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Relationship between hemodynamic parameters and cerebral blood flow during cardiopulmonary resuscitation

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## **Abstract**

**Introduction:** Cerebral blood flow during cardiopulmonary resuscitation (CPR) is a major neuroprognostic factor although not clinically feasible for routine assessment and monitoring. In this context, a surrogate marker for cerebral perfusion during CPR is highly desirable. Yet, cerebral blood flow hemodynamic determinants remain poorly understood and their significance might be altered by changes in head positioning such as flat, head up, and head down during CPR.

**Hypothesis:** We hypothesized that routinely measured hemodynamic parameters would correlate with cerebral brain flow during CPR, independently of the head position.

**Methods:** Associations between cerebral blood flow, measured using microsphere techniques, and hemodynamic parameters were studied from two prior publications. Eight pigs receiving CPR with an automated device and an impedance threshold device in the flat or supine, whole body head down and whole body head up tilt positions were analysed for the derivation sample. Relevant associations were examined for consistency in an external validation sample consisting of 18 pigs randomized to supine position versus head and torso elevation.

**Results:** After adjusting for position, arterial blood pressure and cerebral perfusion pressure during decompression were significantly associated with cerebral blood flow, in the derivation and the external validation samples. No significant associations were found between cerebral blood flow during CPR and right atrial pressure, intracranial pressure, end tidal CO<sub>2</sub>, carotid blood flow, and coronary perfusion pressure in the derivation sample.

**Conclusion:** Decompression arterial blood pressure and cerebral perfusion pressure are relevant candidate surrogate markers for cerebral blood flow during CPR, independently of head position.

## **Keywords:**

Cardiac Arrest

Cardiopulmonary resuscitation

Impedance threshold device

- 71 Active compression decompression CPR
- 72 Cerebral perfusion
- 73 Cerebral blood flow
- 74 Mechanical CPR
- 75 Swine
- 76 Head Up CPR

## Introduction

Most of the deaths in patients successfully resuscitated after out-of-hospital cardiac arrest are attributed to brain injury [1]. Cerebral blood flow during cardiopulmonary resuscitation (CPR) is a critical determinant of permanent brain damage after cardiac arrest [2]. Unfortunately, cerebral blood flow during CPR is not clinically feasible. A surrogate marker for cerebral blood flow during CPR is highly desirable for cardiac arrest prognostication and guiding the clinician decision for pursuing CPR. Yet the complex relationships between hemodynamic parameters and cerebral perfusion during CPR remain poorly understood.

Several hemodynamic predictors of successful CPR have been identified over the past century, including arterial blood pressure during decompression, coronary perfusion pressure (CorPP, i.e., aortic blood pressure minus right atrial pressure), and cerebral perfusion pressure (CerPP, i.e., arterial blood pressure minus intracranial pressure). In 1906, Crile and Dolley observed that diastolic blood pressure (DBP) level was related with the ability to resuscitate animals [3]. In humans, CorPP is currently considered one of the best clinical hemodynamic marker to predict successful resuscitation[4]. However, the simultaneous pressure transmitted to the brain via arteries and venous pressures during CPR lead to a concussive injury with each compression and impairs cerebral blood flow [5, 6]. As a result, cerebral blood flow may not adequately correlate with diastolic blood pressure or CorPP [7].

Other variables, including body or head inclination, may confound the relationships between hemodynamic parameters and cerebral blood flow during CPR and must be taken into account. We recently reported that changes in the head position during whole body tilt (flat, up, and down) with automated CPR and an impedance threshold device (ITD) altered cerebral blood flow [6]. This finding was consistent with another study showing that elevation of the head and

torso was associated with a 2-fold increase in cerebral blood flow in comparison to the supine (SUP) position, for pigs receiving prolonged active compression decompression (ACD) CPR with an ITD. Further, the effect of head position was consistent in different regions of the brain, measured using microsphere [8]. In these studies, the changes observed in CerPP were consistent in terms of magnitude and effect with neutron activated microspheres brain blood flow measurement.

A better understanding of the relationships between cardio-cerebral circulation and commonly measured hemodynamic parameters may lead to new ways to optimize outcomes after cardiac arrest. Therefore, the objectives of this study were to identify hemodynamic parameters associated with cerebral blood flow during CPR and to examine whether potentially relevant associations were consistent in an independent external validation sample.

## **2. Materials and Methods**

### *Study Ethics*

Approval for the animal studies were obtained from the Institutional Animal Care Committee of the Hennepin Healthcare Research Institute. Animal care was compliant with the 2011 National Research Council's Guidelines for the Care and Use of Laboratory Animals, and a certified and licensed veterinarian assured protocol performance was in compliance with these guidelines.

### *Study Design and Measurements*

The blood flow and hemodynamic data used for the derivation [6] and external validation [8] of predictive models were obtained from two prior publications. The techniques for animal surgical

preparation, protocol for anesthesia, and data monitoring and recording procedures used in these two studies have been previously described [5, 6, 8]. Briefly, female Yorkshire farm pigs weighing 38-42 kg were fasted overnight, received intramuscular ketamine (25mg/kg) for initial sedation in the holding pen, and were then transferred to the surgical suite. Anesthesia with inhaled isoflurane at 0.8%-1.7% was provided via mask, and animals were then intubated with a 7.5 mm endotracheal tube. Anesthesia with isoflurane was continued, and ventilation was performed with room air using a ventilator (Narkomed, Telford, PA) with tidal volume 10 mL/kg. The respiratory rate and FiO<sub>2</sub> were adjusted to keep oxygen saturation above 92% and end tidal carbon dioxide (ETCO<sub>2</sub>) between 36 and 40 mmHg. ETCO<sub>2</sub> and oxygen saturation were recorded with a CO<sub>2</sub>SMO Plus® (Novamatrix Systems, Wallingford, CT). Central aortic blood pressure (Ao) was recorded with a micromanometer-tipped catheter (Mikro-Tip Transducer, Millar Instruments, Houston, TX) placed via left femoral cannulation in the descending thoracic aorta at the level of the diaphragm. A second Millar catheter was placed in the right femoral vein, and advanced to the right atrium for monitoring of right atrial pressure (RA). The position of all micromanometer-tipped catheters was confirmed by fluoroscopy before ventricular fibrillation was induced. Intracranial pressure (ICP) was measured by creating a burr hole in the skull, and then insertion of a Millar catheter into the parietal lobe. All animals received a 100 units/kg bolus of heparin intravenously and received a 1000 ml normal saline bolus for a goal right atrial pressure of 3-5 mmHg.

Continuous data including electrocardiographic monitoring, aortic pressure, RA pressure, ICP, and ETCO<sub>2</sub> was recorded. CerPP was calculated as the difference between mean aortic pressure and mean ICP. CorPP was calculated as the difference between aortic pressure and RA pressure during the decompression phase of CPR. All data was recorded at a sample frequency of



250Hz and stored using a computer data analysis program (Acqknowledge; BioPac Systems Inc, Goleta CA).

When the preparatory phase was complete, ventricular fibrillation (VF) was induced with delivery of direct electrical current from a pacing wire placed in the right ventricle. In the derivation sample, mechanical CPR was performed using LUCAS device (L) (Lucas, Stryker, USA) and an ITD (ResQPOD-16), Zoll. L-CPR was performed at a rate of 100 compressions/min, with a 50% duty cycle and depth of 25% of antero-posterior chest diameter. The head and thorax of the animal were elevated at 30° on a specially built tilt table that tilts the head and thorax to +30, 0, and -30 degrees as previously described [5].

In the validation sample, ACD+ITD CPR was performed with an automatic piston device (Pneumatic Compression Controller; Ambu International, Glostrup, Denmark). ACD CPR was performed at a rate of 80 compressions/min, with a 50% duty cycle and depth of 22.5% of antero-posterior chest diameter, and the chest was pulled upwards after each compression with a suction cup on the skin at a decompression force of approximately 10 kg. An ITD was placed at the end of the endotracheal tube. The Head Up (HUP) CPR device used elevated just the head and shoulders and upper thorax 30°, as previously described [5]. While transitioning from supine (SUP) to HUP position, CPR was performed in an uninterrupted manner.

During both L-CPR and ACD+ITD CPR, positive pressure ventilation was delivered with oxygen, titrated to a SpO<sub>2</sub> of ≥92%, with a tidal volume of 10 mL/kg and synchronous respiratory rate of 10 breaths per minute. If the animal was noted to gasp during the resuscitation, time at first gasp was recorded. Appendix 2 reports a summary of the derivation and validation samples studies protocol.

Succinylcholine was administered at a dose of 60 mg (1.5 mg/kg) to inhibit gasping after the third gasp.

#### *Experimental Protocol*

In the derivation sample, after 6 min of untreated VF, CPR was performed continuously with L-CPR + ITD for 5 min epochs in the following sequence: L-CPR + ITD SUP, L-CPR + ITD HUP and then L-CPR + ITD Head Down Position. Neutron activated microsphere were injected in the left ventricle at the beginning of each sequence.

In the validation sample, after 8 min of untreated VF, ACD CPR + ITD was performed with a 30:2 compression: ventilation ratio, and positive pressure ventilation with room air was provided while all pigs were in the SUP to simulate basic life support (BLS). After 2 min of BLS CPR, animals were randomized either HUP CPR or SUP CPR and continuous asynchronous ACD CPR + ITD CPR was continued for 18 min with a 10:1 compression: ventilation ratio to simulate advanced life support (ALS). Neutron activated microsphere were injected in the left ventricle (LV) after 5 min and 15 minutes of intervention.

#### *Microsphere Protocol*

Blood flow to the brain was measured with microsphere injection into the LV. Concurrently with the microsphere injections, reference blood samples were withdrawn continuously over 4 min from the descending aorta at a collection rate of 10 ml min<sup>-1</sup>. Neutron activated microspheres (STERISpheres™, BioPAL™: BioPhysics Assay Laboratory, Worcester, MA) 15 µm in diameter containing Samarium (<sup>152</sup>Sm), Ytterbium (<sup>175</sup>Yb) and Lutetium (<sup>177</sup>Lu) were used. At the end of the procedure animals were sacrificed and then tissue samples from the brain (pons varolii of the brainstem, hippocampus, left and right cortex), were

obtained. Tissue and blood samples were desiccated and sent to the reference BioPhysics Assay Laboratory for analysis.

### *Sample size*

Because we used the original data obtained from two previous studies, no formal sample size determination was performed for the present analyses. Briefly, in the derivation study [6], microsphere measurements of blood flow were a secondary endpoint and were performed as an exploratory sub-study with no sample prespecified. In the validation study [8], we calculated that a sample size of 18 animal (i.e., 9 animals by study group) would achieve 80% power to detect a 40% increase (i.e., mean difference, 0.07 mL/100g/min, estimated standard deviation, 0.05) in brain flow for the ACD+ITD+HUT group compared to the supine ACD+ITD group, with a significance level (alpha) of 0.05, using a two-sided paired t test.

### *Statistical Analysis*

Summary statistics for hemodynamic parameters were reported as mean and standard deviation. We analyzed the univariable association between hemodynamic parameters and cerebral brain flow, using linear regression for continuous dependent variable. The associations were adjusted for head up and head down inclination in the derivation sample and for head up inclination and timing in the external validation sample, respectively. In order to obtain standardized  $\beta$  regression coefficients, all independent hemodynamic parameters were first standardized to have a standard deviation of 1. Therefore  $\beta$  regression coefficients expressed the change in cerebral brain flow per standard deviation increase in independent hemodynamic parameters. This approach allowed comparisons of  $\beta$  regression coefficients across hemodynamic parameters,

provided that the coefficients ignored the original scale of unit for independent parameters. We accounted for the correlation of observations nested within pigs, using random intercept regression.

We assessed overall accuracy and calibration of hemodynamic parameters in predicting cerebral blood flow during CPR. We estimated root mean square error (RMSE) for quantifying the average difference between the predicted and observed values of cerebral blood flow. We also reported calibration slope and calibration-in-the large (i.e., intercept) to assess the agreement between predicted and observed values of cerebral blood flow. For well-calibrated predictive models, the calibration intercept is 0 and the calibration slope 1 [9].

Because the apparent performance of a prediction model is often optimistic [10], we assessed the potential for statistical over-fitting using bootstrapping [11], in internal validation. For this purpose, optimism-corrected RMSE and calibration slope and intercept were computed by generating 200 bootstrap samples drawn with replacement from the original derivation sample [9]. External validation consisted of assessing the overall accuracy and calibration of the hemodynamic parameters in predicting cerebral blood by applying the original models, with their inherent coefficients [9].

Two-tailed *P*-values less than 0.05 were considered statistically significant. Statistical analysis was performed using Stata Special Edition version 14.0 (Stata Corporation, College Station, TX, USA).

## Results

Hemodynamic parameters and cerebral blood flow during CPR were available for 24 observations nested within 8 pigs in the derivation sample (Table 1) and 36 observations nested within 18 pigs (8 and 10 in the HUP and SUP arms, respectively) in the validation sample (Table 2), respectively. It is noteworthy that due to the different methods of CPR used to generate data for these two studies [6,8], absolute values for Ao pressure, intrathoracic pressure, RAP and CerPP were different between the derivation sample and the validation sample (Table 1 and 2).

After adjusting for inclination, Ao pressure during decompression, intrathoracic pressure during compression, mean, and decompression cerebral perfusion pressure, and end tidal CO<sub>2</sub> were associated with cerebral blood flow in the derivation sample (Table 3). Ao Pressure during decompression, intrathoracic pressure during compression, and cerebral perfusion pressure parameters remained associated with cerebral blood flow in the validation sample (Table 3). End tidal CO<sub>2</sub> did not correlate with cerebral blood flow while Ao pressure, RA pressure, CerPP during compression and CorPP were associated with cerebral blood flow in the external validation sample only. Comparable standardized  $\beta$  regression coefficients were observed for Ao and CerPP during decompression, in the derivation and external validation samples, respectively. RMSE ranged from 6 in the derivation sample to 24 in the external validation sample for Ao pressure during decompression and from 6 to 26 for mean cerebral perfusion pressure (Appendix 1). Calibration intercept departed from 0 for intrathoracic pressure during compression and CerPP during decompression while calibration slope departed from 1 for Ao pressure and CerPP (mean and decompression), in the external validation sample (Appendix 1).

## Discussion

The results provide new insight into potential surrogate markers for cerebral blood flow during CPR. We found a consistent relationship between cerebral blood flow and Ao pressure during decompression as well as mean and decompression CerPP, in the derivation and validation samples. These associations were independent of head inclination, supporting their robustness for use with varying CPR procedures. These findings support the use of decompression phase Ao pressure and mean CerPP for assessing different methods of CPR and different positions of the head and thorax during CPR. Based upon these results we hypothesize that the decompression phase Ao pressure and CerPP could potentially be used to estimate the probability for neurological recovery after CPR.

Although a potential major prognostic factor, cerebral blood flow is difficult to measure and monitor directly during CPR. In the present study, isotopes or radio-labeled microspheres were used as reference method for measuring blood flow to vital organs during CPR. Yet, this approach is technically complex, unstandardized, expensive, and requires specific expertise [12]. In contrast, continuous monitoring of Ao pressure during decompression phase with the use of invasive blood pressure transducer is reliable, amenable to standardization, and inexpensive.

CorPP has historically been used in experimental models to assess the impact of different interventions [6, 13, 14]. CorPP is associated with the probability of return of spontaneous circulation (ROSC) in animal and human. In 1990, Paradis et al reported that CorPP values below 15 mmHg were associated with no chance of ROSC in humans whereas a CorPP value threshold of 25 mmHg predicted ROSC with 0.46 specificity and 0.96 sensitivity estimates [4]. Yet the relationship between CorPP and cerebral blood flow and neurological recovery after cardiac arrest remains questioned. Indeed, various physiological processes other than CorPP can

affect cerebral blood flow and neurological function after cardiac arrest. Brain microvascular resistance, intracranial pressure and cerebral venous return are all involved in cerebral blood flow and post-ROSC brain function [15]. In the recent Paramedic 2 trial, epinephrine injections were associated with a higher probability of ROSC (36% vs. 12%) but were also associated with a higher probability of severe neurologic impairment in survivors (31% vs. 18%) [16]. In our study, inconsistent association was found between CorPP and cerebral blood flow, suggesting that CorPP may not be a relevant surrogate for cerebral blood flow.

Cerebral oximetry has shown some promising results as an easy-to-use potential reflect of cerebral blood flow. It has been shown to correlate well with return of spontaneous circulation and with neurologically favorable survival to hospital discharge [17] and might be useful to monitor CPR quality [18].

It has been known for more than a century that a threshold diastolic blood pressure during rhythmic chest compressions is associated with the ability to resuscitate animals [7, 19]. More recently, in a study of 60 animals, diastolic blood pressure discriminated survivors from non-survivors better than ETCO<sub>2</sub> [20]. Failure to attain a diastolic blood pressure >34mmHg during CPR was highly predictive of non-survival [20]. Our study provides potential explanation on how the relationship between Ao pressure during decompression and cardiac arrest survival can be mediated throughout cerebral blood flow. Based upon the new results from the current study, it should be possible to measure diastolic Ao pressure to assess whether if there is a threshold CerPP value that is needed to optimize outcomes after cardiac arrest, regardless if the head and thorax are flat or elevated. Moreover, the results provide a new opportunity to focus on improving neurological outcomes by optimizing decompression phase Ao pressure.

Despite satisfactory apparent predictive performance, RMSE and calibration substantially deteriorated for Ao pressure during decompression and CerPP (mean and during decompression), in external validation sample. This latter observation may arise from differences in CPR procedures, hemodynamic parameter measurements, or selection criteria between the validation and derivation studies. Calibration can be improved by adjusting the original regression intercept or applying a single calibration factor to each original regression coefficient [9].

This study has several limitations. First, we performed unplanned *post hoc* analysis of the original data from two prior studies that were performed for other primary objectives. Some of the associations might be observed by chance although the validation in an independent external sample makes this assumption unlikely. Second, we cannot exclude that inconsistencies in  $\beta$  regression coefficient point estimates between the derivation and validation studies reflect random variability due to limited effective sample sizes. Third, the animals were young, healthy pigs without cardiac disease and the brain physiology may differ in human with preexisting cardiovascular disease. Fourth, we examined the relationship between brain blood flow and hemodynamic parameters but not the relationship between brain blood flow and neurological awakening after cardiac arrest.

## **Conclusion**

Ao pressure during decompression and CerPP (mean and during decompression) correlate with brain blood flow during CPR, independently of the position of the head. Although promising, further prospective validation and calibration is warranted before using these parameters as surrogate for cerebral blood flow during CPR.



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## **Ethical adherence**

This study was approved by the Institutional Animal Care and Use Committee of the Minneapolis Medical Research Foundation (MMRF) of Hennepin County Medical Center (Protocol number 15–12, National Institute of Health No A-3875-01). All animal care was compliant with current DHHS guidelines (Guidelines for the Care and Use of Laboratory Animals, 8th Edition, National Research Council, 2011), Animal Welfare Act regulations (9 CFR Chapter 1, Subchapter A) and Good Laboratory Practice for Nonclinical Laboratory Study under the US Code of Federal Regulations title 21. All studies were performed by a qualified, trained, and experienced research team. A licensed and board certified veterinarian (DACLAM) assured the protocols were performed in accordance with all applicable local, state, and federal requirements in the MMRF facility which is AAALAC International, Inc. accredited.

## **Conflicts of Interest Statement**

Dr. Keith Lurie is a co-inventor of ACD and ITD devices. He founded Advanced CPR Solutions LLC to develop novel resuscitation technologies including Head Up CPR devices. No other authors have a financial conflict of interest.

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Table 1. Cardiopulmonary resuscitation hemodynamics for ventricular fibrillation porcine model according to inclination in derivation sample.

	No.	Inclination*					
		Supine (0°)		Head up (30°)		Head down (-30°)	
Arterial blood pressure, <i>mmHg</i>							
Compression	8	96	(17)	83	(14)	88	(17)
Decompression	8	13	(8)	12	(8)	13	(10)
Intrathoracic pressure, <i>mmHg</i>							
Compression	8	9	(2)	9	(2)	10	(4)
Decompression	8	-10	(4)	-10	(4)	-9	(4)
Mean	8	-2	(1)	-2	(1)	-3	(1)
Right atrial pressure, <i>mmHg</i>							
Compression	8	163	(70)	118	(57)	175	(59)
Decompression	8	-3	(5)	-15	(6)	3	(6)
Mean	8	51	(26)	25	(22)	51	(21)
Intracranial pressure, <i>mmHg</i>							
Compression	8	41	(15)	14	(8)	62	(15)
Decompression	8	15	(5)	-3	(8)	23	(5)
Mean	8	27	(8)	7	(6)	40	(9)
Cerebral perfusion pressure, <i>mmHg</i>							
Compression	8	65	(17)	76	(15)	37	(16)
Decompression	8	-9	(5)	7	(9)	-22	(8)
Mean	8	18	(8)	31	(9)	1	(10)
Coronary perfusion pressure, <i>mmHg</i>	8	18	(8)	28	(9)	7	(9)
End tidal CO <sub>2</sub> , <i>mmHg</i>	8	32	(8)	31	(9)	31	(13)
Brain flow, <i>mL.min<sup>-1</sup>.100g<sup>-1</sup></i>	8	19	(12)	27	(12)	14	(16)

\* Values are means (standard deviation).

Table 2. Cardiopulmonary resuscitation hemodynamics for ventricular fibrillation porcine model according to inclination in external validation sample.

	Supine position (0°)*					Head and thorax elevation (30°)*				
	No.	5 min		15 min		No.	5 min		15 min	
Arterial blood pressure, <i>mmHg</i>										
Compression	10	56	(11)	45	(17)	8	58	(10)	53	(9)
Decompression	10	24	(5)	16	(8)	8	23	(5)	20	(5)
Intrathoracic pressure, <i>mmHg</i>										
Compression	10	1	(1)	1	(1)	8	1	(1)	1	(1)
Decompression	10	-5	(3)	-6	(3)	8	-6	(2)	-5	(1)
Mean	10	0.1	(2)	-0.1	(2)	8	-1	(1)	-0.2	(0.5)
Right atrial pressure, <i>mmHg</i>										
Compression	10	60	(17)	48	(14)	8	49	(16)	43	(14)
Decompression	10	6	(5)	5	(5)	8	3	(4)	2	(4)
Mean	10	29	(6)	23	(4)	8	25	(6)	21	(7)
Intracranial pressure, <i>mmHg</i>										
Compression	10	26	(5)	22	(3)	8	18	(5)	12	(4)
Decompression	10	16	(2)	13	(2)	8	5	(3)	2	(2)
Mean	10	18	(6)	16	(4)	8	10	(7)	6	(5)
Cerebral perfusion pressure, <i>mmHg</i>										
Compression	10	24	(12)	19	(18)	8	38	(10)	40	(8)
Decompression	10	7	(5)	2	(7)	8	17	(3)	18	(4)
Mean	10	13	(7)	8	(10)	8	26	(7)	26	(5)
Coronary perfusion pressure, <i>mmHg</i>	10	18	(8)	11	(10)	8	20	(6)	18	(6)
End tidal CO <sub>2</sub> , <i>mmHg</i>	9	38	(10)	22	(16)	8	40	(6)	29	(14)
Brain flow, <i>mL.min<sup>-1</sup>.100g<sup>-1</sup></i>	10	33	(19)	21	(15)	8	45	(20)	42	(14)

\* Values are means (standard deviation).

Table 3. Hemodynamics associated with blood brain flow in ventricular fibrillation porcine model after adjusting for inclination in derivation and external validation samples.

Hemodynamics	Derivation sample (24 observations, 8 pigs)*		<i>P</i>	External validation sample (36 observations, 18 pigs)*		<i>P</i>
Arterial blood pressure, <i>mmHg</i>						
Compression	3.39	(-2.52 to 9.30)	.26	16.07	(6.10 to 26.04)	.002
Decompression	8.42	(4.00 to 12.85)	<.001	35.11	(14.07 to 56.15)	.001
Intrathoracic pressure, <i>mmHg</i>						
Compression	4.93	(1.13 to 8.74)	.01	7.23	(1.14 to 13.32)	.02
Decompression	6.04	(-0.08 to 12.15)	.05	5.92	(-4.77 to 16.61)	.28
Mean	1.52	(-2.31 to 5.34)	.44	8.35	(-3.36 to 20.07)	.16
Right atrial pressure, <i>mmHg</i>						
Compression	-0.91	(-8.84 to 7.01)	.82	14.80	(5.13 to 24.47)	.003
Decompression	-0.17	(-7.65 to 7.30)	.96	2.25	(-4.08 to 8.58)	.49
Mean	0.01	(-7.32 to 7.34)	.99	12.71	(2.48 to 22.93)	.02
Intracranial pressure, <i>mmHg</i>						
Compression	1.36	(-9.47 to 12.20)	.81	-0.47	(-9.02 to 8.09)	.92
Decompression	4.64	(-5.54 to 14.81)	.37	2.57	(-16.06 to 21.20)	.79
Mean	5.06	(-7.69 to 17.81)	.44	-3.31	(-11.11 to 4.50)	.41
Cerebral perfusion pressure, <i>mmHg</i>						
Compression	1.65	(-5.53 to 8.84)	.65	17.19	(6.18 to 28.20)	.002
Decompression	7.56	(1.10 to 14.02)	.02	33.53	(13.88 to 53.19)	.001
Mean	9.57	(1.40 to 17.74)	.02	28.49	(11.85 to 45.13)	.001
Coronary perfusion pressure, <i>mmHg</i>	5.46	(-1.64 to 12.55)	.13	18.58	(1.24 to 35.91)	.04
End tidal CO <sub>2</sub> , <i>mmHg</i>	5.36	(0.27 to 10.46)	.04	3.58	(-2.54 to 9.70)	.25

\* Values are standardized  $\beta$  regression coefficients (95% confidence interval).  $\beta$  regression coefficients were estimated using linear regression, with blood brain flow (expressed in  $mL \cdot min^{-1} \cdot 100g^{-1}$ ) as the continuous dependent variable and each hemodynamic parameter entered as independent variable at a time.  $\beta$  regression coefficients were expressed for one standard deviation increase in independent continuous variable value. We performed random intercept regression for accounting for the correlation of observations nested within pigs.  $\beta$  regression coefficients were adjusted for head up and head down inclination in the derivation sample and for head up inclination and timing in the external validation sample, respectively.

Appendix 1. Accuracy of hemodynamic parameters in predicting blood brain flow in the derivation and external validation samples.

Parameters	$\beta$ regression coefficient		Performance*	RMSE	Calibration parameter (95% CI)			
	(95% CI)				Intercept		Slope	
Aortic blood pressure during decompression, <i>mmHg</i>	8.42	(4.00 to 12.85)	Apparent	6.47	-0.12	(-8.21 to 7.98)	1.01	(0.67 to 1.35)
Head up	8.47	(2.09 to 14.85)	Internal validation	8.59	-0.70	(-9.45 to 6.01)	1.05	(0.74 to 1.42)
Head down	-5.58	(-11.93 to 0.76)	External validation	23.73	-1.94	(-21.20 to 17.31)	2.11	(1.04 to 3.19)
Intercept	6.38	(-2.73 to 15.50)	-	-	-	-	-	-
Compression intrathoracic pressure, <i>mmHg</i>	4.93	(1.13 to 8.74)	Apparent	5.48	0.10	(-9.49 to 9.70)	0.99	(0.65 to 1.33)
Head up	7.29	(1.92 to 12.67)	Internal validation	7.38	-0.12	(-9.78 to 9.07)	1.01	(0.62 to 1.45)
Head down	-8.39	(-14.10 to -2.67)	External validation	29.39	16.41	(5.07 to 25.75)	1.80	(0.81 to 2.79)
Intercept	2.57	(-12.45 to 17.60)	-	-	-	-	-	-
Decompression cerebral perfusion pressure, <i>mmHg</i>	7.56	(1.10 to 14.02)	Apparent	5.59	0.10	(-9.80 to 10.00)	1.00	(0.64 to 1.35)
Head up	-1.52	(-10.75 to 7.71)	Internal validation	7.33	-0.40	(-8.63 to 8.46)	1.02	(0.64 to 1.48)
Head down	0.76	(-7.13 to 8.64)	External validation	18.75	-94.23	(-155.58 to -32.89)	4.71	(2.47 to 6.95)
Intercept	24.47	(15.57 to 33.36)	-	-	-	-	-	-

(Continued)

Appendix 1 (Continued).

Parameters	$\beta$ regression coefficient		Performance*	RMSE	Calibration parameter (95% CI)			
	(95% CI)				Intercept		Slope	
Mean cerebral perfusion pressure, <i>mmHg</i>	9.57	(1.40 to 17.74)	Apparent	6.05	0.11	(-9.69 to 9.91)	0.99	(0.62 to 1.37)
Head up	-1.20	(-10.50 to 8.09)	Internal validation	8.06	-0.69	(-10.16 to 7.15)	1.03	(0.73 to 1.53)
Head down	4.90	(-6.05 to 15.85)	External validation	25.91	-6.25	(-26.55 to 14.04)	2.79	(1.45 to 4.14)
Intercept	8.21	(-3.82 to 20.23)	-	-	-	-	-	-
End tidal CO <sub>2</sub> , <i>mmHg</i>	5.36	(0.27 to 10.46)	Apparent	5.05	-0.06	(-11.35 to 11.23)	1.00	(0.67 to 1.33)
Head up	8.15	(3.11 to 13.19)	Internal validation	6.71	-0.53	(-80.3 to 7.33)	1.03	(0.71 to 1.38)
Head down	-4.92	(-9.95 to 0.12)	External validation	23.08	13.87	(-1.49 to 29.23)	1.12	(0.36 to 1.87)
Intercept	1.56	(-17.93 to 21.06)	-	-	-	-	-	-

Abbreviations: CI = confidence interval; RMSE = root mean square error

\* Apparent predictive performance was measured in the original derivation sample. In internal validation, optimism-corrected predictive performance was measured using 200 bootstrap samples drawn with replacement from the original derivation sample. In external validation, predictive performance was measured by applying the original model, with its inherent parameter coefficients.