Resuscitation

EUROPEAN
RESUSCITATION
COUNCIL

Clinical paper

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

CrossMark

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

ARTICLE INFO

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 determined 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-

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]

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

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-

Table 1
Demographic data cardiac arrest patients and controls.

Characteristic	Cardiac arrest	Control	P value
Number of patients, n	11	10	
Male, n (%)	9 (81%)	8 (80%)	
Age (years)	57[55–61]	65[31–67]	0.75
SAPS II	60[41–69]	13[7.3–18]	<0.001
APACHE II	26[24–30]	4.5[0.8–9.0]	<0.001
Number of survivors, n (%)	7 (64%)	10 (100%)	0.36

SAPS II: Simplified Acute Physiology Score II.
APACHE II: Acute Physiology and Chronic Health Evaluation II.

ing the MFV signal over time. Then C_a was calculated by dividing the amplitude of the first harmonic of the CABV by the amplitude of the first harmonic of the ABP. HR was defined as the first harmonic frequency of ABP.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 5.0 (GraphPad Software, La Jolla, CA). Data are presented as median with 25th and 75th percentile. Figures also show minimum and maximum (*whiskers*) values. Changes over time were analyzed with the repeated-measures test for nonparametric data. Differences between survivors and non-survivors were analyzed with two-way analysis of variance. The Mann Whitney test was used for comparison between groups. A P-value of <0.05 was considered to indicate significance.

Results

Demographic and clinical data

We included 9 male and 2 female (n = 11) comatose patients after cardiac arrest. The demographic data of the patients and controls are shown in Table 1. Eight patients had ventricular fibrillation or ventricular tachycardia as initial rhythm, 3 patients initially had a pulseless electrical activity or asystole Four patients died in the ICU, all as result of severe postanoxic brain damage. The clinical data are summarized in Table 2. Cardiac arrest patients had a significantly higher hemoglobin on admission (P = 0.03). The pH was lower (P = 0.002) and the arterial carbondioxide tension was significantly higher (P = 0.01) immediately after cardiac arrest compared to normal control patients.

Cerebral blood flow velocity

As expected, MFV increased significantly after cardiac arrest from 28.0[25.0–39.0] upon ICU admission to 78.0[65.0–123.0] cm/s after 72 h, P < 0.001 (Fig. 1). The MFV_{MCA} was similar in sur-

Table 2
Clinical and laboratory data.

Characteristic	Cardiac arrest[a]	Normal	P value
Mechanical ventilation	11 (100%)	0 (0%)	
MAP (mmHg)	91.0[84.5–114.5]	91.1[86.3–105.1]	0.92
Heart rate (bpm)	85.0[80.0–92.0]	69.5[62.5–76.5]	0.09
Temperature (°C)	35.5[34.3–35.9]	37.0[36.8–37.1]	0.006
Noradrenaline	1 (9.1%)	0 (0%)	
Dose (μg/kg/min)	0.12		
Milrinone	0 (0%)	0 (0%)	
Dobutamine	0 (0%)	0 (0%)	
Hemoglobin (g/dL)	14.7[12.9–14.7]	11.6[10.8–12.6]	0.03
pH	7.31[7.26–7.37]	7.45[7.43–7.46]	0.002
PaO$_2$ (mmHg)	102[81–168]	87[78–105]	0.28
PaCO$_2$ (mmHg)	42.0[39.0–43.5]	35.6[34.5–36.8]	0.01

[a] Data represent values upon admission to the ICU.
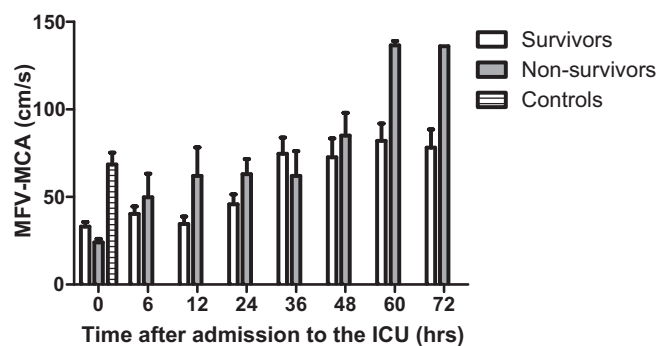
Fig. 1. MFV of survivors and non-survivors in comatose patients succesfully resuscitated from a cardiac arrest and treated with mild hypothermia, during 72 h of ICU admission.
MFV = mean flow velocity.

vivors and non-survivors upon admission to the ICU, but the MFV_{MCA} increased stronger in non-survivors compared to survivors throughout the observation period (P = 0.001). MFV_{MCA} was significantly lower in survivors immediately after cardiac arrest compared to normal controls (P < 0.001), with a gradual restoration toward normal values.

MAP decreased after cardiac arrest from 91.0[83.0–123] on admission to 82.5[77.8–87.8] at 48 h and 88.0[83.0–98.0] mmHg at 72 h (P = 0.009) with no significant differences between survivors and non-survivors (P = 0.09) (data not shown). MAP in the control patients was 92.6[86.3–105.1] and comparable to the cardiac arrest group (data not shown).

Critical closing pressure

After cardiac arrest, the CrCP decreased significantly from 61.4[51.0–77.1] on admission to 41.7[39.9–51.0] mmHg at 48 h, after which it remained stable (P < 0.001), (Fig. 2). The CrCP was significantly higher in survivors compared to non-survivors (P = 0.002). The CrCP immediately after cardiac arrest was significantly higher compared to the control group (P = 0.02).

The C_a represents the change of arterial blood volume in response to change in arterial pressure and is estimated as a ratio of pulse amplitude of CABV derived from the cerebral blood flow velocity and pulse amplitude of the ABP. After cardiac arrest, C_a increased significantly from 0.05[0.05–0.08] upon admission to 0.10[0.08–0.16] mmHg/cm^3 at 72 h (P = 0.02), with no differences between survivors and non-survivors (P = 0.81) (data not shown). C_a values immediately after cardiac arrest were significantly
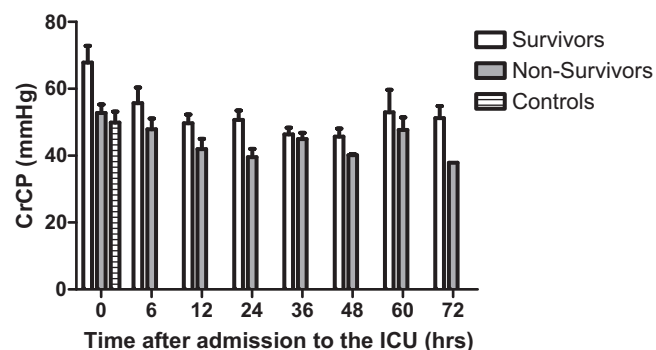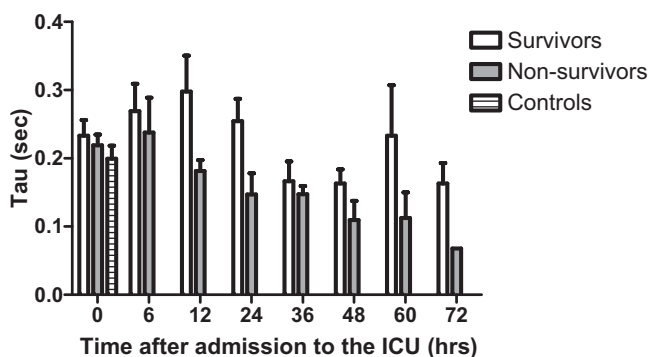

Fig. 2. CrCP of survivors and non-survivors in comatose patients succesfully resuscitated from a cardiac arrest and treated with mild hypothermia, during 72 h of ICU admission.
CrCP = critical closing pressure.
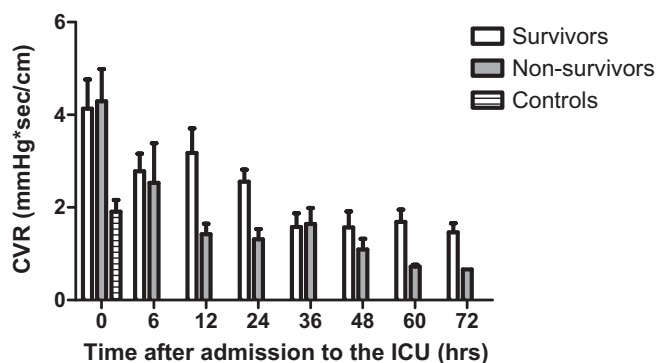
Fig. 3. CVR of survivors and non-survivors in comatose patients succesfully resuscitated from a cardiac arrest and treated with mild hypothermia, during 72 h of ICU admission.
CVR = cerebrovascular resistance.

Fig. 4. Tau (time constant) of survivors and non-survivors in comatose patients succesfully resuscitated from a cardiac arrest and treated with mild hypothermia, during 72 h of ICU admission.

lower compared to normal values ($0.11[0.08–0.25]$ mmHg/cm^3, $P = 0.007$).

The CVR is the resistance of small cerebral arteries and arterioles and was estimated from the ABP and cerebral blood flow velocity. The initial CVR in patients after cardiac arrest was high ($3.91[2.94–5.37]$) and significantly decreased after 72 h to $1.35[0.88–1.81]$ mmHg s/cm ($P < 0.001$), with a stronger decline in non-survivors ($P = 0.02$), (Fig. 3). The CVR on admission was significantly higher in the cardiac arrest group compared to normal controls ($1.67[1.25–2.62]$ mmHg s/cm, $P < 0.001$).

Tau (τ) is the time constant of cerebral arterial bed and is the product of brain arterial compliance C_a and CVR. It estimates how fast cerebral blood arrives in the cerebral arterial bed during each cardiac cycle. Tau decreased significantly from $0.22[0.19–0.26]$ to $0.13[0.11–0.20]$ s ($P = 0.005$), with a stronger decrease in non-survivors compared to survivors ($P = 0.01$) (Fig. 4). Tau in the control group was $0.18[0.15–0.25]$ s, and did not differ significantly from values on admission after cardiac arrest.

Discussion

Cerebral hemodynamic parameters change significantly after cardiac arrest. MFV$_{MCA}$ is low in the first hours after cardiac arrest, with a high CrCP and CVR. During the first 72 h, the MFV gradually increases toward normal values, with a concomitant decrease in CrCP and CVR. This change in cerebrovascular profile after cardiac arrest is most likely the result of a change in cerebrovascular motor tone, switching from vasoconstriction at admission to vasodilation after 72 h.

CrCP is the sum of cerebral artery smooth muscle tone and ICP.[8] In theory, changes in CrCP can originate from changes in both components. Most likely, the increased CrCP after cardiac arrest is the result of cerebral vasoconstriction in the first hours after ROSC. In our patients, the resistance of small cerebral arteries and arterioles, estimated by the CVR, was high and gradually decreased toward normal values. In humans, the transcranial Doppler pulsatility index of the MCA is high during the early post-cardiac arrest period and decreases toward normal values after 24–48 h,[2–4] also implicating increased cerebral arterial resistance. The combination of low cerebral blood flow velocities with high CVR is a characteristic of the "delayed cerebral hypoperfusion phase" described in post-resuscitation animal models.[1] An imbalance between local vasoconstrictors and vasodilators, characterized by high endothelin levels, gradually decreasing nitrate concentrations, and gradually increasing cGMP levels is suggested to underlie the cerebral perfusion changes after cardiac arrest.[3] Other factors that contribute to this reduced blood flow include a reduction in neuronal activity, vasospasm, edema, platelet and leukocyte adhesion and changes in viscosity.[1,3,16–19]

The incidence of intracranial hypertension after cardiac arrest is unknown, and has been studied in only a small number of highly selected patients.[20–24] In those patients, ICP upon admission to the ICU was low, even in patients who developed intracranial hypertension later during the course of admission.[21] As CrCP was high on admission and decreased in the first hours after ROSC, increased ICP is probably not a major factor determining CrCP in our population. This is supported by the fact that CrCP was lower in non-survivors compared to survivors, whereas post-cardiac arrest patients with intracranial hypertension (resulting in high CrCP) had a poor outcome in all studies.[20–24]

Our results stress the importance of maintaining a sufficiently high cerebral perfusion pressure, especially in the first hours after cardiac arrest to avoid secondary brain ischemia. Our data suggest that the widely used MAP range of 65–70 mmHg is probably suboptimal.[25] This is in agreement with a previous study on the optimal cerebral perfusion pressure after cardiac arrest, suggesting an optimal MAP between 85–105 mmHg.[6]

Survivors and non-survivors revealed significantly different cerebral perfusion characteristics during the post-cardiac arrest period. Non-survivors showed a more pronounced increase in MFV$_{MCA}$ in the first 72 h after the arrest. This was accompanied by a stronger decrease in CrCP and CVR in non-survivors. Differences in systemic parameters such as MAP, pH or PaCO$_2$ tension or differences in use of vaso-active drugs did not account for these differences in cerebral perfusion. These data are in accordance with previous observations of a significant decrease in pulsatility index and an increase in MFV$_{MCA}$ in non-survivors after cardiac arrest.[5] Apparently, vasoactive tone is lost in patients with poor outcome, resulting in a decrease in CVR and subsequently an increase in cerebral blood flow. Under normal circumstances, cerebral blood flow is maintained at a constant level through the mechanism of cerebrovascular autoregulation. Autoregulation is disturbed in approximately 1/3 of patients after cardiac arrest, mainly in those with poor outcome.[6,7] A loss of autoregulation may have resulted in increased blood flow with low CVR in the non-survivors. In addition, the ischemia-reperfusion response activates a large number of pathophysiological pathways including oxidative stress, inflammation and coagulation resulting in reactive hyperemia.[26,27] This reactive hyperemia is likely to be more pronounced in more severely affected patients, explaining the increased flow with low resistance in non-survivors.

We compared the cardiac arrest patients upon admission to normal control subjects. MFV$_{MCA}$ was significantly lower immediately after cardiac arrest compared to normal control patients.

CrCP and CVR were higher compared to controls. Use of sedatives and vasopressors is common during the post-cardiac arrest period and may influence the cerebrovascular perfusion characteristics. Normal control patients were measured without any sedatives or vasopressive agents. The post-resuscitation perfusion pattern was different in survivors versus non-survivors, despite similar levels of blood pressure, use of sedatives and vasopressors and laboratory values, strongly suggesting a distinct pathophysiological entity rather than an ICU or drug-induced effect on cerebral blood flow.

A unique feature of the treatment after cardiac arrest was the use of mild hypothermia in our patients. Hypothermia may delay restoration of cerebral blood flow toward normal values, but does not alter the pattern of hypoperfusion followed by normal or hyperperfusion and is probably not a major determinant of the cerebral blood flow after cardiac arrest.[2,28] The contribution of hypothermia to the high CrCP and CVR upon admission cannot be established from this study, but seems relatively minor since both CrCP and resistance decrease while temperatures decline in the first hours after admission.

This study has a number of limitations. First, CrCP cannot be measured in vivo but is estimated using a mathematical model, with its inherent risks of bias. Most importantly, ICP is required for a most accurate calculation of the model. Since ICP is low under normal conditions, it does not significantly alter the estimation of CrCP. ICP is unlikely to have a major influence on our results, as CrCP decreases in non-survivors (whereas raised ICP would increase CrCP). We measured ABP through a catheter in the radial artery. Measurement of the ABP in the MCA would have resulted in a more accurate estimation of cerebral perfusion pressure but is not feasible in patients. Second, the cerebral perfusion changes after cardiac arrest are probably heterogeneously distributed through the brain, with some areas more affected than others. As CrCP is derived from the MFV_{MCA}, these heterogeneities cannot be measured by this technique. This study also has limitations inherent in comparing subjects with regimented hemodynamics and ventilation to awake control subjects. ABP and HR are both components in the method of Varsos, but there were no significant differences in these components between cardiac arrest patients and normal controls. Another component in the method of Varsos is MFV, which is influenced by the diameter of the MCA and thus by pH/carbondioxide tension. pH/carbondioxide tension was different between cardiac arrest patients and normal controls on admission and may have affected the results, but this component normalized early after admission.

Although we studied only 11 patients, the results appear to be physiologically sound.

Conclusions

In conclusion, CrCP is high after cardiac arrest with high cerebrovascular resistance and low cerebral blood flow velocities. 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.

Conflict of interest statement

No conflicts of interest.

References

1. Safar P. Cerebral resuscitation after cardiac arrest: research initiatives and future directions. Ann Emerg Med 1993;22:324–49.
2. Bisschops LL, Hoedemaekers CW, Simons KS, van der Hoeven JG. Preserved metabolic coupling and cerebrovascular reactivity during mild hypothermia after cardiac arrest. Crit Care Med 2010;38:1542–7.
3. Buunk G, van der Hoeven JG, Frolich M, Meinders AE. Cerebral vasoconstriction in comatose patients resuscitated from a cardiac arrest. Intensive Care Med 1996;22:1191–6.
4. Lemiale V, Huet O, Vigue B, et al. Changes in cerebral blood flow and oxygen extraction during post-resuscitation syndrome. Resuscitation 2008;76:17–24.
5. Buunk G, van der Hoeven JG, Meinders AE. Prognostic significance of the difference between mixed venous and jugular bulb oxygen saturation in comatose patients resuscitated from a cardiac arrest. Resuscitation 1999;41:257–62.
6. Ameloot K, Genbrugge C, Meex I, et al. An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: time to drop 'one-size-fits-all' hemodynamic targets. Resuscitation 2015;90:121–6.
7. Sundgreen C, Larsen FS, Herzog TM, Knudsen GM, Boesgaard S, Aldershvile J. Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke 2001;32:128–32.
8. Burton AC. On the physical equilibrium of small blood vessels. Am J Physiol 1951;164:319–29.
9. Dewey RC, Pieper HP, Hunt WE. Experimental cerebral hemodynamics. Vasomotor tone, critical closing pressure, and vascular bed resistance. J Neurosurg 1974;41:597–606.
10. Varsos GV, Richards H, Kasprowicz M, et al. Critical closing pressure determined with a model of cerebrovascular impedance. J Cereb Blood Flow Metab 2013;33:235–43.
11. Varsos GV, Budohoski KP, Czosnyka M, et al. Cerebral vasospasm affects arterial critical closing pressure. J Cereb Blood Flow Metab 2015;35:285–91.
12. Varsos GV, Czosnyka M, Smielewski P, et al. Cerebral critical closing pressure in hydrocephalus patients undertaking infusion tests. Neurol Res 2015;37:674–82.
13. Varsos GV, de Riva N, Smielewski P, et al. Critical closing pressure during intracranial pressure plateau waves. Neurocrit Care 2013;18:341–8.
14. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982;57:769–74.
15. Varsos GV, Kasprowicz M, Smielewski P, Czosnyka M. Model-based indices describing cerebrovascular dynamics. Neurocrit Care 2014;20:142–57.
16. Beckstead JE, Tweed WA, Lee J, MacKeen WL. Cerebral blood flow and metabolism in man following cardiac arrest. Stroke 1978;9:569–73.
17. Bisschops LL, Pop GA, Teerenstra S, Struijk PC, van der Hoeven JG, Hoedemaekers CW. Effects of viscosity on cerebral blood flow after cardiac arrest. Crit Care Med 2014;42:632–7.
18. Forsman M, Aarseth HP, Nordby HK, Skulberg A, Steen PA. Effects of nimodipine on cerebral blood flow and cerebrospinal fluid pressure after cardiac arrest: correlation with neurologic outcome. Anesth Analg 1989;68:436–43.
19. Safar P, Stezoski W, Nemoto EM. Amelioration of brain damage after 12 minutes' cardiac arrest in dogs. Arch Neurol 1976;33:91–5.
20. Iida K, Satoh H, Arita K, Nakahara T, Kurisu K, Ohtani M. Delayed hyperemia causing intracranial hypertension after cardiopulmonary resuscitation. Crit Care Med 1997;25:971–6.
21. Naito H, Isotani E, Callaway CW, Hagioka S, Morimoto N. Intracranial pressure increases during rewarming period after mild therapeutic hypothermia in post-cardiac arrest patients. Ther Hypothermia Temp Manage 2016, http://dx.doi.org/10.1089/ther.2016.0009, ahead of print.
22. Nordmark J, Rubertsson S, Mortberg E, Nilsson P, Enblad P. Intracerebral monitoring in comatose patients treated with hypothermia after a cardiac arrest. Acta Anaesthesiol Scand 2009;53:289–98.
23. Sakabe T, Tateishi A, Miyauchi Y, et al. Intracranial pressure following cardiopulmonary resuscitation. Intensive Care Med 1987;13:256–9.
24. Senter HJ, Wolf A, Wagner Jr FC. Intracranial pressure in nontraumatic ischemic and hypoxic cerebral insults. J Neurosurg 1981;54:489–93.
25. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122:S768–86.
26. Onetti Y, Dantas AP, Perez B, et al. Middle cerebral artery remodeling following transient brain ischemia is linked to early postischemic hyperemia: a target of uric acid treatment. Am J Physiol Heart Circ Physiol 2015;308:H862–74.
27. Pinard E, Engrand N, Seylaz J. Dynamic cerebral microcirculatory changes in transient forebrain ischemia in rats: involvement of type I nitric oxide synthase. J Cereb Blood Flow Metab 2000;20:1648–58.
28. Bisschops LL, van der Hoeven JG, Hoedemaekers CW. Effects of prolonged mild hypothermia on cerebral blood flow after cardiac arrest. Crit Care Med 2012;40:2362–7.