Resuscitation 111 (2017) 110–115

Contents lists available at ScienceDirect

Resuscitation

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

Clinical paper

Low spontaneous variability in cerebral blood flow velocity in non-survivors after cardiac arrest☆

J.M.D. van den Brule*, E.J. Vinke, L.M. van Loon, J.G. van der Hoeven, C.W.E. Hoedemaekers

Department of Intensive Care, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

ARTICLE INFO

Article history:
Received 14 October 2016
Received in revised form 5 December 2016
Accepted 12 December 2016

Keywords:
Mean flow velocity
Mean arterial pressure
Variability
Cerebral bloodflow
Coëfficiënt of variation

ABSTRACT

Objective: To investigate spontaneous variability in the time and frequency domain in mean flow velocity (MFV) and mean arterial pressure (MAP) in comatose patients after cardiac arrest, and determine possible differences between survivors and non-survivors.
Methods: A prospective observational study was performed at the ICU of a tertiary care university hospital in the Netherlands. We studied 11 comatose patients and 10 controls. MFV in the middle cerebral artery was measured with simultaneously recording of MAP. Coefficient of variation (CV) was used as a standardized measure of dispersion in the time domain. In the frequency domain, the average spectral power of MAP and MFV were calculated in the very low, low and high frequency bands.
Results: In survivors CV of MFV increased from 4.66 [3.92–6.28] to 7.52 [5.52–15.23] % at T = 72 h. In non-survivors CV of MFV decreased from 9.02 [1.70–9.36] to 1.97 [1.97–1.97] %. CV of MAP was low immediately after admission (1.46 [1.09–2.25] %) and remained low at 72 h (3.05 [1.87–3.63] %) ($p = 0.13$). There were no differences in CV of MAP between survivors and non-survivors ($p = 0.30$). We noticed significant differences between survivors and non-survivors in the VLF band for average spectral power of MAP ($p = 0.03$) and MFV ($p = 0.003$), whereby the power of both MAP and MFV increased in survivors during admission, while remaining low in non-survivors.
Conclusions: Cerebral blood flow is altered after cardiac arrest, with decreased spontaneous fluctuations in non-survivors. Most likely, these changes are the consequence of impaired intrinsic myogenic vascular function and autonomic dysregulation.

Introduction

The incidence of post-anoxic encephalopathy after cardiac arrest is high, resulting in high mortality and morbidity.[1] Crucial in the ICU treatment after cardiac arrest is to create an optimal environment, for cerebral recovery including adequate cerebral blood flow (CBF).

Under normal circumstances, CBF exhibits rapid spontaneous fluctuations, in order to maintain cerebrovascular homeostasis. The adaptation of CBF to perturbations in cerebral perfusion pressure is regulated by central control mechanisms[2,3] and by an intrinsic variation via myogenic vasoconstriction.[4,5]

Arterial pressure also varies spontaneously. Beat-to-beat changes in arterial pressure are regulated by cardiovascular control mechanisms, such as the arterial baroreflex,[6] the renin-angiotensin system,[7] the vascular myogenic response[8] and the endothelial nitric oxide release.[9] Blood pressure fluctuations elicited by sympathetic modulation of vascular tone occur in the low frequency band (LF, 0.07–0.15 Hz). Intrinsic vascular myogenic changes in arterial blood pressure affects both the LF and very low frequency (VLF, 0.02–0.07 Hz) components of cardiovascular variability. Endothelial NO affects blood pressure variability in the high frequency range in animals (HF, 0.15–0.40 Hz). The effect of NO in humans is controversial since the HF band is largely dependent on respiration. The impact of the renin-angiotensin system on blood pressure variability is unknown. To what level cerebral blood flow variability is

Abbreviations: ABP, arterial blood pressure; CBF, cerebral blood flow; CV, coefficient of variation; HF, high frequency; LF, low frequency; MAP, mean arterial pressure; MCA, middle cerebral artery; MFV, mean flow velocity; TCD, transcranial Doppler; VLF, very low frequency.

☆ 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.2016.12.005.

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

http://dx.doi.org/10.1016/j.resuscitation.2016.12.005

dependent on pressure variability is a matter of debate in healthy subjects and yet unknown in patients after cardiac arrest.[10]

Blood pressure variability is a well known risk factor for end organ damage in patients with chronic conditions such as hypertension.[11,12] In acute ischemic stroke, beat to beat blood pressure variability was associated with death and dependency at 30 days.[13] In contrast, in acute brain injury patients no differences in blood pressure variability between survivors and non-survivors were detected.[14] The impact of blood pressure variability in the time and frequency domains in acute brain damage such as after cardiac arrest, is unknown.

The main objective of our study was to determine the spontaneous variability in the time and frequency domain in mean flow velocity ((MFV) and mean arterial pressure ((MAP) in comatose patients during the first 72 h after cardiac arrest. In addition, possible differences in spontaneous variability between survivors and non-survivors were determined.

Materials and methods

Study

A prospective observational study was performed at the ICU of a tertiary care university hospital the Netherlands. The local Institutional Review Board approved the study and waived the need for informed consent.

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 a Glasgow Coma Score ≤6 after return of spontaneous circulation. We also studied 10 normal control subjects. Seven controls were patients admitted to the ICU for pre-operative haemodynamic optimization one day before elective esophagectomy with reconstructive surgery because of cancer. Three control patients were healthy volunteers that participated in an experimental human endotoxemia study. These controls were included after written informed consent and approval of the protocol by the local Institutional Review Board (document number 2015-2079, NCT02675868).

Exclusion criteria for all groups were an irregular heart rhythm, absent transtemporal bone window, pregnancy, thrombolytic therapy, refractory cardiogenic shock and life expectancy less than 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 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). All patients were sedated with midazolam and/or propofol and sufentanil. Sedation was stopped as soon as the body temperature was ≥36 °C. In case of shivering, patients were paralysed using intravenous bolus injections of rocuronium. All patients were intubated and mechanically ventilated to obtain a PaO_2 > 75 mmHg and a $PaCO_2$ between 34 and 41 mmHg. The radial or femoral artery was cannulated for monitoring of arterial blood pressure (ABP) and sampling of arterial blood. According to our local protocol, MAP was maintained between 80–100 mmHg. If necessary, patients were treated with volume infusion and dobutamine and/or milrinone and/or noradrenaline (norepinephrine).

All measurements in the control group were performed while subjects were awake, without mechanical ventilation and before fluid resuscitation or other pre-operative or research 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 and sampling of arterial blood in all patients.

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

A minimum of 10–12 min windows of MFV, heart rate and MAP were simultaneously recorded on a laptop 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 and $PaCO_2$ were within normal ranges and stable.

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

Data analysis

MAP and MFV data were analysed using custom-written MATLAB scripts (Matlab R2014b, The MathWorks Inc. Massachusetts, USA). MAP and MFV were acquired using a third order zero phase-lag Butterworth filter with a cut-off frequency of 0.5 Hz.

From these MAP and MFV signals, 5-min windows were automatically selected based on the least amount of artefacts. By averaging these 5-min windows of the MAP and MFV signals, mean values of MAP and MFV were acquired.

Coefficient of variation (CV) was used as a standardized measure of dispersion for both MAP and MFV in the time domain. CV was defined as the standard deviation of the signal divided by the mean of the signal and was calculated from all filtered signals. This way, the variation is expressed in percentage of the mean.

In the frequency domain, the average spectral power of MAP and MFV were calculated in the very low (VLF, 0.02–0.07 Hz), low (LF, 0.07–0.15 Hz), and high (HF, 0.15–0.40 Hz) frequency bands. This in order to see whether the variation can be designated to a certain frequency band and whether this origin of variation changes over time in the patients.[20]

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.