Resuscitation 100 (2016) 18–24

Contents lists available at ScienceDirect

Resuscitation

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

Clinical paper

Prognostication of cardiac arrest survivors using low apparent diffusion coefficient cluster volume☆

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ARTICLE INFO

Article history:
Received 6 September 2015
Received in revised form 1 December 2015
Accepted 19 December 2015

Keywords:
Cardiac arrest
Brain ischemia
Coma
Magnetic resonance imaging
Prognosis
Computer-assisted image analyses

ABSTRACT

Introduction: We developed a new neuroprognostication method for cardiac arrest (CA) using the relative volume of the most dominant cluster of low apparent diffusion coefficient (ADC) voxels and tested its performance in a multicenter setting.
Methods: Adult (>15 years) out-of-hospital CA patients from three different facilities who underwent an MRI 12 h after resuscitation were retrospectively analyzed. Patients with unknown long-term prognosis or poor baseline neurologic function were excluded. Average ADCs (mean and median), LADCV (relative volume of low-ADC voxels) and DC-LADCV (relative volume of most dominant cluster of low-ADC voxels) were extracted using different thresholds between 400 and 800×10^{-6} mm^2 s^{-1} at 10×10^{-6} mm^2 s^{-1} intervals. Area under the receiver operating characteristic curve (AUROC) and sensitivity for poor outcome (6-month cerebral performance category score >2) while maintaining 100% specificity were measured.
Results: 110 patients were analyzed. Average ADCs showed fair performance with an AUROC of 0.822 (95% confidence interval [CI], 0.744–0.900) for the mean and 0.799 (95% CI, 0.716–0.882) for the median. LADCV showed better performance with a higher AUROC (maximum, 0.925) in an ADC threshold range of 400 to 690×10^{-6} mm^2 s^{-1}. DC-LADCV showed the best performance with a higher AUROC (maximum, 0.955) compared with LADCV in an ADC threshold range of 600 to 680×10^{-6} mm^2 s^{-1}. DC-LADCV had a high sensitivity for poor outcomes (>80%) in a wide threshold range from 400 to 580×10^{-6} mm^2 s^{-1} with a maximum of 89.2%.
Conclusions: Quantitative analysis using DC-LADCV showed impressive performance in determining the prognosis of out-of-hospital CA patients in a multicenter setting.

Introduction

The incidence of out-of-hospital cardiac arrest (OHCA) in the United States is increasing, with approximately 326,200 EMS-assessed cases in 2011.[1] Despite the many scientific advancements in resuscitation and post-cardiac arrest (CA) care, its prognosis is still grave.[2,3] According to CARES registry data, the chance of achieving a good neurologic outcome was at 8.3%.[4] Therefore, the prognostication of cardiac arrest patients has become important and various modalities have been developed.[5] However, their credibility has been challenged since the widespread adoption of therapeutic hypothermia which often requires the administration of sedatives and paralytics to the patients whose cellular and drug metabolism are often impaired.[6,7]

Recently, brain magnetic resonance imaging (MRI), more specifically diffusion-weighted (DW) imaging, has shown promising

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2015.12.013.
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http://dx.doi.org/10.1016/j.resuscitation.2015.12.013
0300-9572/

results for the long-term prognostication of comatose CA patients.[8–17] The methods are very diverse, but the most common approaches include use of a scoring system or apparent diffusion coefficient (ADC) sampling from hand-drawn regions of interest (ROI) that requires subjective human interpretation of lesion characteristics or brain anatomy. In contrast, the quantitative analysis of whole brain ADC map data can provide objective results. However, how to quantify a large array of ADC values of a brain is not yet clear. The largest study on this topic used averaged ADC values.[9] The second largest study reported the relative volume of low-ADC voxels might be useful.[8] In a similar approach, we previously reported a 2D area of the largest interconnected low-ADC pixels (dominant low-ADC cluster) on selected axial planes provided accurate prognostic information.[16] Another problem is that most previous studies were single center studies, which limits their generalizability. With this background, we thought that a direct comparison of the three quantitative methods in a multicenter setting using computerized analysis methods may provide objective baseline information for the practical application. Therefore, we modified our previous 2D area-based analysis method into a 3D volume-based method and performed a multicenter study comparing the three concepts. Our hypothesis was that the relative volume of the most dominant low-ADC cluster would provide the best prognostic performance.

Materials and methods

Study setting

Three affiliated academic hospitals in South Korea participated. Site A (Seoul National University Bundang Hospital) is located in a city with a population of 1000,000 with more than 80,000 emergency department (ED) visits annually. Sites B (Seoul National University Hospital) and C (Seoul Metropolitan City Boramae Hospital) are located in a large metropolitan city of 10,000,000 with more than 70,000 and 50,000 ED visits annually, respectively. Prehospital basic life support by the emergency medical system are provided by the fire station-based emergency medical technicians hired by the government of South Korea.[18] The management of CA was based on the recommendations of the 2005 American Heart Association cardiopulmonary resuscitation guideline until the 2010 guideline were published and rapidly adopted. Therapeutic hypothermia was recommended as a protocol during the study period. Brain MRI with DW imaging was also recommended as a protocol for the prognostication of comatose patients who were unable to follow verbal commands or show purposeful movement. However, the practical decision for their application was at the discretion of the treating physician. The withdrawal of ongoing life-sustaining care is not considered a legal option in Korea due to the lack of laws or national guidelines.[19] The institutional review board of the study hospitals approved the analysis and provided a consent waiver.

Participants and data collection

The period of patient enrollment differed among the hospitals because of data availability: Site A, 2008–2012; Site B, 2010–2012; and Site C, 2009–2012. Adult (aged 15 or more) OHCA patients who underwent a brain MRI after a return of spontaneous resuscitation (ROSC) were included. The exclusion criteria included the following: (1) unknown long-term prognosis; (2) poor baseline neurologic function (equivalent to a CPC score of 3 or more); and (3) imaging performed too early (within 12 h). Demographic and Utstein element variables including the 6-month cerebral performance category (CPC) score were collected from the OHCA registries of the participating hospitals. In hospital patient conditions including sepsis-related organ failure assessment (SOFA) score, administration of mechanical ventilation and Glasgow coma scale (GCS) at ICU admission as well as GCS at MR imaging were collected from patient medical records. A 6-month CPC score of 1 or 2 was considered a good outcome, whereas that of 3 to 5 was considered a poor outcome. The MR images were retrieved in DICOM (Digital Imaging and Communications in Medicine) format from picture archiving and communication system (PACS) servers at the hospitals. Information about the MR devices and imaging parameters was retrieved from the header fields of the DICOM files.

MR devices and DW imaging protocols

The MR devices and imaging protocols were not the same among the participating hospitals, and they also changed during the study period. Both 1.5- and a 3.0-T imaging systems (Site A: Intera 1.5T and Achieva 3.0T, Philips Health Care, Best, the Netherlands; Site B: SIGNA EXCITE 1.5T and 3.0T and SIGNA HDxt 1.5T, General Electric, Milwaukee, WI; Site C: Achieva 1.5T and 3.0T, Philips Health Care, Best, the Netherlands) with various head coils were used. The most common parameter settings are summarized in Supplemental Table 1.

Image processing and measurement procedures

Please see the online supplements for the detailed description of the image processing and measurement algorithms. Fig. 1 illustrates the entire procedure. Stacked DW and ADC map images of each patient are loaded into MATLAB 2014b (MathWorks, Inc. Natick, MA) as a 3D array of numeric data. Both DW and ADC map arrays are then subjected to automated morphological operations to produce 31 candidate volume masks of a whole brain. Then the authors reviewed the volume masks to select the best result. If none of them were satisfactory, initial parameter values were empirically adjusted until a satisfactory volume mask was generated.

The final skull-stripped volume mask was applied to the source ADC array to produce a whole-brain ADC array. From this ADC array, following predictors were measured: (1) average ADCs—the mean and median ADC of the entire brain; (2) LADCV—the relative volume of voxels with ADC values less than the predefined ADC threshold; and (3) DC-LADCV—the relative volume of the dominant (biggest) cluster of the low-ADC voxels. Given that the performance of the volume predictors may be dependent on the low-ADC threshold used to define the a low-ADC voxel, we repeated the predictor measurement as described above using different ADC threshold levels from 400 to 800×10^{-6} mm^2 s^{-1} at 10×10^{-6} mm^2 s^{-1} intervals.

Statistical analysis

Measurements using the predictors were exported to R package version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) for statistical analyses. The significance of the difference between the good (6-month CPC score of 1 or 2) and poor prognosis groups (6-month CPC scores of 3 to 5) was tested using the Wilcoxon rank-sum test. The area under the receiver operating characteristic curve (AUROC), the sensitivity for a poor outcome (with the specificity set to 100%) and their 95% confidence intervals (CI) were assessed and plotted against the corresponding low-ADC threshold used. The significance of difference in AUROC between the predictors was assessed using a bootstrap resampling method with 2000 replicates,[20] whereas the significance of the difference in the sensitivity for a poor outcome was assessed using the McNemar test. p-Values <0.05 were considered statistically significant.