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Clinical paper

Middle cerebral artery flow, the critical closing pressure, and the optimal mean arterial pressure in comatose cardiac arrest survivors—An observational study☆

Judith M.D. van den Brule*, Eline Vinke, Lex M. van Loon, Johannes G. van der Hoeven, Cornelia W.E. Hoedemaekers

Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, The Netherlands

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ABSTRACT

Aim: This study estimated the critical closing pressure (CrCP) of the cerebrovascular circulation during the post-cardiac arrest syndrome and determined if CrCP differs between survivors and non-survivors. We also compared patients after cardiac arrest to normal controls.

Methods: A prospective observational study was performed at the ICU of a tertiary university hospital in Nijmegen, the Netherlands. We studied 11 comatose patients successfully resuscitated from a cardiac arrest and treated with mild therapeutic hypothermia and 10 normal control subjects. Mean flow velocity (MFV) in the middle cerebral artery was measured by transcranial Doppler at several time points after admission to the ICU. CrCP was determinded by a cerebrovascular impedance model.

Results: MFV was similar in survivors and non-survivors upon admission to the ICU, but increased stronger in non-survivors compared to survivors throughout the observation period ($P < 0.001$). MFV was significantly lower in survivors immediately after cardiac arrest compared to normal controls ($P < 0.001$), with a gradual restoration toward normal values. CrCP decreased significantly from 61.4[51.0–77.1] mmHg to 41.7[39.9–51.0] mmHg in the first 48 h, after which it remained stable ($P < 0.001$). CrCP was significantly higher in survivors compared to non-survivors ($P = 0.002$). CrCP immediately after cardiac arrest was significantly higher compared to the control group ($P = 0.02$).

Conclusions: CrCP is high after cardiac arrest with high cerebrovascular resistance and low MFV. This suggests that cerebral perfusion pressure should be maintained at a sufficient high level to avoid secondary brain injury. Failure to normalize the cerebrovascular profile may be a parameter of poor outcome.

Introduction

Prognosis after cardiac arrest is mainly determined by the neurological injury induced by the circulatory arrest. Return of spontaneous circulation (ROSC) does not automatically restore cerebral perfusion. Cerebral perfusion failure after restoration of circulation is a well known phenomenon in animal models with no-reflow, cerebral hyperperfusion and hypoperfusion that ultimately restores toward normal cerebral blood flow (CBF).[1] Humans have a similar flow pattern after cardiac arrest with low CBF in the initial phase after cardiac arrest that gradually restores toward normal values during the post-resuscitation syndrome.[2–4] This so called "delayed hypoperfusion phase" renders the brain at risk for ischemia and secondary brain injury.

The cerebral vascular tone plays an essential role in changes in CBF after cardiac arrest. Increased cerebrovascular resistance has been suggested to contribute to the delayed hypoperfusion phase, based on high transcranial Doppler pulsatility indexes of the middle cerebral artery (MCA) measured during the early post-cardiac arrest period.[2–4] A subsequent strong decrease in transcranial Doppler (TCD) pulsatility index with increased mean flow velocities (MFV) during the first 24 h after the arrest was mea-

Abbreviations: ABP, arterial blood pressure; C_a, compliance; CABV, cerebral arterial blood volume; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; CrCP, critical closing pressure; CVR, cerebrovascular resistance; HR, heart rate; ICP, intracranial pressure; MAP, mean arterial pressure; MCA, middle cerebral artery; MFV, mean flow velocity; ROSC, return of spontaneous circulation; TCD, transcranial Doppler.

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* Corresponding author at: Radboud University Nijmegen Medical Centre, Department of Intensive Care, P.O. Box 9101, 6500HB Nijmegen, The Netherlands. Fax: +31 24 3541612.
E-mail address: Judith.vandenbrule@radboudumc.nl (J.M.D. van den Brule).

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sured in non-survivors, whereas in survivors these parameters normalized.[5] In addition, autoregulation is disturbed in approximately 1/3 of patients after cardiac arrest, mainly in those with a poor outcome.[6,7] Taken together, these data indicate that the cerebrovascular resistance is altered after cardiac arrest, mainly in patients with a poor neurological outcome.

The critical closing pressure (CrCP) is a method to describe and quantify characteristics of the cerebrovascular bed in more detail and is defined as the lower limit of arterial blood pressure below which vessels collapse and flow ceases.[8,9] Because CrCP cannot be measured directly, several models have been developed to estimate CrCP indirectly from other measurable physiological parameters or their derivatives. CrCP in the model of Burton is the sum of intracranial pressure (ICP) and vascular wall tension.[8] Varsos et al. proposed a modification of the CrCP calculation, using a model of cerebrovascular impedance. With this model, the generation of negative values for CrCP is prevented and the model can accurately detect changes in vascular properties induced by changes in ICP, $PaCO_2$ and blood pressure.[10] CrCP is a valuable and clinically relevant tool in cerebrovascular research, as it allows to estimate changes in cerebrovascular tone and minimal cerebral perfusion pressure to prevent collapse of vessels and ischemia.[11–13]

The aim of the current study was to estimate CrCP of cerebrovascular motor tone during the post-cardiac arrest syndrome and to determine if CrCP differs between survivors and non-survivors. To place these values in a broader context, we also compared CrCP in post-cardiac arrest patients to normal controls.

Methods

Study

A prospective observational study was performed at the ICU of a tertiary university hospital in the Netherlands. All experiments were in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Population

We studied 11 comatose patients successfully resuscitated from a cardiac arrest and treated with mild therapeutic hypothermia. Inclusion criteria were age ≥18 years and coma (Glasgow coma scale ≤ 6) after return of spontaneous circulation. "Survivors" and "non-survivors" denote survival to hospital discharge. As a control group, we included 10 subjects without brain injury. Seven controls were patients admitted to the ICU for pre-operative hemodynamic optimization one day before esophagectomy. Three controls were healthy volunteers who participated in an experimental study. These healthy volunteers were included after written informed consent and approval of the protocol by the local Institutional Review Board. For the patients after cardiac arrest and patients admitted for hemodynamic optimization the local Institutional Review Board waived the need for informed consent. Exclusion criteria for all patients were an irregular heart rhythm, insufficient transtemporal bone window, pregnancy, thrombolytic therapy, refractory cardiogenic shock or a life expectancy <24 h.

Patient management

The post-cardiac arrest patients were treated with hypothermia by rapid infusion of 30 mL/kg bodyweight of cold Ringer's lactate at 4 °C followed by external cooling using two water-circulating blankets (Blanketroll II, Cincinnati Subzero, The Surgical Company, Amersfoort, The Netherlands). Temperature was maintained at 32–34 °C for 24 h, followed by passive rewarming to normothermia (defined as 37 °C). Cardiac arrest patients were sedated with midazolam and/or propofol and sufentanil. Sedation was stopped as soon as temperature was ≥36 °C. In case of shivering, patients were paralyzed using intravenous bolus injections of rocuronium. All patients were intubated and mechanically ventilated to obtain PaO_2 >75 mmHg and $PaCO_2$ 34–41 mmHg. Mean arterial pressure (MAP) was maintained between 80–100 mmHg. If necessary, patients were treated with volume infusion and dobutamine and/or milrinone and/or noradrenaline (norepinephrine).

Controls were admitted to the ICU the day before surgery for hemodynamic optimization or to the research unit of the ICU. All measurements in this group were performed while subjects were awake, without mechanical ventilation and before fluid resuscitation, pre-operative or study related interventions were initiated.

Data collection

Demographic, pre-hospital and clinical data were collected upon and during admission. An arterial catheter was used for monitoring of blood pressure in all subjects.

MFV in the middle cerebral artery (MFV_{MCA}) was measured by TCD through the temporal window with a 2-Mhz probe (Multi-Dop T Digital, Compumedics DWL, Singen, Germany) according to the method developed by Aaslid et al.[14] The probe was positioned over the temporal bone window above the zygomatic arch and fixed. This procedure ensured that the angle and individual depth of insonation remained constant during investigation. The temporal acoustic window and Doppler depth giving the highest velocities were used for all measurements. Two investigators performed all measurements (J.B. and C.H.). Recordings were made with subjects in supine position, the head elevated to 30°.

A minimum of 10–12 min windows of MFV, heart rate and arterial blood pressure (ABP) were simultaneously recorded on a computer and stored on a hard disk with a sample rate of 200 Hz by an A/D converter (NI USB-6211, National Instrument, Austin, TX, USA). During the measurements, PaO_2, $PaCO_2$ and temperature were within normal ranges and patients were normotensive.

In patients after cardiac arrest, measurements were performed on admission to the ICU and at 6, 12, 24, 36, 48, 60 and 72 h. Subjects in the control group were measured once.

Data analysis

ABP and MFV data were analyzed using custom-written MATLAB scripts (Matlab R2014b, The MathWorks Inc., Massachusetts, USA). First, the time series were filtered with an 5th-order low-pass Butterworth filter (25 Hz), to ascertain signal stationarity. Second, periods of 5 min of artefact- and calibration-free data were selected by visual inspection for subsequent analysis. Last, mean blood pressure and cerebral blood flow velocity were obtained synchronically using a 4th order low-pass Butterworth filter.

CrCP

CrCP was determined according to the method suggested by Varsos et al.[10,15]

$$CrCP = ABP - \frac{CPP}{\sqrt{(CVR \cdot Ca \cdot HR \cdot 2\pi)^2 + 1}}$$

With CVR cerebrovascular resistance, C_a compliance of the vascular bed and HR heart rate. The multiplication of CVR and C_a is called the time constant Tau (τ). CPP is defined as ABP – ICP, however in this study ICP was not measured. Therefore ABPmean was used as an approach of CPP, as described by Varsos et al.[10] CVR was calculated by dividing ABPmean by MFVmean. To determine C_a, cerebral arterial blood volume (CABV) was calculated by integrat-

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