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Non-invasive cerebral perfusion monitoring in cardiac arrest patients: a prospective cohort study

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ABSTRACT

Objectives: To determine if non-invasive cerebral perfusion estimation provided by a new acousto-optic technology can be used as a reliable predictor of neurological outcome.
Patients and Methods: We performed a prospective, observational cohort study of consecutive comatose patients successfully resuscitated from out-of-hospital cardiac arrest. Patients were monitored using c-FLOW (Ornim Medical) from critical care unit admission up to 72 h, full awakening, or death. Primary outcome was favourable neurological outcome at hospital discharge, defined as a Cerebral Performance Category score of 1 or 2.
Results: A total of 21 patients were enrolled, without any loss to follow-up. Mean perfusion index over the monitoring period was not associated with functional outcome at hospital discharge (OR 1.03 [0.93, 1.17]). Adjustment for initial rhythm, time to return of spontaneous circulation and Glasgow coma scale motor score did not significantly alter the results (OR 1.06 [0.99, 1.12]). Mean perfusion index showed a poor discriminative value with an area under the curve of 0.60 for functional outcome (0.64 for survival). Correlation between the probes was weak (Pearson coefficient 0.35).
Conclusion: Cerebral perfusion monitoring using a c-FLOW device in survivors of cardiac arrest is feasible, but reliability of the information provided has yet to be demonstrated. In our cohort, we were unable to identify any association between the perfusion index and clinical outcomes at discharge. As such, clinical management of cardiac arrest patients based on non-invasive perfusion index is not supported and should be limited to research protocols. The trial was registered with ClinicalTrials.gov, number NCT02575196.

1. Introduction

Cerebral perfusion optimization is a crucial component of the management of brain-injured patients. However, available noninvasive technologies to monitor cerebral blood flow (CBF) suffer from many limitations preventing their regular bedside use. A recent method based on the acousto-optic effect might offer a solution. Released in 2015, the c-FLOW™ (Ornim Medical) claims to allow portable, continuous, real-time, non-invasive monitoring of brain perfusion. Born from hybridization of optical and ultrasound technologies, it uses focused ultrasound to modulate light in the near-infrared spectrum in tissue, allowing depth-selective continuous monitoring of capillary blood flow [1].

Cerebral perfusion can fluctuate tremendously following return of spontaneous circulation (ROSC) after cardiac arrest. CBF is reduced by 50 %–80 % in the first hours [2] following arrest secondary to cerebral vasoconstriction, probably mediated by endothelin release [3] and increased intracellular free calcium. Subsequent to this initial phase of hypo-perfusion, pressure autoregulation and metabolic coupling are impaired [4] and rebound hyperemia presumably occurs in the ensuing

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hours [5], followed again by a second more protracted reduction in CBF (the low-reflow phenomenon). These changes are but one aspect of the multiple mechanisms of injury that underlie neuronal injury after transient global ischemia and reperfusion. In the worst case scenario, cardiac arrest patients suffer diffuse and symmetric ischemic brain injury which manifests as laminar necrosis on diffusion weighted imaging [6].

Given the prominent CBF perturbations that occur after cardiac arrest, noninvasive monitoring of cerebral perfusion is an attractive clinical application. To date most studies in this area have focused on regional brain tissue haemoglobin saturation monitoring [7,8], or transcranial Doppler-derived measurements of cerebral blood flow velocity measurements [9]. To our knowledge, no on has attempted to measure brain perfusion after cardiac arrest using acousto-optic based technology.

We therefore sought to determine, in this pilot study of resuscitated comatose cardiac arrest patients, if CBF estimation provided by the c-FLOW device is (1) feasible and reliable (2) correlated with neurological outcome, and (3) capable of identifying a clinically useful threshold value that could dictate therapeutic intervention.

2. Patients and Methods

2.1. Study Population

We performed a single-center, phase 2, prospective, observational, pilot inception cohort study of consecutive adult patients successfully resuscitated from a cardiac arrest between October 2015 and March 2016. Adult patients with sustained ROSC within 60 min of arrest that were unresponsive and unable to follow command (i.e. comatose) were eligible. Subjects with partially or fully dependent functional status prior to arrest, as well as those with concomitant primary neurological injury (traumatic brain injury, subarachnoid haemorrhage, massive stroke or intracerebral haemorrhage) were excluded. Those with severe co-morbidity or terminal illness making survival to three months unlikely were also excluded. The study was approved by the Icahn School of Medicine Institutional Review Board. A waiver of the requirement for written informed consent was secured to allow us to collect information in the immediate post-resuscitation phase as the study posed no risk to the patient. Consent was obtained from a legally authorized representative as soon as feasible, and from the patient if they regained consciousness. ORNIM Medical provided two c-FLOW™ monitors for research purposes, but were not involved in study design, data collection and analysis, or in the drafting of this manuscript.

2.2. Clinical Management and Data Collection

Post-resuscitation care was provided per contemporary guidelines. All patients were admitted to a critical care unit. Haemodynamic support was exclusively pharmacologic (i.e. vasopressors) in our cohort. Every patient was mechanically ventilated at admission and targeted temperature management (35 °C in most cases) was applied unless a contraindication was present.

Demographic data, medical history and clinical features at onset were obtained by interview with family members and review of the medical record shortly after admission. Data collected included cardiac arrest and resuscitation characteristics including location of arrest, suspected cause of arrest, initial rhythm, and time to ROSC. Admission neurological status was evaluated with the Glasgow Coma Scale (GCS), the Full Outline of UnResponsiveness (FOUR score), and pupillary light reactivity.

2.3. c-FLOW™ Monitoring

As soon as possible after admission to the ICU, probes were applied bifrontally using proprietary adhesive mountings and standard ultrasound gel and connected to the c-FLOW™ monitor. The monitor displays a Cerebral Flow Index (CFI) for each probe, which describes changes in cortical CBF in arbitrary units ranging from 0 to 100, with 0 representing no flow. The CFI is updated every 3 s. The probes emit near-infrared laser light (808 nm) and determine the concentration of oxy and deoxy-haemoglobin based on distinct absorption characteristics of each. This light is tagged (i.e. its frequency distribution is changed) by a concomitant ultrasound beam, allowing depth-specific readings. A proprietary algorithm provides flow change estimation, relayed in the form of CFI. Of note, CFI is a strictly relative value that is correlated with but does not directly correspond to actual CBF in mL/100 g/min. Each patient was studied with one of the two available monitors. Treating clinicians were blinded to CFI values. Monitoring was left in place until death, full awakening, or for a maximum of 72 h. CFI monitoring was temporarily interrupted to allow for imaging, electroencephalography, or other procedures such as percutaneous coronary intervention. Individual data was downloaded immediately after probe removal.

2.4. Outcome Assessment

The primary outcome was favourable neurological outcome at hospital discharge. A cerebral performance category score (CPC) of 1 (mild or no neurological deficit) or 2 (moderate cerebral disability) was considered a good neurological outcome. Members of the research team assessing CPC were unaware of monitoring results. Secondary outcomes were survival to hospital discharge and monitoring feasibility, based on a percentage of adequate readings over monitoring time.

2.5. Statistical Analysis

Continuous and normally distributed variables were summarized by providing the mean and standard deviation and compared using independent sample Student's *t*-test with equal variance. Categorical variables were expressed as absolute and relative frequencies and compared using the chi-square test, or Fisher's exact test in the presence of expected small values. Logistic regression was used to measure the association between mean CFI and the odds of favourable functional outcome and of survival at discharge. Univariable and multivariable logistic regressions were employed to investigate unadjusted and adjusted odds ratios (ORs) with 95 % confidence intervals. Variables expected to affect the outcome and survival were analysed and initial rhythm, time to ROSC and admission GCS motor score, the three most powerful predictors of outcome in our cohort, were included in the multivariable model. Invalid readings due to poor signal as well as aberrant values were discarded before analysis. A receiver operating characteristic (ROC) curve was plotted and the area under the curve (AUC) calculated to evaluate the ability of CFI to discriminate between good and poor functional outcome as well as between survivors and non-survivors. Sensitivity analyses were conducted using median CFI, the first 24 h mean CFI, lowest CFI value and CFI variability. They were also repeated using only the probe with the highest, then the probe with the lowest, mean CFI values. We also controlled for which of the two monitors were used. Individual simultaneous readings obtained from each probe in any given patient were compared using Pearson correlation and paired *t*-test. Finally, we conducted post-hoc analyses on dynamic measures of CFI to explore the potential association between (1) exposure to low flow in the first 24 h using areas-under-the curve (AUC) of CFI over time and (2) CFI trends in the first 12 and 24 h by computing a regression line of CFI over time, and outcome. All analyses were performed using RStudio version 1.0.136. The trial was registered with ClinicalTrials.gov, number NCT02575196.

3. Results

3.1. Admission Characteristics and Functional Outcome at Hospital Discharge

A total of 26 patients were eligible during the study period, of which 21 were enrolled. Reasons for exclusion were time to ROSC over 60 min (2 patients), fully dependent functional status before arrest (1 patient) and research personnel being unavailable (2 patients). Characteristics of included and excluded patients did not significantly differ. There was no loss to follow-up.

Five of the 21 patients (24 %) had a good neurological outcome, and 3 of these patients were discharged to home. Amongst the 16 patients with unfavourable outcome, 12 (75 %) were dead at discharge and four were discharged to a facility with a CPC score of 3 (conscious but severely disabled); there was no patient in a vegetative state at discharge. Of the 12 patients who died, the cause of death was brain death in 2 patients, re-arrest or multi-organ failure in 3, and limitation or withholding of life sustaining therapies based on a dismal neurological prognosis in 7 patients. The limitation or withholding of life sustaining therapy based on prognosis was made no earlier than 4 days after ROSC. In our cohort, a shockable rhythm, a shorter time to ROSC, and a reassuring admission neurological exam (based on the FOUR score and GCS motor score) were associated with a favourable functional outcome (Table 1).

3.2. Association Between CFI Values and Outcome

Mean CFI over the monitoring period was not associated with functional outcome at hospital discharge (OR 1.03 [0.93, 1.17], Table 2). Adjustment for initial rhythm, time to ROSC and GCS motor score did not significantly alter the results (OR 1.06 [0.99, 1.12]). Mean CFI showed a poor discriminative value after ROC curve analysis (Fig. 1), with an AUC of 0.60 for favourable functional outcome (CPC 1 or 2) and 0.64 for death at discharge. Analyses of multiple other CFI parameters were also negative (Table 2). Highest CFI in the first 24 h or overall was 98 for everyone and could not be analysed. Results were similar for association with survival, whether in univariate (OR 1.02 [0.95–1.09]) or multivariate (OR 1.05 [0.95, 1.17]) analyses. Sensitivity analyses did not yield different results. In post-hoc analyses, exposure to low flow in the first 24 h, as detected using the AUC of CFI over time, was not significantly different between patients with favourable or unfavourable outcome. CFI trends in the first 12 h and in the first 24 h were also not significantly different between patients with favourable or unfavourable outcome.

Table 2
Absolute CFI values and univariate odds of favourable neurological outcome at hospital discharge according to CFI parameters.

CFI parameter analysed	Good outcome	Poor outcome	OR	95 % CI	P value
Mean	60.2	57.5	1.03	0.93, 1.17	0.58
Median	57.4	55.0	1.02	0.93, 1.14	0.65
Mean in first 24 h	58.5	53.2	1.04	0.94, 1.21	0.52
Median in first 24 h	50.0	51.6	0.98	0.80, 1.13	0.84
Median – left probe	63.0	50.2	1.16	1.02, 1.41	0.13
Median – right probe	56.2	66.6	0.97	0.90, 1.02	0.09
Mean – highest probe	66.3	67.6	1.00	0.93, 1.06	0.89
Mean – lowest probe	56.0	50.5	1.19	0.99, 1.53	0.12
Lowest value	30.4	28.7	1.06	0.88, 1.27	0.55
Lowest value 24 h	33.5	37.9	0.98	0.78, 1.06	0.75
Variability			0.87	0.65, 1.12	0.29
Mean – device 1	59.2	50.1	1.18	0.99, 1.51	0.37
Mean – device 2	64.3	64.9	0.98	0.63, 1.42	0.86

3.3. Monitoring Feasibility and Reliability

Monitoring was started on average 15 h after ROSC, with 62 % of the patients started in the first 12 h after arrest (Table 1). Inadequate readings represented on average 16 % of all recorded values and were secondary to leads falling off, dried ultrasound gel, or failure of the adhesive mountings. Overall correlation between the left and right probes (Fig. 2) was weak and potentially non-existent (Pearson coefficient 0.35, P-value 0.13), with a mean difference between CFI values of

Table 1
Distribution of baseline, clinical, and monitoring characteristics according to neurological outcome.

	All patients (n = 21)	Good outcome (n = 5)	Poor outcome (n = 16)	P value
Baseline characteristics				
Mean age, years	60 ± 17	58 ± 12	61 ± 19	0.63
Male	10 (48)	3 (60)	7 (44)	0.63*
Medical history				
Hypertension	17 (77)	5 (100)	12 (75)	0.53*
Diabetes	11 (50)	4 (80)	7 (44)	0.31*
Prior MI	3 (14)	0 (0)	3 (19)	0.55*
Cardiac arrest characteristics				
Out-of-hospital	10 (48)	1 (20)	9 (56)	0.31*
Cardiac cause of arrest	11 (52)	4 (80)	7 (44)	0.34*
FV/VT initial rhythm	10 (48)	4 (80)	6 (38)	0.15*
Time to ROSC, minutes	23 ± 14	13 ± 3	26 ± 15	0.007
Admission characteristics				
SOFA score, mean (± SD)	8.6 ± 3.1	7.6 ± 2.6	8.9 ± 3.4	0.38
Lactates, mean (± SD)	7.0 ± 3.9	4.5 ± 3.2	7.8 ± 3.6	0.13
FOUR score, mean (± SD)	4.3 ± 4.3	10.6 ± 4.3	2.6 ± 2.3	0.01
GCS motor, mean (± SD)	2.8 ± 2.1	4.1 ± 2.0	1.8 ± 1.5	0.01
Bilateral unreactive pupils	10 (48)	1 (20)	9 (56)	0.56*
Monitoring characteristics				
Delay from arrest to monitoring, hours	13 ± 11	13 ± 17	14 ± 8	0.88
Monitoring duration, hours	49 ± 21	44 ± 21	50 ± 21	0.69
Percentage of monitoring time with adequate signal	84 ± 12	82 ± 9	85 ± 15	0.57

Data are N (%), or mean ± SD.
* Fisher's exact test.

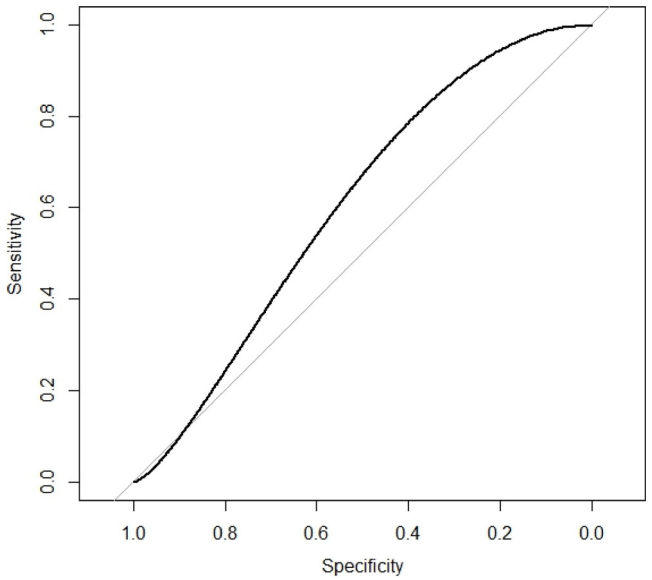

Fig. 1. Receiver operating characteristic (ROC) curve analysis of favourable neurological outcome at discharge by mean CFI value during the monitoring period. Area under the curve (AUC): 0.60.

13 (P-value 0.003). At the patient level, CFI values obtained over time by the two probes had a negative correlation in 3 patients, a low or negligible correlation in 12 patients, and high correlation in only 3. Another technical problem arose after realization that every time the probes were removed for a few seconds to renew the ultrasound gel between the adhesive mounting and the probe, values obtained before and after were significantly different, although not systematically recorded.

4. Discussion

Our study could not demonstrate any association between CFI measurements and neurological outcome or survival at hospital discharge in a population of unconscious cardiac arrest survivors. To our knowledge, this is the first study designed to evaluate the association between acousto-optic CBF measurements and clinically relevant outcomes. No threshold value could be identified to potentially guide clinicians for therapeutic interventions. Although small studies had previously demonstrated CBF variations in the aftermath of cardiac arrest, they were also unable to associate these potentially important physiologic changes to the outcome [9]. It is therefore possible that the negative results in our study reflect a real absence of association between cerebral perfusion and outcome, as our power to detect one standard deviation in CFI values between favourable and unfavourable functional outcome was 90 % at a significance level of 0.05.

However, discrepancies between values simultaneously obtained by the probes cast serious doubts on the clinical significance of CFI as a monitoring tool. The within-patient mean difference between left and right was three times larger than the mean difference between two groups with different outcomes (Table 2). Even though the c-FLOW does not purport to provide absolute CBF values, the lack of correlation between probes both at group and at individual levels provides confusing data. In 2012, a pre-clinical study compared changes in CFI to changes in CBF as measured with ^{133}Xenon single photon emission computer tomography in healthy patients after intravenous bolus of acetazolamide [10]. Although CBF and CFI both went up at first, they harboured an inverse relationship after 45 min. Moreover, the

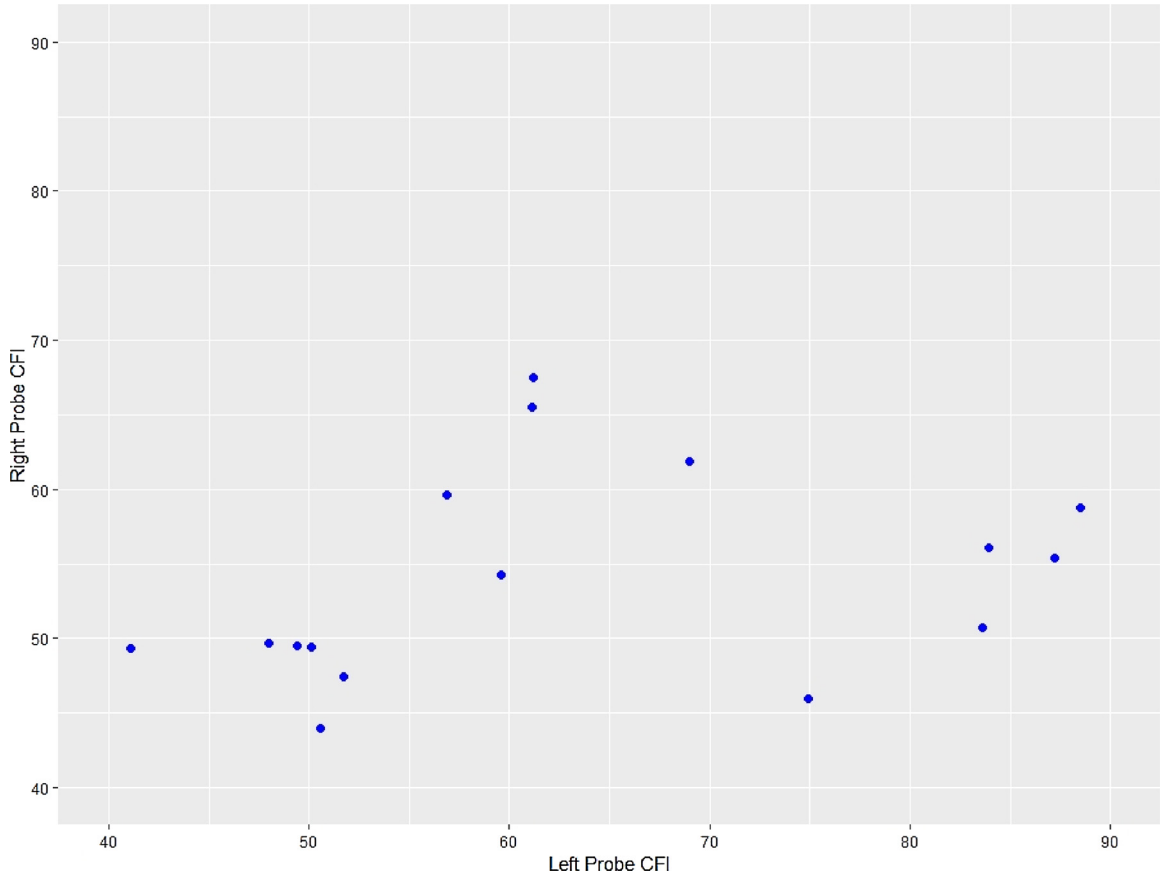

Fig. 2. Relationship between left and right probes median CFI values (overall median left CFI = 51 and median right CFI = 61) Pearson coefficient 0.35, P-value 0.13. Two points missing (data on 19 correlations out of 21 patients) as one of the probes was deemed too unreliable and has been rejected in analysis in 2 patients.

technology did not compare well to transcranial Doppler in a cardiac arrest patient population with regard to its ability to track changes in blood flow velocity [10]. Even more worrisome, a recent study found significantly higher CFI values in brain dead patients than in healthy patients, as well as marked difference between hemisphere, confirming our findings [11].

The strengths of our study include the following. Our cohort of patients represented a homogeneous type of brain injury, namely post anoxic encephalopathy. Exclusion criteria and brain imaging confirmed the absence of underlying or concomitant asymmetric or structural brain damage. Clinical management was in line with the most recent guidelines. Monitoring was started in a timely fashion, in less than 12-h post-ROSC in most patients. Sensor positioning and maintenance were made exclusively by research team members who were trained by ORNIM personnel. Two different monitors were used with similar conclusions, effectively ruling out software or hardware malfunction. Clinicians were blinded to CFI values and could not have altered their management based on the study results. An expert team made prognostication according to contemporary guidelines. Limitation or withholding of life sustaining therapies were never applied before 72 h. The CPC was calculated by research team members who were unaware of the patient's CFI values. Survival at discharge with favourable neurological outcome defined as a CPC 1 or 2 is consistent with current Utstein guidelines.

Our study also suffers limitations. The a priori link between CBF and outcome in the cardiac arrest population has never been proven in humans, which limits our ability to draw solid conclusions on CFI validation. Moreover, we did not have a gold standard CBF monitoring to provide adequate comparison. However, the study objective was not to assess the device accuracy. The observational design and small number of patients also limit our ability to control for potential confounding, although both treating team and outcome evaluators were blinded. Finally, ORNIM has recently released a modified version of their algorithm to calculate CFI, which was not evaluated.

In conclusion, cerebral perfusion monitoring using a c-FLOW device in survivors of cardiac arrest is feasible, but reliability of the information provided has yet to be demonstrated. In our cohort, we were unable to identify any association between the perfusion index and clinical outcomes at discharge. As such, clinical management of cardiac arrest patients based on non-invasive perfusion index is not supported and should be limited to research protocols.

Ethics Approval and Consent to Participate

The study was approved by the Icahn School of Medicine Institutional Review Board. A waiver of the requirement for written informed consent was secured to allow us to collect information in the immediate post-resuscitation phase as the study posed no risk to the patient. Consent was obtained from a legally authorized representative as soon as feasible, and from the patient if they regained consciousness.

Consent for Publication

Not applicable.

Availability of Data and Material

All data generated or analysed during this study are available from the corresponding author on reasonable request.

Authors Contributions

All authors have made substantial contributions to some or all of the following: (1) conceptualization, methodology, software, validation, formal analysis, investigation or data curation and (2) original draft preparation, review or editing.

Funding

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CRediT authorship contribution statement

Charles L. Francoeur: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Visualization. **James Lee:** Investigation. **Neha Dangayach:** Conceptualization, Supervision. **Umesh Gidwani:** Resources, Supervision. **Stephan A. Mayer:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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