Neurophysiological Preservation of The Live Isolated Pig Brain Under Extracorporeal Pulsatile Perfusion Control

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Abstract

Elucidation of the specific molecular underpinnings involved in brain metabolism and neuro-pharmacological interventions has long been constrained by the systemic physiological influences of the various concerted organs in the human body. Patient specific systemic physiology provides significant variability in neurovascular hemodynamics and brain perfusate composition, thereby confounding evaluation of specific independent variables on cerebral metabolic outcomes. This work seeks to provide a model to combat such limitations by surgically isolating the brain from its systemic counterparts all the while maintaining native-like neurophysiological parameters.

Closed-loop control of perfusion to the brain is accomplished via Extracorporeal Pulsatile Circulatory Control (EPCC), a software-based patient/subject-specific pulsatile perfusion control system developed by us to maintain native-like vascular hemodynamics. Pulsatility has been significantly implicated in the maintenance of higher order neuronal activity, cerebral oxygenation, and vascular signaling[1]. Blood composition control is realized via choice of perfusate infusion into the system's reservoir.

To test this model, in response to individualized physiological waveform input, the EPCC system successfully maintained native-like vascular systolic and diastolic pressure magnitudes while mimicking the desired waveforms in pig subjects. Under isolation, we confirmed the viability of higher order brain function through the evaluation of continuous brain depth recordings, which yielded near identical values before and after initiation of EPCC. This methodology involving complete isolated circulatory control opens up an era of new possibilities in neurovascular experimentation, potentially leading to significant advancements in neuropharmacology and metabolic disorder characterization.

Methodology

Vascular access to cerebral architecture is established via the perfusion of the two trunks in the pig aortic arch: the brachiocephalic and left subclavian arteries. Selective Isolation of the aortic arch via surgical clamping in both the ascending and descending aorta allows for specialized perfusion. Prior to EPCC bypass, two 2F Fiber-Optic Pressure Catheters are incorporated immediately distal to the point of arterial cannulation in the aorta and right common carotid respectively to record native hemodynamics. Simultaneously, brain depth probes are recording parietal brain activity. A single representative pressure waveform recorded during native readings is isolated and utilized as an input for the EPCC control algorithm.

Initially, systemic circulation by standard bypass is initiated following arterial cannulation and venous cannulation in the superior vena cava. Upon isolation clamping, perfusion from the EPCC directly establishes closed loop control perfusion to the brain. Upper extremity perfusion is mitigated via application of surgical tourniquet, thereby ensuring vertebral artery perfusion and limitation of collateral confounds.

Methodology

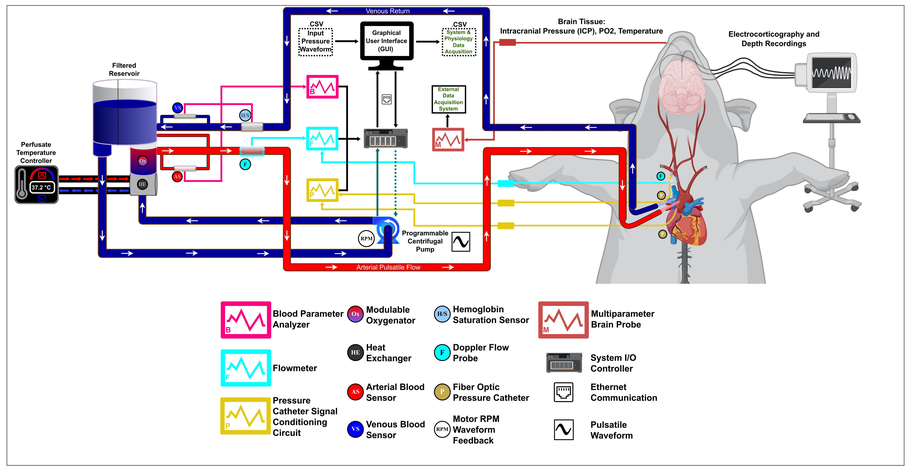

Fig 1: Isolated Perfusion Circuit Schematic [1]

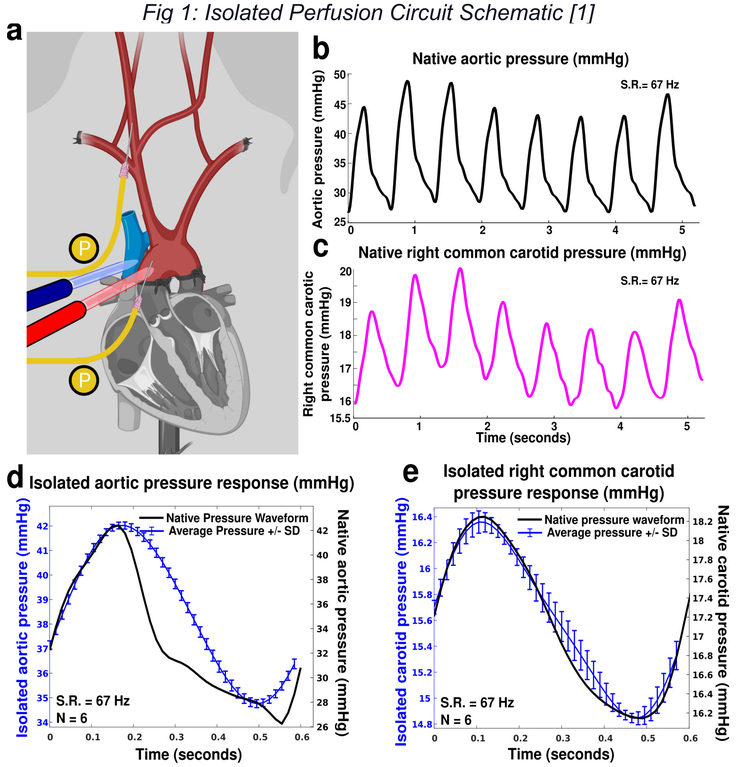

*Fig 2: **a)** Surgical Isolation Illustration. **b-c)** Native Recordings **d-e)** Isolated Comparisons [1]*

Results

Experimentation involving closed-loop perfusion control via EPCC demonstrated efficacy in maintaining near-native like neurophysiological properties under isolated perfusion. Comparative neurovascular properties showed close to native functionality in vascular response under EPCC at both aortic and carotid sites of measurement. In response to an inputted characteristic native waveform with a systolic to diastolic ratio of 42.4/26.2 mmHg (MAP 31.6) with a native heart rate of 98.7 BPM, isolation aortic response consistently performed with a systolic to diastolic ratio of 42.0 ± 0.15/34.8 ± 0.16 (MAP 37.2).

Contd.

Accordingly, carotid pressure response was evaluated in real time. In correspondence with the selected aortic waveform aforementioned, the expected native carotid response was to have a systolic to diastolic ratio of 18.2/16.1 (MAP 16.8) respectively. Under EPCC, isolation recordings were found to have a consistent systolic to diastolic ratio of 16.4 ± 0.09/14.8 ± 0.05 mmHg (MAP 15.3) respectively.

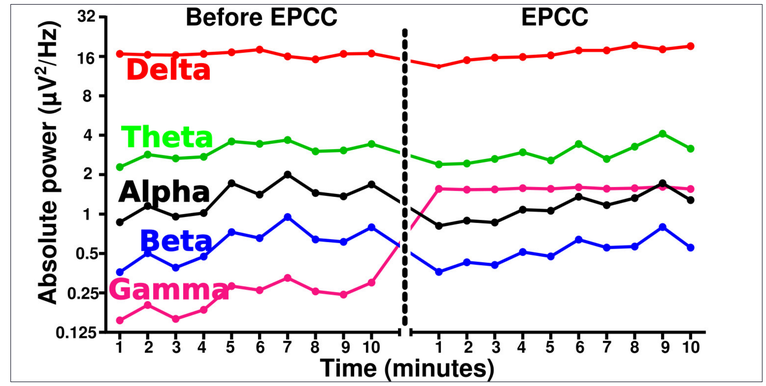

Fig 3: Before and After EPCC Depth Power Recordings [1]

Cerebral activity under EPCC was preserved as demonstrated in Figure 3. The brain depth probe recordings showed minimal change in the delta, theta, alpha, and beta frequency ranges over the recorded intervals before and after initiation of EPCC. Evaluation was conducted by temporal assessment of absolute power sampled at 1000 S/sec. Theta fluctuations can be attributed to noise, which was later suppressed by re-grounding of electronic equipment.

Conclusion & Future Direction

EPCC demonstrates efficacy in maintaining near-native levels of both neurovascular parameters and preservation of cerebral activity. This model will serve as a platform for future experimentation involving high level metabolic studies, neuropharmacology, and vascular pathology with the goal of enhancing the understanding cerebral functionality from the molecular level all the way up to higher order function.

Acknowledgments

The intellectual property behind EPCC is covered by a PCT international patent: WO2023250497A2. Funds for this initiative were through internal UT Southwestern funds (JMP). The figures and text associated with this application have been published under Nature's Scientific Reports.

*[1] Shariff, M., Dobariya, A., Albaghdadi, O. et al. Maintenance of pig brain function under extracorporeal pulsatile circulatory control (EPCC). Sci Rep **13**, 13942 (2023). https://doi.org/10.1038/s41598-023-39344-7*