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Editorial

Optimizing early assessment of neurological prognosis after cardiac arrest

Cómo optimizar la valoración precoz del pronóstico neurológico tras la parada cardiaca

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Cardiac arrest (CA) continues to be a major public health issue in our environment, with an estimated incidence in Europe of 118 cases/100 000 population per year. Survival to discharge, which varies highly among countries but is about 8% overall, reflects the huge room for improvement remaining in the management of this complex condition.[1] Cardiac dysfunction after resuscitation is the main cause of death in the first 72 hours and is, overall, the second most common cause of in-hospital mortality after CA. This dysfunction particularly occurs in the first 24 hours after admission, given that evidence shows that the cardiac index reaches its lowest point 8 hours after recovery of spontaneous circulation and starts to improve again after 24 hours, often returning to normal at 72 hours.[2] About 10% to 15% of patients recovered from an out-of-hospital CA experience profound cardiogenic shock and will require circulatory support.[3] When this initial phase of hemodynamic instability is overcome, the most frequent cause of death is an irreversible neurological deficit that usually culminates in limitation of therapeutic effort (LTE). The neurological sequelae are the cause of death in two-thirds of out-of-hospital CA patients.[3] Determination of the severity and reversibility of this neurological deficit is one of the main challenges facing clinicians managing CA.

Clinical practice guidelines and various consensus documents all favor a multimodal assessment involving patient examination, electroencephalography, biomarkers, and imaging techniques.[3,4] This approach entails the performance of complementary tests of varying complexities, coordination among different professionals, and an inevitable delay, with the aim of establishing an approximate prognosis from 72 hours after the CA.[4–6] This multimodal assessment is recommended because no single examination can consistently achieve 100% accuracy. With the combination of all of the information, one can attempt to define in the most reliable manner possible the potential for neurological recovery (PNR) and, based on the integrated findings, consider the appropriateness of the life support measures. The main considerations, level of accuracy, and time at which these recommended complementary examinations should be interpreted are summarized in table 1. Definition of an unfavorable prognosis and poor PNR can lead to LTE decisions, and the complementary tests should thus provide high specificity and accuracy. The false-positive rate that has been established as acceptable is 0.1%, according to a survey completed by expert professionals.[3] In addition, we must highlight the added difficulty represented by the temporal discordance between the hemodynamic instability developing in the first 24 hours of hospitalization after CA and the complex definition of an accurate neurological prognosis. In this context, one of the problems faced by clinicians in the management of these patients is the need to make complex therapeutic decisions at an early stage, with a prognosis marked by myocardial dysfunction when the neurological prognosis and PNR are not yet established.[7,8] This may involve the performance of fruitless procedures in patients with poor neurological prognosis, with substantial resource consumption and false hopes for relatives concerning recovery.[5] On the other hand, LTE in this phase may limit the chances of recovery in some patients.

In an interesting article published recently in *Revista Española de Cardiología*, Arbas-Redondo et al.[9] propose the use of the bispectral index (BIS) and suppression ratio (SR) as accessible monitoring tools in the early phase and at the bedside to obtain information on the PNR and, with it, guide any required clinical decision-making. The authors analyzed a series of 340 patients admitted after a CA with available BIS and SR values and a mean age of 61.7 years; 72 (21.2%) were women. After the first comprehensive neurological evaluation, 211 (62.1%) had a good neurological course (Cerebral Performance Category [CPC] score 1-2) and 129 had an unfavorable prognosis (CPC 3-5). The main factors associated with a good neurological course were an initial shockable rhythm, witnessed arrest, low serum lactate levels, and elevated pH. The hourly values of the BIS and SR during the first 48 hours significantly differed by neurological course. In patients with a good course, the mean values of the BIS were significantly higher while the mean values of the SR were significantly lower. In addition, the differences found in the BIS and SR were more marked in the first 12 to 24 hours of monitoring. A cutoff for the BIS > 26 during the first 12 hours predicted a good neurological course with a sensitivity of 89.5% and specificity of 75.3% (area under the

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Table 1
Classical variables in the multimodal assessment of neurological prognosis.

	Specificity	Sensitivity	Time of maximum accuracy	Influence of sedation/ relaxants	Considerations
Patient examination					The examination should be performed without sedatives or relaxants
Pupillary reflex	100% (96 h)	20%-25%	≥ 72 h	Yes	Subjective, pupillometry is recommended
Corneal reflex	Variable	25%-40%			
Motor response to pain	—	60%			
SSEP N20	100%	45%	≥ 24 h	No	Requires qualified staff, difficult interpretation. Availability varies among centers. In patients subjected to hypothermia, a delayed evaluation (72 h) is recommended
EEG					Requires qualified staff, difficult interpretation. Availability varies among centers
Status myoclonus	99%-100%	69%-82%	≥ 72 h	Yes	
Continuous-reactive	82%-92%				
Neuron-specific enolase	75%-100%	7.8%-83.6%	≥ 48-72 h	No	Affected by hemolysis and neuroendocrine tumors. Importance of its kinetics. Heterogeneity among laboratories
Brain CT	Variable	28%-40%	< 24 h	No	Heterogeneity in the calculation. Need to create reference values for center
Gray matter/white matter ratio					
Brain MR	100%	50%	48-220 h	No	Limited availability, varies among centers

CT, computed tomography; EEG, electroencephalography; MR, magnetic resonance; SSEPs, somatosensory evoked potentials.

ROC curve [AUC], .869). Similarly, a cutoff for the SR > 24 during the first 12 hours predicted a poor course with a sensitivity of 91.5% and specificity of 81.8% (AUC, .906). In their conclusions, the authors highlight the predictive ability of both parameters to help to optimize the prediction of PNR.

The BIS is based on electroencephalographic principles, translates the waves into a numerical value between 0 and 100, and collects the percentage of time in which activity is suppressed (wave amplitude < 0.5 μV).[10] It was designed to monitor depth of anesthesia during surgery, although its use has been widened to monitor depth of sedation in intensive care units. In this context, the BIS has several advantages: it is easy to obtain and interpret, it is noninvasive, it can be determined at the bedside in critical care units, and it can be continually recorded. The application of the BIS to prognosis is nonetheless associated with some difficulties. Considerable heterogeneity is evident in the studies both in relation to the target population (out-of-hospital and in-hospital CA, use of hypothermia, use of sedation and/or muscle relaxants) and in the assessment of the BIS (time of measurement, use of minimum, maximum, and average values, measurement quality), which makes it difficult to reach robust conclusions. The authors recognize these limitations[9] and highlight the fact that they failed to analyze the impact of sedative dose on BIS and SR values. In this regard, a recent systematic review of the literature[11] determined an AUC of .92 for a BIS cutoff < 32 to define a poor neurological prognosis and did not report differences in the diagnostic ability of BIS by application of hypothermia, sedation, or neuromuscular blockade. The prognostic value of the BIS and SR independently of sedation has been identified in other work.[12] In addition, the complex clinical context of CA makes it likely that some confounding factors have not been included in most studies. In their article, Arbas-Redondo et al.[9] provide a valuable analysis of the incremental predictive ability of BIS and SR values for known predictors of PNR (age, witnessed arrest, bystander resuscitation, initial rhythm, no-flow interval, time to recovery of spontaneous circulation, glycemia, pH, and serum lactate at admission), with a significant increase in the AUC values with the inclusion of the BIS and SR variables in the predictive models.

Despite the limitations, there are pertinent data in the literature concerning the use of the BIS to predict neurological prognosis. Burjek et al.[13] reported that the BIS value in the seventh hour after ICU admission exhibited the best prognostic value. Similarly, experimental models regarding cerebral ischemia-reperfusion injury showed that mitochondrial dysfunction and free radical production drive the neurotoxicity that occurs in the first 6 hours after a CA.[2] Patients with a poor neurological prognosis had a significantly lower mean BIS value and, for every 10-point drop in the BIS, the odds ratio of poor neurological recovery increased by 59%.[13] Also reported has been the prognostic value of the SR and, particularly, the changes seen in that rate after sedation withdrawal. A possible explanation for this relationship is that the most injured brains are more sensitive to sedation, which is why they show major changes in the SR with sedation initiation and withdrawal.[12] In addition, the BIS has exhibited good ability to predict brain death in patients recovered from refractory CA via extracorporeal membrane oxygenation both in hypothermia and after rewarming. Jouffroy et al.[14] identified a BIS value < 30 as the cutoff point with the best sensitivity (96%) and specificity (82%) for predicting brain death. This has relevant clinical implications because an early diagnosis of brain death can limit costs and reduce stress on loved ones as they await an outcome and can help the patients to become donors before the development of any instability that might irreversibly damage their organs.[14] Another very valuable use of the BIS is in the highly sensitive and specific detection of a status epilepticus pattern.[15] This also has major clinical relevance because up to one-third of patients with CA have often under-diagnosed convulsions, and mortality exponentially increases with their duration. On the other hand, the performance of an electroencephalogram in the first few hours after a CA can be logistically complicated in many centers and varies by availability or time or day of admission.

Table 2
Scales for prognostic evaluation after cardiac arrest.

Scale	Variables included							AUC
$MIRACLE_2$	Witnessed CA	Nonshockable rhythm	Rhythm change during CA	Nonreactive pupils	Age	pH < 7.20	Epinephrine administration	0.90
OHCA	Time to CPR	Initial rhythm	Time of CPR	Lactate	Creatinine	—	—	0.82
CAHP	Time to CPR	Nonshockable rhythm	Time to ROSC	Location of CA	Age	pH	Epinephrine administration	0.93
TTM	CA at home	Nonshockable rhythm	pCO_2	Bilateral absence of corneal and pupillary reflexes	Age	pH	Epinephrine administration	0.84

AUC, area under the curve, defined in the population of the original study; CA, cardiac arrest; CAHP, cardiac arrest hospital prognosis; CPR, cardiopulmonary resuscitation; OHCA, out-of-hospital cardiac arrest; pCO_2, partial pressure of CO_2; ROSC, recovery of spontaneous circulation; TTM, target temperature management.

Overall, there is no reference value for the BIS in the literature for establishing a specific neurological prognosis. In the work by Arbas-Redondo et al.,[9] the evaluation applied by the authors according to the protocol of the center and the cutoff point established were highly accurate for identifying a poor prognosis (CPC score 3-5) because, at 3 months, only 1 patient (0.3%) was categorized as having a good prognosis (CPC score 1-2). Another important aspect regarding the application of the BIS in clinical practice is the role of electromyography as the main source of error in their interpretation. Accordingly, and as recommended by Arbas-Redondo et al.,[9] a structured measurement protocol is required that assesses the quality of the recording and weighs up the use of muscle relaxants before BIS interpretation.

Ultimately, the BIS can be considered a valuable tool for the evaluation of neurological prognosis, a particularly difficult task in the first few hours of admission when patients have more hemodynamic instability. Its interpretation must go hand-in-hand with indicators with established value and available at admission, such as no-flow interval, cardiopulmonary resuscitation (CPR) time (low-flow interval), the total time from resuscitation to recovery of spontaneous circulation, the baseline pH and lactate, and the bedside neurological examination. Nonetheless, these data are not without their own limitations, given that the information collected from witnesses who provide an estimated or illustrative time is not 100% reliable. In addition, the clinical examination is usually difficult in patients undergoing sedation and analgesia, and sometimes administered muscle relaxants, and even more so in patients managed with therapeutic hypothermia. These limitations have prompted the development in recent years of different scales whose calculation may provide an additional means for clinical decision-making. These scales are summarized in table 2. The Out-of-Hospital Cardiac Arrest (OHCA)[7] score considers initial rhythm, no-flow interval, low-flow interval, lactate, and creatinine; the Cardiac Arrest Hospital Prognosis[8] (CAHP) score collects time to CPR, initial rhythm, time in CA, CA setting, age, pH, and epinephrine administration; the Target Temperature Management (TTM)[6] score includes initial rhythm, time to CPR, total CPR time, age, CA at home, epinephrine administration, bilateral corneal/pupillary reflex, motor response, pH, and pCO_2; and, finally, the $MIRACLE_2$ score[5] collects initial rhythm, change of rhythm during CA, witnessed CA, age, nonreactive pupils, pH $<$ 7.20, and epinephrine administration. Despite their potential usefulness, these scores have been designed using specific cohorts, and this may result in limited external validity.[6] In addition, classic risk scales for severely ill patients (eg, APACHE II[16]) have also been used, which provide inferior prognostic information by omitting specific data on recovered CA.[17] Furthermore, we must highlight the predictive value of some factors such as serial measurement of enolase to optimize the prediction of PNR in patients with recovered CA.[17]

In summary, a neurological prognosis must be established for CA in the initial phase of hemodynamic instability as a basis for any circulatory support-related decisions. As shown in the findings of Arbas-Redondo et al.,[9] the BIS could be valuable for this early assessment and offers advantages related to its low invasiveness and high availability. It can also be determined in patients administered hypothermia, sedation, and muscle relaxants but, to be reliable, its evaluation must be meticulous and protocol-based and conducted by experienced persons. Regardless, and as recommended by the authors, none of the above should replace the multimodal assessment recommended in the clinical practice guidelines. Any hypothetical LTE due to poor neurological prognosis must be as accurate and specific as possible and based on the combined assessment of different aspects of the exceedingly complex neuronal function.

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