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Acute-stage MRI Cerebral Oxygen Consumption Biomarkers Predict 24-hour Neurological Outcome in a Rat Cardiac Arrest Model

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Abstract

Brain injury following cardiac arrest (CA) is thought to be caused by a sudden loss of blood flow resulting in disruption in oxygen delivery, neural function, and metabolism. However, temporal trajectories of the brain's physiology in the first few hours following CA have not been fully characterized. Furthermore, the extent to which these early measures can predict future neurological outcomes has not been determined. The present study sought to perform dynamic measurements of cerebral blood flow (CBF), oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygen (CMRO₂) with MRI in the first 3 hours following the return of spontaneous circulation (ROSC) in a rat CA model. It was found that CBF, OEF, and CMRO₂ all revealed a time-dependent increase during the first 3 hours after ROSC. Furthermore, the temporal trajectories of CBF and CMRO₂, but not OEF, were different across rats and related to neurologic outcomes at a later time (24 hours after ROSC) ($p < 0.001$). Rats who manifested better outcomes revealed faster increases in CBF and CMRO₂ during the acute-stage. When investigating physiological parameters measured at a single time-point, CBF ($\rho = 0.82$, $p = 0.004$) and CMRO₂ ($\rho = 0.80$, $p = 0.006$) measured at approximately 3 hours post-ROSC were positively associated with neurologic outcome scores at 24 hours. These findings shed light on brain physiological changes following CA, and suggest that MRI measures of brain perfusion and metabolism may provide a potential biomarker to guide post-CA management.

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Graphical Abstract

Early-stage measurement of cerebral metabolic rate of oxygen and cerebral blood flow (2.5h after return of spontaneous circulation) correlates with the 24-hour neurologic outcome, indicating the potential of oxygen metabolism as a biomarker to facilitate cardiac-arrest management.

Keywords

cardiac arrest; oxygen consumption; neurologic deficit score; cerebral blood flow; cerebral metabolic rate of oxygen; TRUST; phase contrast; MRI

INTRODUCTION

Cardiac arrest (CA) carries low survival rate (~10%) and unfavorable outcomes.^{1,2} Poor functional outcomes and mortality in CA are primarily driven by brain injury that occurs from a sudden loss of blood supply to the brain. The lack of blood flow leads to rapid changes in intracellular and extracellular ion concentrations with the development of intracellular acidosis. Furthermore, the failure of maintaining ionic balance results in membrane disruption, irreversible neuronal injury and, eventually, cell death.³ As a critical management strategy for CA, effective cardiopulmonary resuscitation (CPR) has been shown to help achieve the return of spontaneous circulation (ROSC) and result in improved neurologic outcomes.^{4,5} However, physiological changes in the brain immediately after CPR and ROSC that may underlie the improved outcomes are not fully understood.⁶ Blood circulation and oxygen metabolism are among the key processes in CA, the disruption of which is thought to play a critical role in the failure in maintaining neuronal function.⁷ Therefore, understanding dynamic patterns in cerebral circulation and oxygen metabolism may help gain insight into the early events in brain and hemodynamic function following CA. It is also known that many survivors suffer from significant disabilities.⁸ However, the

optimal timing of post-ROSC intervention and methods to minimize disability remains unclear. Therefore, a reliable early-stage biomarker based on brain circulation and metabolism that can predict later neurologic outcome is of significance in improving current CA management.

With technical advances in MRI during the past decade, it is now feasible to evaluate cerebral oxygen homeostasis non-invasively.^{9,10} Brain circulation can be measured by cerebral blood flow (CBF), which denotes the amount of blood delivered to brain tissue per unit time.¹¹ On the other hand, oxygen extraction fraction (OEF) can be estimated by arteriovenous differences in oxygen content. Cerebral metabolic rate of oxygen (CMRO₂) can then be estimated from the product of CBF and OEF.¹² Over the past few years, both global and regional MRI techniques for these physiological parameters have been proposed.^{13–15} While the regional methods have the advantage of spatial specificity, their scan time tends to be longer with a lower signal-to-noise ratio. Furthermore, CA is a systemic perturbation, thus its impact on brain physiology is expected to be global.

Therefore, in this study, we utilized non-contrast-agent T₂-relaxation-under-spin-tagging (TRUST)^{16,17} and phase-contrast (PC)^{18,19} MRI techniques to investigate OEF, CBF, and CMRO₂ in a dynamic fashion during the first 3 hours after CA and ROSC in a rat model. To quantitatively evaluate neurologic recovery, a validated neurologic deficit score (NDS)²⁰ was determined at 24h after ROSC. The dependences of 24h NDS values on brain physiological parameters and their rate-of-change during the first 3 hours after ROSC were examined.

EXPERIMENTAL

Animal preparation

The experimental protocols involved in this study have been approved by the Johns Hopkins Medical Institute Animal Care and Use Committee and were conducted in accordance with the National Institutes of Health guide for the care and use of laboratory animals. A total of 10 Wistar rats (male; 11~12 weeks; 400~450 grams; Charles River, Wilmington, MA, USA) were used in this study. Rats were housed in a quiet environment with 12h day/night circles and free access to food/water.

The asphyxia CA and CPR procedures followed a previously validated protocol.^{21,22} Briefly, under isoflurane anesthesia, rats were endotracheally intubated with a 14G catheter (TERUMO Surflash intravenous catheter) and mechanically ventilated at 35 breathes per minute by a rodent ventilator (Harvard Apparatus Model, San Diego, CA, USA). Left femoral artery and vein were cannulated with polyethylene 50 tubing catheters (Intramedic Non-Radiopaque Polyethylene Tubing PE 50, Becton Dickinson) for monitoring arterial pressure and fluid/medication administration, respectively. Prior to asphyxia, isoflurane was switched off. A washout period of 5 min was used with the first 2 min administering 100% oxygen and the latter 3 min room air. At 2 min into the washout period, 2.0 mg/kg vecuronium bromide (Abbott Labs, North Chicago, IL, USA) was administered intravenously for muscle paralysis. After the 5-min washout period, global asphyxial CA was induced by stopping and disconnecting the ventilator and clamping the tracheal tube for 7 min. CA was defined by mean arterial pressure (MAP) <10 mmHg and asystole. After the

7-min asphyxia period, CPR was performed by unclamping the tracheal tube, restarting mechanical ventilation, administering epinephrine (5 µg/kg, i.v.), NaHCO₃ (1 mmol/kg, i.v.), and manual sternal chest compressions (200/min) until ROSC (MAP>50 mmHg and pulse waveform). The animals were allowed to recover spontaneously after resuscitation. Blood pressure was recorded for 15 minutes after ROSC, before all invasive catheters were removed and the animal was extubated. All later physiological and NDS assessments were time-stamped with reference to the onset of ROSC.

After ROSC, the rat was transported to the MRI suite and placed onto a water-heated animal bed (temperature controlled) and immobilized with a bite bar and a pair of ear pins. The animal bed was then positioned in the center of the magnet. At this stage, the rat was still in a narcosis state without exhibiting voluntary motion when placed on the animal bed or reacting to sound generated by switching gradients in the MRI scanner. Anesthesia was therefore not used during the MRI session. Respiration rate of the rat was monitored throughout the MRI experiment.

MRI Experiments

All MRI experiments were performed on an 11.7T Bruker Biospec system (Bruker, Ettlingen, Germany) equipped with a horizontal bore and actively shielded pulsed field gradients (maximum intensity of 0.74 T/m). Images were acquired using a 72-mm quadrature volume resonator as transmitter and a four-element (2×2) phased array coil as receiver. The B₀ field over the mouse brain was homogenized by a global shimming (up to 2nd order) based on a subject-specific pre-acquired field map.

TRUST was originally developed¹⁶ and applied^{23–25} on human MRI, and recently optimized for preclinical usage²⁶. It relies on the spin-tagging principle to isolate venous blood signal after a pair-wise subtraction. Several different T₂ weightings were employed to modulate the signal intensities of venous blood, which were then fitted to a monoexponential model for the estimation of venous T₂. Venous oxygenation (Y_v) can thereafter be obtained using a T₂-oxygenation calibration plot.²⁷ Based on previous technical studies,¹⁷ imaging parameters of TRUST MRI were: TR/TE = 3500/6.3 ms, FOV = 30×30 mm², matrix size = 128×128, slice thickness = 1.0 mm, EPI factor = 16, inversion-slab thickness = 2.5 mm, post-labeling delay = 1000 ms, eTE = 0.25, 20, 40 ms, number of average = 2, and scan duration = 5.6 min. Since the dynamic range of arterial oxygenation (Y_a) is much narrower than that of Y_v, we assumed a constant Y_a value (Y_a=99%)^{28–30} for the calculation of OEF (i.e., OEF=0.99-Y_v).

PC MRI encodes flow information in its phase image to provide flow-velocity map using magnetic field gradients. Integration of flow velocity over voxels containing the arterial vessel yields an estimation of blood flow, and summation of blood flow values across the major feeding arteries, i.e., left/right internal carotid artery (LICA/RICA) and basilar artery (BA), yields total CBF. Unit-volume CBF (in ml/100g tissue/min) can then be obtained by normalizing the total CBF by brain weight, which can be evaluated from a T₂-weighted MRI scan in unison with an assumed tissue density (1.04 g/ml³¹). Imaging parameters for PC MRI were:¹⁹ TR/TE = 15/3.3 ms, FOV = 30×30 mm², matrix size = 500×500, slice

thickness = 1.0 mm, encoding velocity = 30 cm/s for LICA/RICA (15 cm/s for BA), number of average = 4, receiver bandwidth = 100 kHz, flip angle = 25°, and scan duration = 1.0 min.

CMRO₂ was calculated using the Fick principle,¹² i.e., $CMRO_2 = C_a \cdot OEF \cdot CBF$, where C_a denotes the oxygen-carrying capacity of blood, assumed to be 8.82 μmol/ml.^{32,33}

A typical MRI session started at approximately 25 min after ROSC. Then, another 35 min were needed for the animal positioning, field-map acquisition, shimming, and MRI anatomic scans. Therefore, the dynamic physiological MRI scanning starts at approximately 60 min after ROSC. Each time point in dynamic physiological MRI comprises of a TRUST scan and three PC scans (LICA, RICA, and BA, respectively), and these scans were repeated every 16 min until the rat exhibited strong motion or until 3 hours after ROSC, whichever came first.

Neurological evaluation

The NDS assessment is a validated neurological examination in rodent models to evaluate the neurologic outcomes after global cerebral ischemic injury.^{20,22} Details of the NDS scoring are described in the Supplementary Materials. Briefly, it contains seven subcomponents as follows. Arousal level was assessed by pinching their toes and counting spontaneous respiration rate. Brainstem function was assessed by shining light to their eyes and placing food near their nose. Motor assessment was performed by observing the leg and toe movement of the rat. Pain-related sensory assessment was performed by pinching their skin and observing their response. Motor behavior was assessed by placing them in an open field or a suspended beam and observing their walking behavior. A behavior index was obtained by placing the rat on different platforms or at different positions and observing how they respond. Finally, the presence and frequency of seizure was determined by observing the animal throughout the procedure mentioned above. Scores for each subcomponent were added up to provide a total NDS, which ranges from 0 (worst) to 80 (best). NDS was determined 24 hours after ROSC. Two rats died after finishing the MRI session but before the NDS session (at 5 and 15 hours after ROSC, respectively), and, accordingly, their NDS were assigned to be 0 (the lowest value). We have previously validated this score with regular and advanced histologic studies.^{34,35} Note that the neurologic recovery beyond 24 hours after ROSC has been studied previously and was found to show minimal differences from that at 24 hours.^{22,36} Therefore, the present study focused on the 24-hour NDS measures.^{20–22}

Data Processing and Analysis

The MRI data processing was performed in a blinded fashion where the duration of CA, ROSC time, and NDS of the animal studied were not provided to the person doing the MRI-data processing and analysis.

The TRUST and PC MRI data were processed with custom-written MATLAB scripts (MathWorks, Natick, Massachusetts). A linear mixed-effect model was performed to examine the time dependence of CBF, OEF, and CMRO₂. Further, the NDS scores of animals were added to the model, and an interaction term, Time × NDS, was tested. The NDS scores were converted into ranks because of the non-Gaussian distribution of the values. Additionally, Spearman's rank correlation was utilized to examine the relationship

between physiological MRI measures at different single time-point and the NDS score. In addition to the values of the physiological MRI, their rate-of-change was also calculated and compared with NDS. A $p < 0.05$ was considered significant.

RESULTS

Rats undergoing the identical 7-min asphyxia CA procedure exhibited different outcomes, as indicated by the 24-hour NDS scores in Table 1 (Range 0~78, Mean $\pm$ SD 56 $\pm$ 30, N=10). For the MRI data, four rats showed motion after the 156-min dynamic scan and six rats completed all dynamic scans, which ended after the 172-min scan.

Representative datasets of TRUST and PC are displayed in Figure 1. As can be seen in Figure 1a, pure venous blood signal can be extracted after pair-wise subtraction between control and labeled images. Venous blood T_2 can then be estimated by fitting the blood-signal intensities of three eTE (0.25, 20, and 40 ms) to a monoexponential function (Figure 1b). By using a calibration plot (Figure 1c), whole-brain Y_v is obtained for the OEF calculation. Figure 1d shows the maximum-intensity-projection (MIP) image of time-of-flight (TOF) MRI to visualize the major feeding arteries (LICA, RICA, and BA). A separate PC scan was performed for each feeding artery with representative complex-difference (CD) image and velocity map shown in Figure 1e. Region-of-interest (ROI) was drawn manually in the CD image (yellow polygon) and then applied to the velocity map for the CBF estimation. The three major feeding arteries, LICA, RICA, and BA, had a voxel count of 49 $\pm$ 10, 45 $\pm$ 14, and 18 $\pm$ 3 voxels, respectively, with the spatial resolution (60 μ m) used in the present study.

The time courses of OEF, CBF, and CMRO₂ after ROSC are shown in Figures 2a–c. All three parameters showed an increase ($p = 0.006$) in the first few hours after CA, suggesting a recovery of the brain's hemodynamic and metabolic function. Next, we examined whether the recovery of these physiological parameters were dependent on the individual rat's functional outcome. We found a significant Time $\times$ NDS interaction effect in CBF ($p < 0.001$) and CMRO₂ ($p < 0.001$), but not in OEF ($p = 0.07$), suggesting that more rapid and sustained recovery in flow and metabolism are associated with a better outcome. To visualize this effect, for display purposes we split the rats into two sub-groups based on their 24-hours NDS scores (a higher NDS group: Range 69~78, Mean $\pm$ SD 74 $\pm$ 4, N=5; and a lower NDS group: Range 0~64, Mean $\pm$ SD 37 $\pm$ 34, N=5). The corresponding results are shown in Figures 2d–f. It can be seen that, while the OEF time courses showed no difference between groups, there was a clear disparity in terms of CBF and CMRO₂ time courses. Specifically, the higher-NDS group revealed a continuous and more rapid increase in CBF and CMRO₂ with time. On the other hand, the lower-NDS group showed a small increase initially, followed by a plateau and even a trend of decreasing.

The correlations between single-time-point MRI physiological parameters and 24-hour NDS score are shown in Figure 3a. Each entry in Figure 3a denoted the correlation coefficient (ρ) value of the Spearman's rank correlation between a physiological measurement (OEF, CBF, or CMRO₂) at a single time point (60, 76, 92, 108, 124, 140, or 156 min) and the 24-hour NDS value. It can be seen that, at <100 min following ROSC, none of the physiological

parameters revealed a correlation with NDS score ($p = 0.27$). On the other hand, at later time points, CBF and CMRO₂ (but not OEF) showed increasing correlations with NDS scores, especially for CMRO₂. The scatter plots between NDS and CBF ($\rho=0.82$, $p=0.004$), and between NDS and CMRO₂ ($\rho=0.80$, $p=0.006$) at the last time point of 156 min after ROSC are shown in Figures 3b and 3c, respectively. These results show that cerebral blood flow and metabolism measured at 2–3 hours after injury had a significant predictive value for 24-hour neurologic outcomes. As an exploratory analysis, we also studied the correlation between physiological parameters and NDS scores at 172 min post-ROSC (N=6 without strong motion artifacts out of a total of 10 animals). We observed a significant correlation between CBF and NDS ($\rho=0.84$, $p=0.04$) but not between CMRO₂ and NDS ($\rho=0.75$, $p=0.10$) at this time point. We also note that, of the four rats showing motion at 172 min, two belonged to the higher and two belonged to the lower NDS group. Thus, the time at which the animal started to wake up did not appear to have a predictive value for NDS value.

The scatter plot between the rate-of-change in CMRO₂ and NDS is provided in Figure 4. For each rat, the rate-of-change was calculated using a linear regression between the CMRO₂ value and the time from 60 min to 156 min after ROSC. It was found that the rate-of-change in CMRO₂ was correlated with NDS ($\rho=0.74$, $p=0.014$), while that of OEF ($p=0.298$) and CBF ($p=0.052$) was not significant. Rate-of-changes in OEF, CBF, and CMRO₂ were also calculated for time windows of 60~124 min and 60~140 min, with corresponding results summarized in Table S2 of the Supplementary Materials. The smaller window lengths did not produce stronger correlations.

MAP data during the first 15 minutes after ROSC were averaged and compared to NDS. No significant correlations (Spearman's rank correlation $\rho=0.30$, $p=0.39$) were found between these two parameters. In addition, respiration rate at each time point was examined. Linear mixed-effect model revealed that respiration rate during 60~156 min after ROSC was not time-dependent ($p=0.13$, see Figure S1 in supplementary materials). Moreover, Spearman's rank correlation between respiration rate and the NDS was not significant at any of the time points ($p = 0.28$).

DISCUSSION

To the best of our knowledge, this study represents the first report of the assessment of non-invasive physiological MRI markers to predict 24-hour NDS. Our findings suggest that, during the first three hours following CA and ROSC, the brain's perfusion, oxygen uptake, and oxygen consumption all revealed a steady increase. Furthermore, animals that exhibited more rapid and greater increase in oxygen consumption showed a better neurologic deficit score at 24 hours, compared to those that had worse outcomes.

The increases in OEF, CBF, and CMRO₂ (Figures 2a–c) are consistent with a self-recovery process of the brain after ROSC. However, there were heterogeneities across rats in terms of temporal trajectories of these physiological parameters. In particular, CBF and CMRO₂ appear to be related to the extent of functional recovery. As shown by the interaction-effect analysis and plots in Figures 2d–f, in animals with favorable outcomes, more neurons were presumably restored after ROSC, thus brain oxygen consumption and blood flow were

higher. In contrast, in the group with poor recovery, CBF and CMRO₂ only increased modestly and even showed a trend of decrease at later time points, suggesting that there was limited recovery in neural activity in this group and the recovery was not sustainable. These findings also suggest that the first 3 hours after CA and ROSC represents a critical time-window for therapeutic interventions. Between CBF and CMRO₂, we speculate that the effect is primarily driven by the metabolism, with blood flow showing a similar effect due to flow-metabolism coupling. This notion is supported by the observation of a strong correlation between CBF and CMRO₂ (Figure 5).

This study suggested that measurement of brain physiological parameters at acute stage can predict neurological outcomes at 24 hours post-ROSC. Based on our results, higher CMRO₂ measured at 156 min was associated with better outcomes (Figure 3c). The earlier time-points, on the other hand, did not show a significant predictive value, suggesting that it takes 2–3 hours for the fate of the neurons (recovery or death) to become clear after ROSC. Additionally, the rate-of-change in CMRO₂ across time was also found to be able to predict outcomes (Figure 4). In particular, rats with the fastest rate of reduction in CMRO₂ between 60 to 156 min did not survive beyond 24 hours after ROSC (N=2). Fast CMRO₂ reduction indicates dysfunction of the brain cells, hence these cells are not metabolizing, and, consequently, the survival rate decreases as well.

Early prediction of functional outcome following CA is an unmet medical need. For instance, hypothermia has been broadly adopted to promote the neurological outcome of CA cases under a general guideline instead of a subject-specific decision by reference to a quantitative biomarker. Therefore, the development of early-stage biomarker to predict later neurological outcome has attracted substantial interest over the past decade. Several techniques including quantitative electroencephalography (EEG)^{37,38}, microdialysis of metabolites³⁹, plasma levels of 8-iso-PGF_{2α} and 15-keto-dihydro-PGF_{2α}⁴⁰, and blood pressure measurements^{41,42} have been proposed. The present study of cerebral oxygen metabolism measurement represents another potential approach to provide a noninvasive and quantitative marker for general CA managements. It should also be noted that the metabolic MRI techniques used in this work is readily translatable to humans and have been applied in studies of human brain disorders^{24,25,43}. A single time point of equivalent data takes about 5 min to collect on human MRI.¹⁰ The present study also examined the relationship between blood pressure measured at 15 minutes post-ROSC and NDS, but did not find a significant association. This finding is different from a previous report in human pediatric patients⁴² and may be due to the disparate causes of CA between the studies. It should also be noted that the study of Topjian *et al.*⁴² required 102 patients in order to observe an association.

Results of this study should be interpreted in the context of limitations. First, this study did not perform histological analyses of the brain on this cohort, which would provide a direct assessment of the extent of ischemic injury and neuronal death in relation to cerebral autoregulation, perfusion, and CMRO₂. However, we have previously validated this model with histologic outcome.^{34,35} Furthermore, it is also known that the histopathologic analysis and infarct volumes in preclinical studies does not necessarily correlate well with functional outcome of human clinical trials.⁴⁴ Second, our oxygen consumption measurements are limited to a global assessment. Regional measurements (e.g., perfusion and diffusion^{45,46})

may provide important insights on cerebral selective vulnerability after CA. Finally, due to the logistical needs before performing dynamic physiological MRI measurements, oxygen consumption measurement within 60 min after ROSC was not available. Finally, the value of Y_a was based on an assumption rather than on experimental measurement. A previous study by Yeh *et al.* reported an arterial oxygen pressure of 111.7 mmHg²⁹ (corresponding to an oxygen saturation of 98~100%³⁰) at 60 min after ROSC, suggesting that our assumption of arterial oxygenation (99%) is reasonable.

In summary, CA rats are characterized by increases in OEF, CBF, and CMRO₂ during the first 3 hours after ROSC. Among these physiological parameters, higher CBF and CMRO₂, but not OEF, were predictive of better neurological outcomes at 24 hours post-ROSC, especially when evaluated at 2–3 hours after the ROSC. If reproduced in human studies, these observations may have important implications for clinical CA management by providing an early MRI biomarker to help determine early intervention and improve neurological outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BA	Basilar artery
CA	Cardiac arrest
CBF	Cerebral blood flow
CD	Complex difference
CMRO₂	Cerebral metabolic rate of oxygen
CPR	Cardiopulmonary resuscitation
EEG	Electroencephalography
LICA	Left internal carotid artery
MAP	Mean arterial pressure
MIP	Maximum intensity projection
NDS	Neurologic deficit score
OEF	Oxygen extraction fraction
PC	Phase contrast

RICA	Right internal carotid artery
ROI	Region of interest
ROSC	Return of spontaneous circulation
TRUST	T ₂ relaxation under spin tagging

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Figure 1.

Representative results of (a-c) TRUST and (d-e) PC MRI. (a) Pair-wise subtraction of control and labeled images yields pure blood signal. The target vein, *i.e.* the sinus confluence, is shown in the red square. (b) Blood signals at different eTE values were fitted to estimate venous blood T₂ and then (c) converted into Y_v for the OEF calculation. (d) Slice locations of PC MRI overlaid on TOF images. Three separate PC scans intersecting left ICA, right ICA, and BA were performed. (e) ROIs (yellow polygons) were drawn on complex-difference images and then applied to velocity maps to calculate blood flow.

Figure 2.

Averaged time courses of OEF, CBF, and CMRO₂ following ROSC. (a-c) Time courses averaged over all ten rats. (d-f) Time courses of higher and lower NDS groups. For display purposes, the animals were median-divided into two groups of equal sizes (N=5 per group) based on their NDS scores.

Figure 3.

The relationship between single-time-point MRI measures at acute-stage and 24-hour NDS values. (a) ρ -map of Spearman's rank correlation between physiological measurement (OEF, CBF, or CMRO₂) at different time points (60, 76, 92, 108, 124, 140, and 156 min) and 24-hour NDS. (b) Scatter plot between NDS and 156 min CBF. (c) Scatter plot between NDS and 156 min CMRO₂. Each dot represents data from one rat.

Figure 4. Scatter plot between NDS and rate-of-change in CMRO₂ between 60 and 156 min post-ROSC. Each dot represents data from one rat.

Figure 5. Correlation between CMRO₂ and CBF measurements of all time points (up to 156 min) in all rats. Different colors indicate data from different rats.

Table 1:

NDS values and MRI physiological parameters at 156 min for individual rat

Measure	Rat Number									
	1	2	3	4	5	6	7	8	9	10
NDS	78	78	76	71	69	64	62	60	0	0
OEF	40.6	39.4	29.4	20.8	18.0	40.2	45.0	21.9	14.7	36.4
CBF	72.5	104.1	84.9	62.7	84.7	50.1	42.6	50.1	61.8	37.1
CMRO ₂	249.7	347.9	211.7	110.6	129.3	170.8	162.7	93.1	77.0	114.5