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TECHNICAL NOTE

A comprehensive neuromonitoring approach in a large animal model of cardiac arrest

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Abstract

Background: Anoxic brain injuries represent the main determinant of poor outcome after cardiac arrest (CA). Large animal models have been described to investigate new treatments during CA and post-resuscitation phase, but a detailed model that includes extensive neuromonitoring is lacking.

Method: Before an electrically-induced 10-minute CA and resuscitation, 46 adult pigs underwent neurosurgery for placement of a multifunctional probe (intracranial pressure or ICP, tissue oxygen tension or $PbtO_2$ and cerebral temperature) and a bolt-based technique for the placement and securing of a regional blood flow probe and two sEEG electrodes; two modified cerebral microdialysis (CMD) probes were also inserted in the frontal lobes and accidental misplacement was prevented using a perforated head support.

Result: 42 animals underwent the CA procedure and 41 achieved the return of spontaneous circulation (ROSC). In 4 cases (8.6%) an adverse event took place during preparation, but only in two cases (4.3%) this was related to the neurosurgery. In 6 animals (13.3%) the minor complications that occurred resolved after probe repositioning.

Conclusion: Herein we provide a detailed comprehensive neuromonitoring approach in a large animal model of CA that might help future research.

KEYWORDS
anoxic injury, heart arrest, ischemiareperfusion, post-arrest, resuscitation

1 | INTRODUCTION

CA remains a leading cause of death and morbidity worldwide[1] and brain injurie remains responsible for most deaths among survivors.[2] Many treatments have been proposed,[3,4] but the discrepancies between experimental results and their translation into clinical practice reinforce the necessity for better preclinical models.[5]

Pigs are appropriate as CA models because of anatomic similarity between cardiovascular systems, the possibility of applying standardized resuscitation maneuvers, and their tolerability for invasive procedures and frequent blood sampling.[6-8] Similarly, they possess a gyrencephalic brain with regional susceptibility to ischemia-reperfusion comparable to humans. Also, their brain is large enough to allow the placement of multiple human monitoring devices.

Various CA models are reported in the literature[9-11] but no multimodal neuromonitoring approach has been described in detail so far. Thus this manuscript aims to provide a model of prolonged CA in swine that includes multiple neuromonitoring devices.

2 | METHODS

The Institutional Review Board for Animal Care of the Free University of Brussels (Belgium) approved all experimental procedures (Ethical Committee approval: 704N), in compliance with ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines. Care and handling of the animals were in accord with National Institutes of Health guidelines (Institute of Laboratory Animal Resources).

2.1 | General preparatory phase

On the day of the experiment the animal (*Sus Scrofa Domesticus*, 6 months old, both sexes) were fasted for 12 hours and were sedated with an intramuscular injection of midazolam (1 mg/kg) and ketamine (10 mg/kg) in the neck. Electrocardiogram (ECG) monitoring was initiated and after cannulation of a marginal ear vein, a continuous infusion of sufentanyl-citrate (0.2–1 μg/kg/h) was started.

A 4.5 Fr catheter was inserted in the femoral artery and connected to a pressure transducer (Edwards). After the injection of 1 mg atropine-sulfate, 3 μg/kg of sufentanyl-citrate and 1.2 mg/kg of rocuronium, an 8 mm inside diameter endotracheal tube (Medtronic) was placed and mechanical ventilation initiated in volume-controlled mode (Drägerwerk) with a tidal volume of 8 ml/kg, 5 cmH_2O of PEEP, and FiO_2 of 1, and inspired sevofluorane was started. Ventilation parameters were adjusted to achieve an end-tidal CO_2 of 35–45 mmHg and a PaO_2 >70 mmHg with the minimum FiO_2. A rocuronium (1–4 mg/kg/h) and sufentanyl-citrate (3.5 μg/kg/h) infusion was maintained, and balanced crystalloids (Plasmalyte) started.

After 2g of amoxicillin-clavulanate, a 14 Fr Foley catheter was surgically placed in the bladder thorough a midline incision; a triple lumen central venous catheter (Arrow) was placed in the external jugular vein and the drug infusion was transferred to it. A 6 Fr introducer (TERUMO) was placed proximally to the triple-lumen catheter to allow introduction of a pacing wire. Lastly, an 8.5 Fr introducer was placed contralaterally and a continuous cardiac output Swan-Ganz (Edwards) catheter was advanced into the pulmonary artery. The animal was proned and the bed angled to a 30° anti-Trendelenburg position.

2.2 | Neurosurgical procedure

The forehead of the animal was shaved and disinfected with povidone-iodine. At approximately 0.5 cm from the midline, an inverted mirrored F incision was executed on both sides, and two cutaneous flaps were made to expose the frontal bones (Figure 1).

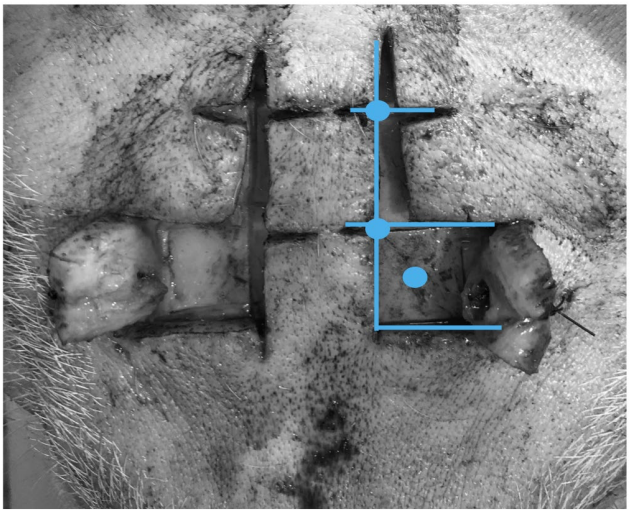

FIGURE 1 Inverted F incision in the scalp with flaps. Blue lines represent incision lines; blue circles represent areas for skull drilling

Using an electric drill (Ruijin Medical), six burr holes were placed in the skull. In the rostral butt holes, a 10-mm length microdialysis catheter (CMA-microdialysis) was inserted after cutting the fixation flaps to allow penetration of the hole engulfed in bone wax (Figure 2), and then tunneled into the flap, and a continuous perfusion (CNS fluid, CMA-microdialysis) at the rate of 0.3 μl/min was started. In the remaining holes, four bolts were placed (Bolt CH5, Raumedic-AG). A bolt consists of a screw with seal and a fixing cap and once secured to the skull, it allows the insertion of a custom-built needle to open the dura mater with minimal traumatism. After positioning the probe, the screwing of the fixing cap narrows the sealing component, securing the probe at the desired depth. On one side, a probe allowing the simultaneous measurement of cerebral temperature, ICP and $PbtO_2$ (Neurovent PTO2, Raumedic-AG) was inserted and connected to its monitor (Raumedic-AG); on the other side, a laser-Doppler flowmetry probe was placed (Oxyflow4000, Oxford Optronic). In each of the caudal bolts, a 5-contact intracerebral stereoelectroencephalography (sEEG) wire (Dixi medical) was inserted (Figure 3). The animal was turned supine, and the table angled to 0 degrees. To prevent damage to the probes, the head was held beyond the edge of the table, and the spine was kept aligned via a perforated massage table headrest (Figure 4), which prevented compression of the probes while providing support for the head.

2.3 | Cardiac arrest induction

After placing the automatic chest compressor (LucasIII, Jolife AB/Stryker), two latero-lateral defibrillating pads (Stad-padzII, Zoll Medical) were connected to a defibrillator (Zoll M series, Zoll Medical). A pacing wire was advanced through the 6 Fr introducer until it reached the endocardium and then connected to a 9V battery to induce ventricular fibrillation (VF), which was confirmed by the

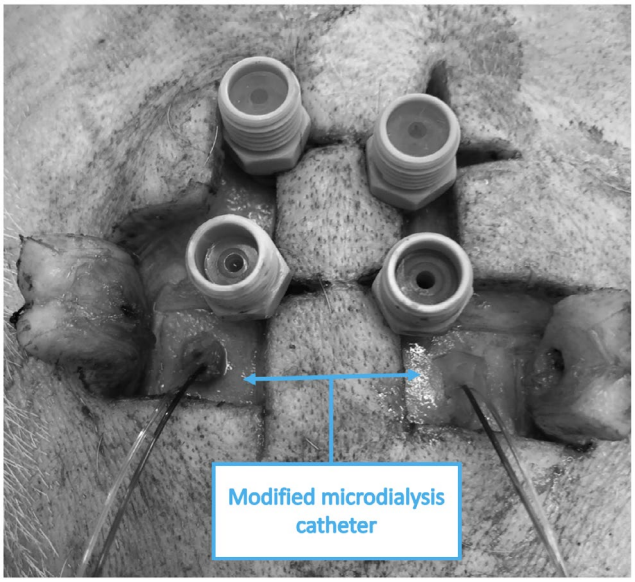

FIGURE 2 Bolts and modified microdialysis catheters after intracranial placement, before connection to the CNS perfusion pump

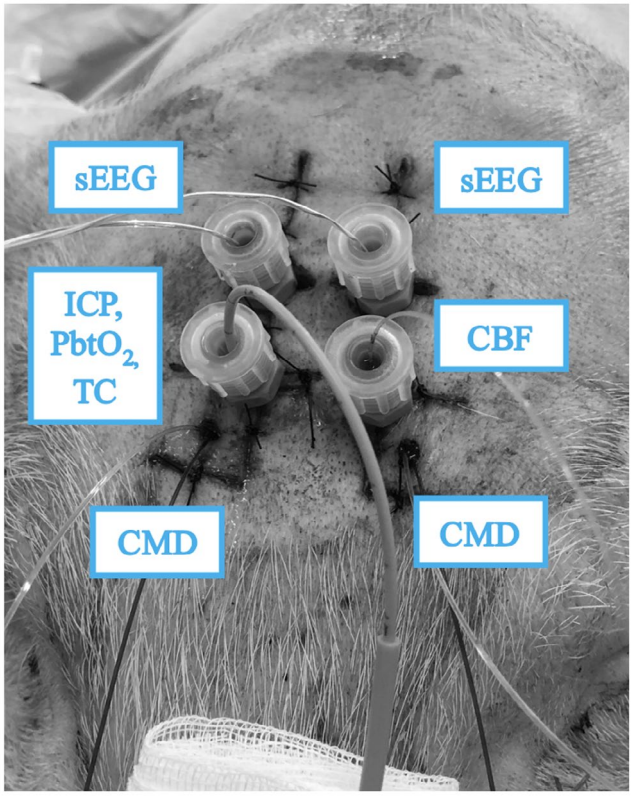

FIGURE 3 All neuromonitoring probes in place before the start of the experiment. Microdialysis catheters are tunneled in the scalp and four probes are secured to the bolts. sEEG, stereoelectroencephalography; CMD, cerebral microdialysis catheter; CBF, cerebral blood flow probe; ICP, intracranial pressure; Tc, brain temperature; $PbtO_2$, brain oxygen tension

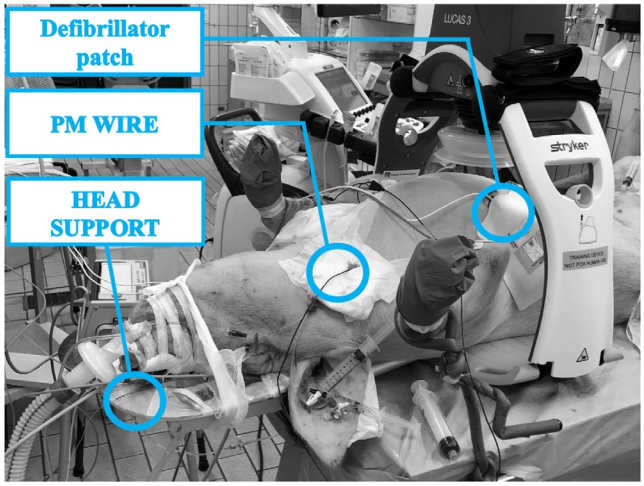

FIGURE 4 Animal in position before CA induction. PM, pace maker

ECG waveform and the decrease in arterial pressure. The ventilation was stopped, and the animal left untreated for 10 minutes.

2.4 | Resuscitation maneuvers

Chest compressions were started at 100/minute for 5 minutes and ventilation was resumed with a FiO_2 of 1. After one minute, an intravenous injection of epinephrine (30 μg/kg) was administered, and the anesthetic gas resumed. At the end of the 5 minutes, a 4J/kg biphasic countershock was delivered. In the case of unsuccessful resuscitation, CPR was continued for an additional minute, and another shock was delivered. CPR was stopped if ROSC wasn't achieved within 10 shocks.

2.5 | Post-resuscitation care

After ROSC, the animals were turned to the prone position and treated with target temperature management using an external feedback device (Arctic-Sun 5000, Bard). At the end of the observation period, the animals were sacrificed under deep anesthesia with an injection of potassium-chloride. Death was confirmed by VF ECG pattern and the drop of arterial blood pressure.

3 | RESULTS

Forty-six animals were eligible for CA. In 4 animals (8.6%), the protocol couldn't be completed due to traumatic neurosurgery (2 animals), a pulmonary catheter-triggered ventricular arrythmia (1 animal) and in another case the animal was excluded because of refractory supraventricular arrythmia while inducing VF.

Of the remaining 42 animals that underwent both neurosurgery and CA, 41 achieved ROSC (97.6%) and were observed for 12 hours. Among those, the weight was 49 kg (IQRs 45–53), and 24 were males (58.5%). CPR lasted for 300 seconds (IQR 300–360) and 1 shock (IQR 1–2) was necessary to achieve ROSC. Minor complications after ROSC occurred in 6 (14.6%) animals: in three cases (7.3%) they were related to the position of the brain probes resulting in a poor signal whereas in the others the measurement was considered not reliable. Apart from those, in the 12 hours post-ROSC all monitoring devices resulted in valid measurements.

4 | DISCUSSION

In the post-resuscitation phase, there is growing evidence that multimodal neuromonitoring might have a therapeutic benefit, since episodes of cerebral hypoxia appear to be frequent and ICP values are heterogeneous.[12-14]

Three elements characterize our approach: (1) the use of a bolt-based mini-invasive technique extended to several cerebral probes, (2) the systematic use of a perforated head support during CPR to preserve the neuromonitoring tools from CPR-related damage, and (3) the modification of the microdialysis catheter by cutting the fixation flaps to allow its insertion in the burr-hole engulfed in bone wax.

Other groups have previously reported the use of invasive neuromonitoring in large animal models of CA, but either did not report multiple measurements such as CMD, EEG, brain temperature[15] or the probes were placed via a craniotomy[16-18] or were limited to one multifunctional probe.[17] A multimodal approach has been described with measurement of ICP, PbtO2 and CMD, but all the probes were placed in one burr hole with the help of a neurosurgeon.[19,20] Moreover, it is not clear if and how the probes were secured during CPR and complication rates were not reported. Our model has some limitations: we did not revive animals, which would have allowed for neurobehavioral tests; we included young healthy animals with no comorbidities; and the prone position used is not suited for studies requiring repeated echocardiographic evaluations.

In conclusion, we have described here few improvements to a large animal CA model that allow for multimodal neuromonitoring and could serve in future research.

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CONFLICT OF INTEREST

The Authors have no conflict of interests to declare that compromise the quality of this article.

AUTHOR CONTRIBUTIONS

FA, GB, FST, JC and FS conceived the experiment; FA, FS, LAH, LP, BG, AH and AK conducted the experiments; FA wrote the first draft of the manuscript; all authors substantially contributed to the final draft of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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