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Clinical paper

Association between delay to coronary reperfusion and outcome in patients with acute coronary syndrome undergoing extracorporeal cardiopulmonary resuscitation☆

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ABSTRACT

Aim: The prognostic effect of early coronary reperfusion therapy with extracorporeal cardiopulmonary resuscitation (ECPR) in patients with cardiac arrest due to acute coronary syndrome (ACS) has yet to be clarified. We investigated the relationship between time interval from collapse to start of ECPR (CtoE) and coronary reperfusion (CtoR) time and neurological outcome in patients with cardiac arrest due to ACS.

Methods: A cohort of 119 consecutive patients (63 ± 12 years old) with ACS who underwent ECPR and percutaneous coronary intervention(PCI) at our hospital was registered from January 2005 to June 2016. We analyzed patient clinical outcome, which was defined as survival with good neurological outcome at 30 days. We divided the patients into four groups according to CtoR time: Group 1 (time <60 min: n = 19), Group 2 (60 ≤ time < 90 min: n = 19), Group 3 (time ≥ 90 min: n = 70) and Group 4 (unsuccessful coronary reperfusion: n = 11).

Results: One hundred patients (84%) were successful of PCI. A Kaplan–Meier curve showed that Group 1 had the best outcome among the four groups (good neurological outcome at 30 days; 74% vs 37% vs 23% vs 9%, P < 0.0001). In receiver operating characteristics analysis for good neurological outcome at 30 days, the cutoff values for CtoE was 40 min. The delay CtoE and CtoR time were independent predictors of poor neurological outcome at 30 days after adjusting multiple confounders (CtoE time; Hazard ratio (HR):1.026, 95% confidential intervals(CI): 1.011–1.042, P = 0.001), (CtoR time; HR: 1.004, 95% CI: 1.001–1.008, P = 0.020).

Conclusions: A shorter CtoE and CtoR predicts better clinical outcome in patients with ACS undergoing ECPR.

Introduction

Early revascularization should be strongly considered for patients with acute coronary syndrome (ACS) complicated by cardiogenic shock.[1] ACS is responsible for a high frequency of cardiac arrests, and it is reported that percutaneous coronary intervention (PCI) in post-resuscitation care improves the outcome of these patients.[2–8]

Among cardiac arrest patients, there are some cases of failure of return of spontaneous circulation (ROSC) despite the delivery of advanced cardiac life support. In these refractory cases of cardiac arrest, the use of veno-arterial extracorporeal membrane oxygenation (ECMO)-assisted cardiopulmonary resuscitation (ECPR) is proposed for both in-hospital cardiac arrest (IHCA)[9,10] and out-of-hospital cardiac arrest (OHCA).[11,12]

ECPR plus intra-arrest PCI is associated with improved outcomes in patients who are unresponsive to conventional CPR due to ACS.[13] VA ECMO have been successfully implemented in refractory cardiac arrest to restore perfusion promptly, to allow for subsequent CAG and PCI and to bridge until recovery of cardiac function.[14]

The ACCF/AHA STEMI guidelines recommend that hospitals providing primary PCI to patients with ST-segment elevation myocardial infarction (STEMI) should treat patients within 90 min of contact with the medical system or admission to hospital.[15] However, the optimal treatment period for the patients with car-

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diac arrest due to ACS undergoing ECPR has not been decided. In addition, the prognostic effect of early coronary reperfusion therapy with ECPR in patients with cardiac arrest due to ACS has yet to be clarified.

We investigated the relationship between the time interval from collapse to coronary reperfusion and favorable outcome in patients with ACS undergoing ECPR. We also tried to determine the optimal time to treatment for ECPR in these patients.

Methods

Study population

The Institutional Review Board of Tokyo Metropolitan Bokutoh Hospital approved this study. Written informed consent was obtained from all their family members, and also was done later in survivors. Between January 2005 and June 2016, 377 patients received extracorporeal life support (ECLS) at our hospital. We excluded 125 patients receiving ECLS for non-cardiac arrest. In addition, we excluded 117 patients receiving ECLS for non-ACS and 16 patients without CAG and PCI. The remaining 119 patients with ACS were enrolled in this study (Fig. 1). We divided the patients into four groups according to the time interval from collapse to the recognition of coronary reperfusion: Group 1, collapse to coronary reperfusion time (CtoR time) <60 min (n = 19); Group 2, CtoR 60 ≤ time < 90 min (n = 19); Group 3, CtoR time ≥90 min and Group 4, unsuccessful coronary reperfusion (n = 11). We selected cutoff points of 60 min and 90 min for short onset to balloon time in light of previously reported data.[16–20]

ACS was diagnosed by more than two on-site interventional cardiologists and intensivists according to previous symptoms of cardiac arrest, laboratory data, ECG, and/or CAG.

ECPR indications and system

Relative indications for the introduction of ECPR were the following[1]: ventricular fibrillation on the electrocardiogram (ECG) during CPR with or without witnessed cardiac arrest, which was unresponsive to agents or defibrillation[2]; presumed cardiogenic cardiopulmonary arrest (CPA) on arrival of the rescue team,[3] presumed cardiogenic CPA after patient arrival at the hospital, and [4] presumed cardiogenic CPA with a witness in a patient who can be transported to our hospital within 30 min. The ECPR system consists of a centrifugal pump, a polypropylene hollow-fiber membrane oxygenator, and a circuit that is heparin bonded, as reported previously.[21]

Emergency coronary angiography (CAG) and PCI

CAG and PCI were performed immediately after ECPR. We defined coronary reperfusion time as the time that we recognized Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 or 3 with angiography in an acute occlusion of a coronary artery or if there was an unstable coronary stenosis that could be considered the cause of cardiac arrest.

Successful angioplasty was considered the achievement of a minimum stenosis diameter of less than 20% in the presence of TIMI grade 3 flow.

Data collection

For the purpose of this study, all patients undergoing ECPR were identified prospectively. Laboratory data, etiology, pre-existing comorbidities, weaning from ECMO, 30 days mortality, neurological outcome at 30 days and other factors were retrospectively collected from the medical records. We defined door-to-ECMO time as the time from patient arrival at hospital to the time of initiation of ECMO for patients with OHCA, and as the time from arrival of emergency physicians or cardiologists at the patient's bedside to the time of initiation of ECMO for patients with IHCA.

Clinical outcome

The primary outcome was defined as neurological outcome at 30 days after ECPR. The secondary outcome included all-cause death at 30 days, in-hospital mortality and 3-month mortality.

Neurological outcomes were assessed using the Glasgow–Pittsburgh Cerebral Performance Category scale (CPC). CPC1 and CPC2 were classified as good neurological outcomes and CPC3 to CPC5 were classified as poor neurological outcome.

After hospital discharge, all patients were followed up every month at our hospital's outpatient clinic up. All clinical events were confirmed by medical charts or by contacting the referring physician and/or patient's family, and all events were registered by the attending physicians. The diagnosis of clinical events was adjudicated by 2 independent cardiologists who were blinded to the findings of emergency procedure.

Statistical analysis

Values are presented as mean ± SD for continuous variables and as numbers and percentages for categorical variables. Categorical variables were compared among the groups with the Kruskal–Wallis test when appropriate, and continuous variables were compared with one-way ANOVA. The Fisher exact test was used when expected counts in greater than 20% of cells were less than 5. The Kaplan–Meier method was used to estimate cumulative mortality rates among the three groups. Survival differences in each group were compared using log-rank tests. Receiver-operating characteristic (ROC) analysis was used to determine optimal cut-off values of the collapse to start of ECPR (CtoE) time for prediction of neurological outcome at 30 days. The best cut-off value was defined as the point with the highest sum of sensitivity and specificity. Results displayed for univariable analysis were based on clinically relevant and laboratory-based variables. We assessed collinearity for multivariable models by Peason's correlation and excluded the parameters which had collinearity. Multivariable Cox proportional hazards models were developed to calculate hazard ratio (HR) and 95% confidence intervals (CIs). We performed stepwise forward selection considering any valuables with values of $P < 0.05$ to identify potential risk factors for neurological outcome at 30 days. As subgroup analysis, the impact of CtoR time on good neurological outcome at 30 days was assessed with the dichotomous variables of the CtoE time in the same way. All probability values were 2-sided, and probability values of $P < 0.05$ were considered statistically significant. Statistical analysis was performed using R3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics and in-hospital care

The baseline clinical characteristics of the four groups are shown in Table 1. Blood platelets were significantly lower in Group 3 and lactate levels were significantly lower in Group 1 among the 4 groups.

In-hospital care, PCI findings and outcomes are shown in Table 2. Mean collapse to ECPR (CtoE) time was 34 ± 16 min, door-to-ECPR time was 19 ± 9 min, and collapse to coronary reperfusion (CtoR) time was 116 ± 58 min. There were no reduction in the CtoR and CtoE over time in this study. Hypothermia therapy was performed

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