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Clinical paper

Hypoxic hepatitis after out-of-hospital cardiac arrest: Incidence, determinants and prognosis☆

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ABSTRACT

Aim: Hypoxic hepatitis (HH) may complicate the course of resuscitated out-of-hospital cardiac arrest (OHCA) patients admitted in intensive care unit (ICU). Aims of this study were to assess the prevalence of HH, and to describe the factors associated with HH occurrence and outcome.
Methods: We conducted an observational study over a 6-year period (2009–2014) in a cardiac arrest center. All non-traumatic OHCA patients admitted in the ICU after return of spontaneous circulation (ROSC) and who survived more than 24 h were included. HH was defined as an elevation of alanine aminotransferase over 20 times the upper limit of normal during the first 72 h after OHCA. Factors associated with HH and ICU mortality were picked up by multivariate logistic regression.
Results: Among the 632 OHCA patients included in the study, HH was observed in 72 patients (11.4% (95% CI: 9.0%, 14.1%)). In multivariate analysis, time from collapse to ROSC [OR 1.02 per additional minute; 95% CI (1.00, 1.04); $p = 0.01$], male gender [OR 0.53; 95% CI (0.29, 0.95); $p = 0.03$] and initial shockable rhythm [OR 0.35; 95% CI (0.19, 0.65); $p < 0.01$] were associated with HH occurrence. After adjustment for confounding factors, HH was associated with ICU mortality [OR 4.39; 95% CI (1.71, 11.26); $p < 0.01$] and this association persisted even if occurrence of a post-CA shock was considered in the statistical model [OR 3.63; 95% CI (1.39, 9.48); $p = 0.01$].
Conclusions: HH is not a rare complication after OHCA. This complication is mainly triggered by the duration of resuscitation and is associated with increased ICU mortality.

Introduction

Despite significant advances in post-cardiac arrest (CA) care,[1] hospital mortality remains high in out-of-hospital cardiac arrest (OHCA) patients in whom pre-hospital cardiopulmonary resuscitation (CPR) allowed return of spontaneous circulation (ROSC).[2,3] In these patients, mortality in the intensive care unit (ICU) is triggered by both post-CA shock (and associated organ damages) and brain injury.[3]

The post-ROSC period is characterized by the onset of the post-CA syndrome that encompasses all manifestations of the systemic ischemia/reperfusion (I/R) injury induced by CA and CPR.[4] This systemic I/R injury mostly affects the brain and may worsen the neurological prognosis but may also trigger multiple organ damage, which may potentially be worsened by a post-CA shock occurring in nearly 70% of case.[3]

Few studies are applied to described the epidemiology and the prognostic impact of organ damage after CA.[5–9] Particularly, liver damages occurring after CA are understudied.[9] Primary experimental description of hepatic consequences of CA allowed to link the observed biological and histological hepatic abnormalities after CA to the hypoxic hepatitis (HH) entity,[10] better known under the old appellation of "ischemic hepatitis" or "shock liver".[11] Recently, many observational studies have described the biological course and have assessed the outcome of HH, particularly in critically ill patients.[12–17] However, OHCA patients are underrepresented in these studies.

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Aims of this study were to describe the prevalence and the development of HH in a cohort of OHCA patients admitted in ICU after ROSC. Secondary goals were to investigate the factors associated with the occurrence of HH and to evaluate the association of HH with the ICU mortality in this population.

Methods

Study design and population

All consecutive patients admitted in our tertiary medical ICU (Cochin University Hospital, Paris, France) between January 2009 and December 2014 after a non-traumatic OHCA followed by ROSC were included in the study. OHCA patients without liver function tests (LFT) performed during the first 72 h were excluded, as well as patients who died in the first 24 h after admission. Patients who presented an in-hospital cardiac arrest were not included in the present study. The ethic committee of the French Intensive Care Society approved this study.

Patients' management

OHCA patients in whom ROSC is successfully achieved after pre-hospital CPR are referred to our tertiary ICU, which is recognized as a "CA center" for Paris and its suburbs. OHCA patient management after ICU admission in our center is standardized, following the international guidelines,[18] and is described in Electronic Supplementary Material (ESM).[3,7] Only major therapies are administered during the first days in ICU. Enteral nutrition is usually not started before the first 24–48 h and parenteral nutrition is not used during the initial acute period. The use of all hepatotoxic treatments is forbidden; specifically, the use of acetaminophen is avoided during targeted temperature management.

Definitions

Hypoxic hepatitis: HH is usually defined by "a dramatic but transient increase in aminotransferase (AT) above 20 times the upper limit of normal (ULN) in a clinical setting of cardiac, respiratory or circulatory failure with exclusion of other cause of acute liver cell necrosis".[11] Histological proof is not required when the clinical definition is fully met. Aspartate aminotransferase (AST) is less specific of liver than alanine aminotransferase (ALT) and may increase for other obvious reasons such as myocardial infarction or rhabdomyolysis.[19,20] Thus, we used a slightly modified definition of HH in the specific setting of CA: we only considered an increase of ALT serum level above 20 times the ULN (45 IU L^{-1}, i.e. higher than 900 IU L^{-1}) to define HH after OHCA. In this definition, we focused on the first 72 h after OHCA because in HH[11] the rise of AT occurs precociously after the triggering event and because hemodynamic instability after CA is generally transient and reversible within a few days.[4,5]

Post-CA shock was defined as the need for continuous vasopressor infusion (norepinephrine or epinephrine) during more than 6 h after ROSC to maintain a mean arterial pressure above 60 mmHg despite adequate fluid loading.[3]

Cardiac failure was defined as the need for inotrope infusion (dobutamine or epinephrine) during the first 72 h after ICU admission.

Hypoglycemia: Spontaneous hypoglycemia was defined as blood glucose capillary value under 2.2 mmol L^{-1} (40 mg dL^{-1}) in absence of concomitant administration of insulin.[13]

Rhabdomyolysis: Rhabdomyolysis was defined as an elevation of serum creatinine phosphokinase (CPK) above 1000 IU L^{-1} during the first 72 h after admission.[19]

Data collection

All data related to the CA, ICU management and outcome of OHCA patients included in the study were extracted from the French Parisian database in which data are prospectively collected according to Utstein style.[21,22] Our database was previously described and is declared to the French National Committee for Informatics and Liberties.[3,7] Patients' medical computerized charts were reviewed for baseline characteristics including comorbidities, medical history of hepatic disease (cirrhosis, viral hepatitis or malignancy infiltration) or vitamin K antagonist (VKA) treatment. Laboratory data (including LFT) were extracted from the patient data management system (Centricity Critical Care Clinisoft®, GE Healthcare Europe, Helsinki, Finland) and were classified according to different predefined time-points: at admission (T0, i.e. until 6 h after admission) and every 24 h from the 24th hour (T1) to the 120th hour (T5) after admission. Laboratory tests available during the 24-h period focused on each time-point were analyzed, except for the admission time point (T0). When blood test values from this specified period were available, the worst value measured was kept. LFT included ALT (ULN: 45 IU L^{-1}), AST (ULN: 45 IU L^{-1}), bilirubin (ULN: 17 μmol L^{-1} or 1 mg dL^{-1}), gammaglutamyl transferase (GGT, ULN: 35 IU L^{-1}) and alkaline phosphatase (ALP, ULN: 120 IU L^{-1}); biochemical measurement methods were not modified during the study period. Others relevant laboratory tests collected were: arterial blood pH and lactate at admission (T0), CPK, lactate dehydrogenase (LDH) and prothrombin (PT) ratio.

Statistical analysis

Descriptive analysis: Descriptive statistics were reported as medians [25th, 75th percentiles] and proportions (percentage) for continuous and categorical variables, respectively. Baseline characteristics were compared between patients with and without HH using Pearson chi-square test and Mann–Whitney test for categorical and continuous variables, respectively. Analysis of PT ratio did not include patients treated with VKA or who received fresh frozen plasma (FFP) transfusions during the first 72 h.

Factors associated with HH: Factors associated with HH were analyzed in univariate analysis and then in multivariate logistic regression with HH variable as the dependent variable. Independent variables included in the multivariate model were Utstein variables (i.e. age, gender, public setting, presence of witness, bystander CPR, initial rhythm, resuscitation duration efforts), pre-existing comorbidities (i.e. chronic cardiac and respiratory disease) and pre-existing known hepatic illness. We performed a backward selection of variables; those with a p-value lower than 0.05 were kept in the final model.

Factors associated with ICU mortality: Utstein variables and occurrence of HH were included in a univariate comparison between patients discharged dead or alive from ICU. Variables were then selected along a backward selection in a multivariate logistic regression.

Good-of-fitness of these two models was assessed by the Hosmer–Lemeshow test.

Sensitivity analysis: We used different definitions of HH and evaluated their association with ICU mortality with multivariate logistic regression, as described above. The following modified definitions were used: (1) ALT > 900 IU L^{-1} or AST > 900 IU L^{-1} (20 × ULN)[11,12]; (2) ALT > 1000 IU L^{-1}; (3) ALT > 1000 IU L^{-1} or AST > 1000 IU L^{-1} [16]; (4) ALT > 450 IU L^{-1} (10 × ULN)[15]; (5) ALT > 3375 IU L^{-1} (75 × ULN).[11]

All tests were 2-sided with $p < 0.05$ considered statistically significant. We performed analyses using STATA/SE 14.0 software (College Station, Texas).