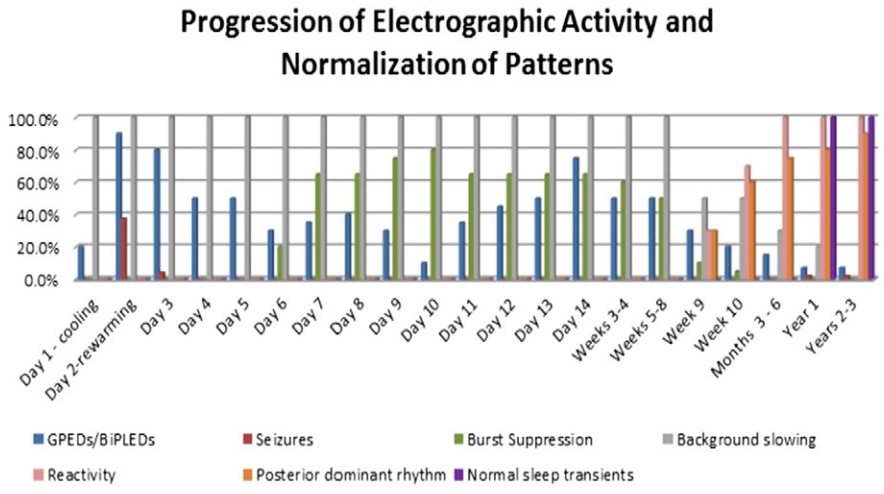

Fig. 5. Changes in electroencephalogram over the course of recovery.

Conflict of interest

There are no conflicts of interest.

Acknowledgments

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