Early Prognostic Evaluation After Mild Therapeutic Hypothermia in Sudden Cardiac Arrest Survivors

Valoración pronóstica precoz de pacientes con muerte súbita recuperada sometidos a hipotermia terapéutica

To the Editor,

The presence of severe neurological sequelae following sudden cardiac arrest leads to heavy resource use. Therapeutic hypothermia is indicated to prevent severe brain damage (SBD) although this treatment\textsuperscript{2,3} and prognostic evaluation in this setting are controversial. Prognostic evaluation basically has 2 objectives: first, to inform the family of the possibilities of recovery and, second, to aid diagnostic and therapeutic decisions. A neurological evaluation using several variables is recommended from the third day after injury. In contrast, information on the early prediction of SBD has received much less attention.

The aim of this study was to design a model for predicting SBD using the admission data of consecutive patients who survived cardiac arrest of probable cardiac origin and who underwent therapeutic hypothermia.

Data from patients admitted to the cardiology intensive care unit at our center were collected between November 2009 and January 2014. Their clinical and analytical data were recorded, as well as their clinical course while in hospital. Hypothermia was applied using an Artic-Sun\textsuperscript{8} device (33 °C 24-hour and rewarming at 0.25 °C/h). Neurological outcome was measured using the Cerebral Performance Category (CPC) scale. Patients with a CPC 3 to 5 and those who died during hypothermia were considered to have SBD. In patients with no recovery of consciousness after completing hypothermia and withdrawal of sedation, an electroencephalogram was performed 72 to 96 hours after admission, as well as an evoked potentials test to determine the presence of the N20 wave, which indicates cortical response.

A model for predicting SBD was designed using various variables available early on. The analysis included the variables available at admission that showed a statistical association (P < .2) with the onset of SBD. The predictive model was obtained using binary logistic regression and ROC curve analysis (PASW Statistics 19.0; Chicago, Illinois, United States), prioritizing the simplicity of the measure and the reproducibility of its component variables, as well as the statistical criteria of the lowest Mallows’ Cp, the greatest area under the ROC curve (AUC), and maximum parsimony of the model.

The total number of patients treated (n = 100), 1 was excluded for being deemed unsuitable. The patient characteristics and their in-hospital clinical course are summarized in the Table.

The incidence of SBD was 57 of 99 (57.6%). The distribution by CPC categories at discharge was: CPC1, 34 of 99 (34.3%); CPC2, 8 of 99 (8.1%); CPC3, 5 of 99 (5.1%); CPC4, 38 of 99 (38.4%); and CPC5, 12 of 99 (12.1%); the 2 remaining patients (2.1%) died before reaching normothermia.

At admission, the variables associated with SBD were initial lactate level, metabolic acidosis, myoclonus, absence of motor activity, time to start of cardiopulmonary resuscitation, and age. Other variables associated with SBD were myoclonic status at the end of hypothermia, persistent metabolic acidosis, and the absence of cortical response in evoked potentials.

The technical aspects and complications associated with the treatment were not correlated to SBD.

The final predictive model, comprising 3 components (age, initial lactate, and myoclonus at admission) showed an AUC of 0.85 (95% confidence interval, 0.76–0.94). The Figure shows the ROC curve of the predictive model.

In patients undergoing therapeutic hypothermia, neurological recovery may be delayed by the effect of sedation or by therapeutic hypothermia in the brain. Current recommendations stipulate that neurological evaluation should be delayed for more than 72 hours and should be based on multiple predictors, as no individual variable can completely rule out a delayed recovery.

There is little information on early prognostic evaluation in patients with sudden cardiac arrest. Recently, Aschauer et al\textsuperscript{4} analyzed a series of 1932 patients with out-of-hospital sudden cardiac arrest and obtained a risk of death score at 30 days with 4 variables with a remarkable predictive capacity (AUC = 0.81). The main difference with our series was the objective variable. In our opinion, all-cause mortality (bleeding, infections, etc) and SBD are outcomes with significant conceptual differences and different socioeconomic consequences. In addition, some of the variables included, despite being powerful predictors (amount of adrenaline administered, minutes to recovery of spontaneous circulation), are sometimes difficult to measure accurately given the emerging nature of the event. In our series, priority was given to the

![Figure. ROC curve of severe brain damage prediction with the final predictive model.](http://dx.doi.org/10.1016/j.rec.2014.09.007)
simplicity, objectivity, and reproducibility of the variable measurement, while recognizing the existence of multiple SBD predictors, as shown in other studies. The model obtained was parsimonious, using only 3 predictors and optimal predictive capacity.

Nevertheless, the practical applicability of these findings involves the design of a risk score by weighing up the importance of each variable and establishing bands of scores applicable to other series. We believe that to do this, a larger sample size would be necessary, as well as external validation with a different sample. Other limitations relate to a single-center register and the partial availability of factors such as neuron-specific enolase, electroencephalograms, and inflammatory markers.

It is important to highlight that this early prognostic approach must not under any circumstances replace a detailed multidisciplinary evaluation once sedation has been withdrawn, as decisions regarding maintenance of the therapeutic effort should be made carefully and be based on parameters with near-100% specificity. The primordial objective of this study was to illustrate a simple and quick way of making an early neurological evaluation in this situation. Given the routine sequence of actions (induction-maintenance-rewarming-withdrawal of sedation), information is usually scarce in the first 72 hours and our findings can complement a later evaluation and improve the information for the patient's family, especially when neurological recovery seems likely.
Circadian Blood Pressure Pattern and Cognitive Function in Middle-aged Essential Hypertensive Patients

Patrón circadiano de la presión arterial y función cognitiva de pacientes de mediana edad con hipertensión esencial

To the Editor,

Several studies have shown a relationship between hypertension and cognitive impairment, especially in elderly people. However, data on the relationship between the circadian blood pressure (BP) pattern and cognitive function are conflicting. Differences among studies could be due to sample characteristics: most participants were elderly, diabetic, had previous history of cardiovascular disease, or were undergoing antihypertensive therapy, which could influence their cognitive status. This study investigated the relationship between the circadian BP pattern and cognitive function in a homogeneous sample of asymptomatic, middle-aged, never-treated essential hypertensive patients.

Fifty-six never-treated essential hypertensive patients (37 men), aged 50-60 years (mean [SD] age 54.3 [3.1] years) without clinical evidence of target organ damage were consecutively selected from the Hypertension Unit of Hospital Clinic, Barcelona, Spain. Exclusion criteria included type 2 diabetes mellitus (fasting plasma glucose > 6.6 mmol/L), carotid stenosis > 50% measured by ultrasonography, alcohol intake > 30 g of pure ethanol per day, sleep apnea syndrome, clinical evidence of cerebrovascular or coronary heart diseases, cardiac failure, atrial fibrillation, papilledema, and renal impairment (serum creatinine > 115 μmol/L).

All patients underwent 24-hour ambulatory BP monitoring. The nocturnal drop in BP was calculated as the difference between average daytime and nighttime systolic BP (SBP) values.

Cognitive function was evaluated by a battery of neuropsychological tests that included an Intelligence Quotient estimation (Vocabulary and the Kohn block design subtests of the Spanish adaptation of the Wechsler Adult Intelligence Scale), tests of attention and working memory (Digit Forward and Backward Span test, respectively, from the Wechsler Adult Intelligence Scale-Revised), and tests for evaluating memory (the Russell Revision of the Logical Memory subscale and the Visual Reproduction subscale of the Wechsler Memory Scale).

Thirty-four hypertensive patients were found to be nondippers (nocturnal SBP fall less than 10%). The main baseline characteristics, including age, sex distribution, body mass index, serum fasting glucose, lipid profile, renal function, duration of hypertension, and smoking status did not differ between these 2 groups. Nondippers had significantly higher values of nighttime SBP and diastolic BP than dippers (Table 1).

In the neuropsychological evaluation, no differences in intelligence, education, or anxiety or depression scales were observed between the 2 groups. Nondippers had lower scores on the working memory test and the logical memory test than dippers but this difference was not statistically significant (Table 2). Nondipper hypertensive patients performed significantly worse on the visual memory test than dippers. This association remained significant (P = .033) after adjustment for 24-hour SBP and diastolic BP values, and also for age and level of education (P = .029). In addition, we found a significant correlation between the nocturnal drop in SBP and better performance on the visual memory test (r: 0.407; P = .003).

This study shows an association between the presence of nondipping BP status and worse performance on the visual memory test. In addition, there was a significant correlation between the nocturnal drop in SBP and better performance on the visual memory test.

Kilanderr et al. reported in 999 patients aged 70 years old that the mean cognitive score was lower in nondippers than in dippers. In this study, cognitive function was mainly assessed by the Mini-Mental State examination, and some of the individuals were diabetic or had a previous history of stroke. In the present study, cognitive function was assessed by means of a battery of neuropsychological tests that is more sensitive to early or subtle cognitive impairment than the Mini-Mental State examination. It is known that age-related cognitive decline is more pronounced in speed performance functions than in verbal or visual spatial tests. High BP seems to first alter memory domains, such as visual reproductions-immediate and delayed recall. Kawas et al. showed that poor visual memory performance may represent an early expression of Alzheimer disease years before diagnosis. However, it is unclear whether the mild disturbance in the visual memory test may represent the skills most susceptible to disruption and those that decline first as a result of high BP.

Table 1

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<th>Twenty-four-hour Blood Pressure Values</th>
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<td>Dippers</td>
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<td>24-h SBP, mmHg</td>
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DBP, diastolic blood pressure; SBP, systolic blood pressure. Values are expressed as mean (standard deviation).