



Clinical paper

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



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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.

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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).

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.

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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 response⁸ 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

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 PaO₂ > 75 mmHg and a PaCO₂ 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, PaO₂ and PaCO₂ 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.

Table 1
Demographic data of cardiac arrest patients and normal controls.

Characteristic	Cardiac arrest	Normal controls	P value
Number of patients, n	11	10	
Male, n (%)	9 (81%)	8 (80%)	
Age (years)	57 [55–61]	65 [31–67]	0.75
Number of survivors, n (%)	7 (64%)	10 (100%)	0.36

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 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 a result of severe postanoxic brain damage. The demographic data of the control group are also summarized in Table 1.

The clinical data on admission are summarized in Table 2. Cardiac arrest patients had a significantly higher hemoglobin concentration on admission (p=0.03). The pH was lower (p=0.002) and the PaCO₂ was significantly higher (p=0.02) immediately after cardiac arrest compared to the normal control patients, but normalized rapidly after admission. Nine percent of the cardiac arrest patients received noradrenaline on admission to maintain the MAP within the target range. The normal controls were awake and breathing spontaneously on room air.

MAP was measured continuously in the patients after cardiac arrest and changed significantly (p=0.04) during the study period according to a U-shaped pattern (electronic Supplement Fig. 1). MFV was low (28.00 [25.00–39.00] cm/s) upon admission after cardiac arrest and increased significantly to 78.00 [65.00–123.00] cm/s at 72 h (p=0.008, electronic Supplement Fig. 2). There were no differences in MAP at any measuring point between survivors and non-survivors (p=0.09, data not shown). MFV increased more in non-survivors (from 33.00 [25.00–40.00] to 71.50 [61.25–96.75] cm/s) compared to survivors (from 23.50 [20.25–28.25] to 136.00 [136.00–136.00] cm/s) in the cardiac arrest group (p<0.001).

Variability in the time domain

MFV

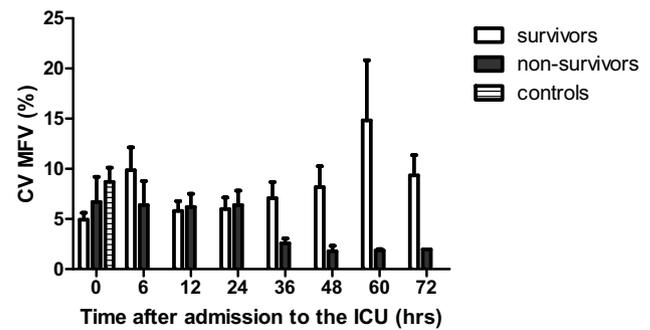
The CV of MFV after cardiac arrest remained stable with 5.37 [3.38–7.74] on t=0 and 7.49 [4.09–14.97] % at 72 h after admission (p=0.44, data not shown). In survivors the CV of MFV increased from 4.66 [3.92–6.28] to 7.52 [5.52–15.23] %. In contrast, in non-

Table 2
Clinical and laboratory data of cardiac arrest patients and normal controls on admission.

Characteristic	Cardiac arrest ^a	Normal controls	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
Norepinephrine	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.

A



B

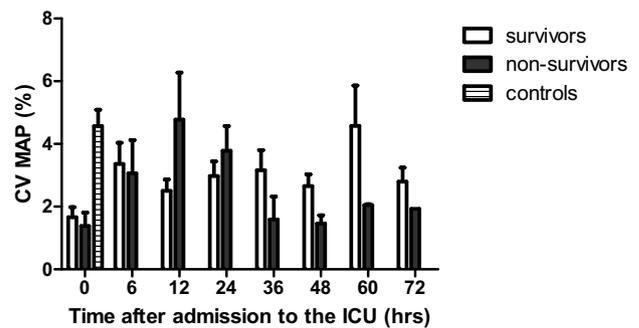


Fig. 1. (A) CV of MFV in survivors and non-survivors successfully resuscitated from a cardiac arrest and treated with mild therapeutic hypothermia, during 72 h of ICU admission and CV of MFV in normal controls. (B) CV of MAP in survivors and non-survivors successfully resuscitated from a cardiac arrest and treated with mild therapeutic hypothermia, during 72 h of ICU admission and CV of MAP in normal controls.

CV MFV = coefficient of variation of mean flow velocity.
CV MAP = coefficient variation mean arterial pressure.

survivors the CV of MFV decreased from 9.02 [1.70–9.36] to 1.97 [1.97–1.97] % (Fig. 1). The CV of MFV was 7.40 [4.95–12.98] in normal controls (Fig. 1), and did not differ significantly compared to the cardiac arrest group (p=0.14).

MAP

The CV of MAP in the cardiac arrest group was low immediately after admission to the ICU (1.46 [1.09–2.25]) and remained low at 72 h (3.05 [1.87–3.63]) (p=0.13, Fig. 1). There were no differences in CV of MAP between survivors and non-survivors in the cardiac arrest group (p=0.30, Fig. 1). Normal controls had a significantly higher CV of MAP (4.10 [3.23–6.43]) compared to the cardiac arrest group on admission (p=0.004, Fig. 1).

Variability in the frequency domain

MFV

In the frequency domain, the average spectral power of MFV increased from 0.28 [0.06–0.69] to 11.38 [1.58–30.86] (cm/s)² between admission and 72 h after the arrest in the VLF band (p=0.008, Fig. 2). This increase in spectral power of MFV in the VLF band was due to an increase in the favourable outcome group during admission from 0.38 [0.10–0.59] to 15.54 [2.67–31.31] (cm/s)² (p=0.001), whereas VLF spectral power remained low in the patients with an unfavourable outcome (0.19 [0.06–1.00] to 1.58 [1.58–1.58] (cm/s)² (p=0.23) (Fig. 3). There were no changes in

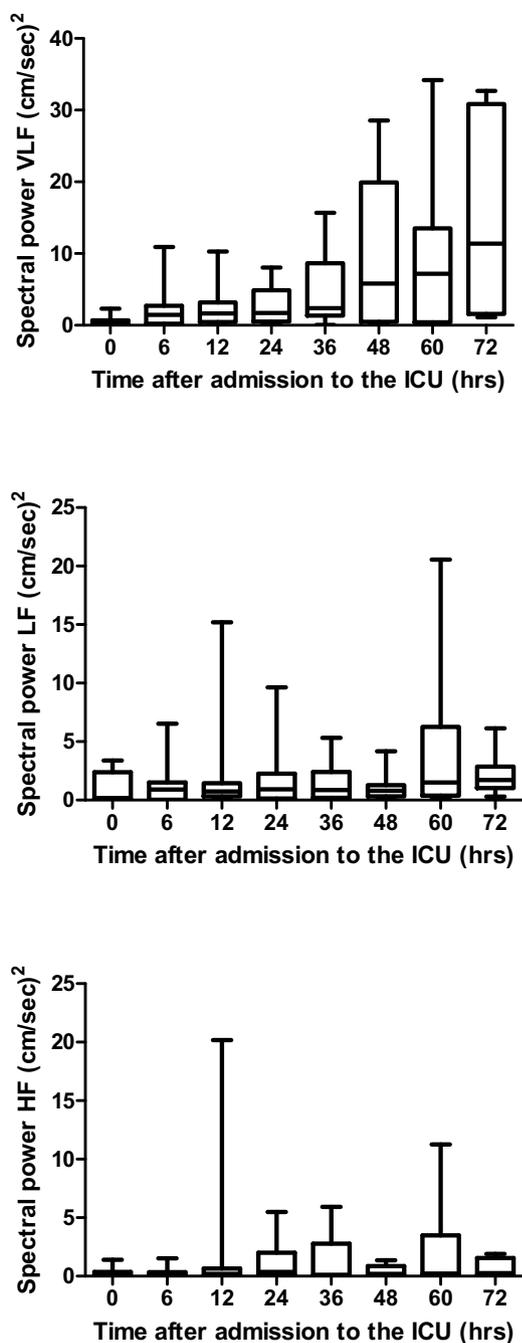


Fig. 2. The average spectral power of MFV increased, in the whole cardiac arrest group, between admission and 72 h after the arrest in the VLF band. There was no increase or decrease in the LF and HF bands. MFV = mean flow velocity. VLF = very low frequency. LF = low frequency. HF = high frequency.

average spectral power of MFV in the LF and HF bands after admission (respectively $p = 0.55$ and 0.65 , Fig. 2).

The average spectral power of MFV in the VLF band was significantly lower in the cardiac arrest group on admission compared to the control group ($0.28 [0.10-0.69]$ to $9.01 [4.53-19.71]$ $(\text{cm/s})^2$, $p = 0.002$, Fig. 3). The average spectral power of MFV did not differ significantly between cardiac arrest patients on admission and controls in the LF ($0.17 [0.11-2.38]$ to $1.99 [0.47-2.45]$ $(\text{cm/s})^2$, $p = 0.21$) and HF ($0.11 [0.07-0.37]$ to $0.05 [0.03-0.12]$ $(\text{cm/s})^2$, $p = 0.13$) bands. In addition, no differences between survivors and

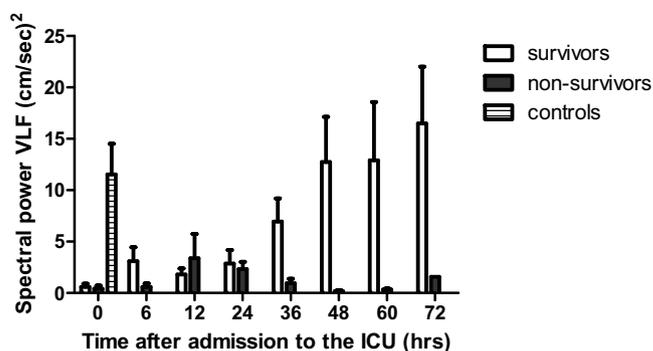


Fig. 3. Spectral power of MFV in the VLF band in survivors and non-survivors successfully resuscitated from a cardiac arrest and treated with mild therapeutic hypothermia, during 72 h of ICU admission and spectral power of MFV in the VLF band in normal controls. MFV = mean flow velocity. VLF = very low frequency.

non-survivors were found in the LF and HF bands (electronic Supplement Fig. 3).

MAP

The average spectral power of MAP did not change in the first 72 h after cardiac arrest in the VLF ($p = 0.76$), LF ($p = 0.91$), and HF ($p = 0.14$) frequency bands (data not shown).

The average spectral power of MAP in the VLF frequency band increased in survivors from $0.70 [0.50-1.93]$ to $2.10 [1.03-5.54]$ mmHg^2 during admission, while remaining low in non-survivors $0.34 [0.01-0.47]$ to $0.68 [0.68-0.68]$ mmHg^2 ($p = 0.03$, Fig. 4).

There were no significant differences for average spectral power of MAP and MFV between survivors and non-survivors in the LF and HF bands (data not shown).

The average spectral power of MAP was significantly lower in the cardiac arrest group on admission compared to the control group in the VLF ($0.57 [0.27-1.02]$ to $5.79 [3.59-10.02]$ mmHg^2 , $p = 0.001$), LF ($0.37 [0.13-0.67]$ to $2.6 [1.99-4.68]$ mmHg^2 , $p < 0.001$) and HF ($0.08 [0.01-0.40]$ to $0.91 [0.26-2.24]$ mmHg^2 , $p = 0.02$) bands.

Discussion

The spontaneous variability of MFV_{MCA} was low after cardiac arrest. MFV variability returned to normal values in survivors whereas variability decreased further in non-survivors after car-

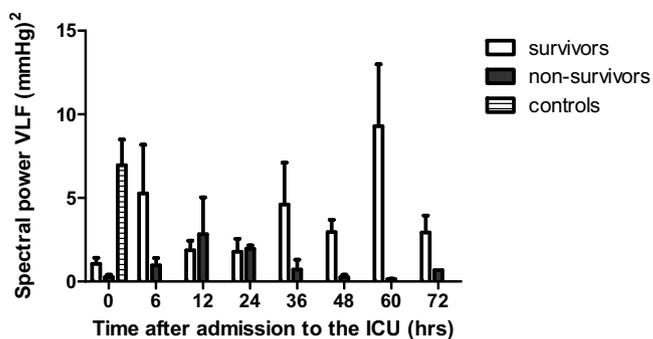


Fig. 4. Spectral power of MAP in the VLF band in survivors and non-survivors successfully resuscitated from a cardiac arrest and treated with mild therapeutic hypothermia, during 72 h of ICU admission and spectral power of MAP in the VLF band in normal controls. MAP = mean arterial pressure. VLF = very low frequency.

diac arrest. The variability of the MAP remained low during the entire study period after cardiac arrest.

The average power in the VLF spectrum of the MFV_{MCA} was low after cardiac arrest and restored towards normal values in survivors. The persistently low power in the VLF domain in non-survivors suggest perturbations in the intrinsic myogenic vascular function.⁸ In normal subjects, the correlation between cerebral blood flow velocity and MAP fluctuations is low for frequencies below 0.1 Hz, suggesting that in this frequency range other factors may lead to fluctuations in cerebral blood flow velocity.²¹ Indeed, in normal volunteers, changes in MFV_{MCA} oscillations in a frequency of 0.03–0.15 Hz can precede those in blood pressure and heart rate.²² This suggests that these low frequency oscillations have a more central cerebral origin and are transmitted “upstream” to the larger cerebral arteries. Probably, these low frequency oscillations arise in the cerebral circulation as a result of autonomic (sympathetic) stimulation.

Cerebral blood flow is tightly regulated at the level of the neurovascular unit through a myriad of metabolic, myogenic and autonomic pathways.²³ Cerebral blood flow is decreased after cardiac arrest and restores towards normal values in survivors.²⁴ Non-survivors have a significantly stronger increase in MFV_{MCA} in the first 72 h after the arrest.²⁵ Apparently, vasoactive tone is lost in patients with poor outcome, resulting in a decrease in cerebral vascular resistance and subsequent increase in cerebral blood flow. These observations are in accordance with our current study that intrinsic myogenic vascular function and sympathetic autonomic regulation may be impaired in non-survivors after cardiac arrest. The importance of the autonomic nervous system in regulation of the cerebral blood flow is well documented in humans. Upper thoracic sympathectomy in patients with palmar hyperhidrosis resulted in increased blood volume and blood flow velocities in the MCA.²⁶ Trimetaphan (a so-called ganglion blocker, because it blocks the cholinergic synaptic transmission in sympathetic and parasympathetic pathways) changes static and dynamic cerebral autoregulation in humans, indicating that removal of autonomic neural activity plays an important role in the regulation of cerebral blood flow.²⁷

Beat to beat changes in cerebral blood flow are under the control of myogenic and autonomic mechanisms under normal conditions. Cardiac arrest induces a strong inflammatory response, accompanied by changes in NO production and production of reactive oxygen species resulting in endothelium-dependent relaxation.^{28,29} An imbalance between local vasoconstrictors and vasodilators, characterized by high endothelin levels and initially low but gradually increasing cGMP levels is suggested to underlie the cerebral perfusion changes after cardiac arrest.³⁰ 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.^{30–35} We hypothesize that these pathophysiological changes can contribute to the changes in MFV_{MCA} variability after cardiac arrest and influence the state of dynamic autoregulation in these patients.

The spontaneous variability in MAP in post-cardiac arrest patients was significantly lower compared to age- and sex-matched control patients. Similarly, heart rate variability is reduced in both low and high frequency power spectra in survivors and non-survivors after cardiac arrest, suggesting a decrease in autonomic cardiovascular function, that affects MAP variability in a similar manner.^{36,37} The relatively low average spectral power of MAP in the VLF frequency band supports this hypothesis of autonomic failure.

This study has a number of limitations. We performed an observational study in a relatively small population. We cannot exclude that in our patients use of medication may have influenced these results. In the first hours after cardiac arrest, use

of sedatives and vasopressive agents were common, whereas β -blockers were frequently used after rewarming to normothermia. All patients were treated with hypothermia. Hypothermia by itself results in increased heart rate variability in both the lower and higher frequency spectra, most likely as a result of the hypothermia induced bradycardia.³⁸ The use of sedatives, vasoactive agents and hypothermia was similar in survivors and non-survivors after cardiac arrest. In addition, differences in systemic parameters such as MAP, pH or $PaCO_2$ did not account for these differences in MFV_{MCA} and MAP variability (data not shown). We cannot exclude other unmeasured effects on cerebral blood flow and the individual patient's autoregulatory threshold is unknown. Although the observational nature of this study did not allow modification of these possible confounders, the observed pathophysiological differences in cerebral blood flow velocity and arterial blood pressure strongly suggest a disease specific pathophysiologic process.

The changes in spontaneous fluctuations in MFV_{MCA} and MAP suggest changes in dynamic autoregulation after cardiac arrest. We did not quantify the strength of the dynamic autoregulation in this population. Transfer function analysis is considered the gold standard for the estimation of dynamic cerebral autoregulation. Since this technique relies on spontaneous (or induced) fluctuations in MFV_{MCA} and MAP, reduced variability in one of both input signals will strongly reduce the reliability of the resulting output signal.²⁰

Conclusions

Cerebral blood flow is altered after cardiac arrest, with decreased spontaneous fluctuations in patients with a poor outcome. Most likely, these changes are the consequence of the associated severe brain damage, resulting in impaired intrinsic myogenic vascular function and autonomic dysregulation. These perturbations in cerebrovascular regulation may account for the loss of vasoactive tone and the increased cerebral blood flow velocity in non-survivors after cardiac arrest.

Conflict of interest statement

No conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.resuscitation.2016.12.005>.

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