

INTRODUCTION AND RESEARCH GOAL

Spreading depolarization (SD) is a transient, intense cellular depolarization, that propagates slowly (2-6mm/min) across the cerebral grey matter. Typical electrophysiological features of SD are a large negative shift of the slow electrical or DC potential, and silencing of spontaneous cortical activity (spreading depression). The near complete depolarization of neural and glial cells consume energy, generating an increased metabolic need for ATP and glucose. SD-s are accompanied by typical cerebral blood flow (CBF) changes, which restore the normal metabolic state. The SD-related CBF response is composed of at least three distinct elements: a profound hiperemia is preceded by an early vasoconstriction, and followed by a long lasting oligemia. In cerebral ischemia, the SD-related CBF response becomes atypical, which may exacerbate the ischemic damage. The inconsistent kinetics of the SD-related CBF response during ischemia makes the identification of the underlying mechanisms difficult. Our aim was to create SD-related CBF responses with a reliably reproducible kinetics during ischemia in the rat brain, as compared with the non-ischemic SDs.

MATERIALS AND METHODS

Male Sprague-Dawley rats were anesthetized with halothane (1.3-1.8%) or with isoflurane (2-2.2%) in N₂O:O₂. Mean arterial pressure (MAP) was monitored continuously via a femoral artery catheter. The common carotid arteries were exposed through a cervical incision, looped with a silicone coated fishing line and transiently ligated for 40 minutes (2VO) during the acquisition (n=8). Sham-operated rats served as control (n=6). Animals were placed into a stereotactic frame, and two small craniotomies (1.5 and 3 mm diameter) were prepared with a dental drill on the right parietal bone. The dura was carefully opened avoiding bleeding. Direct current electrocorticogram (DC-ECOG), electroencephalogram (EEG) and CBF were acquired via the rostral craniotomy (-3 mm caudal, 5 mm lateral from bregma). SD-s were elicited by topical application of 1M KCl through a craniotomy distant to the recording site.

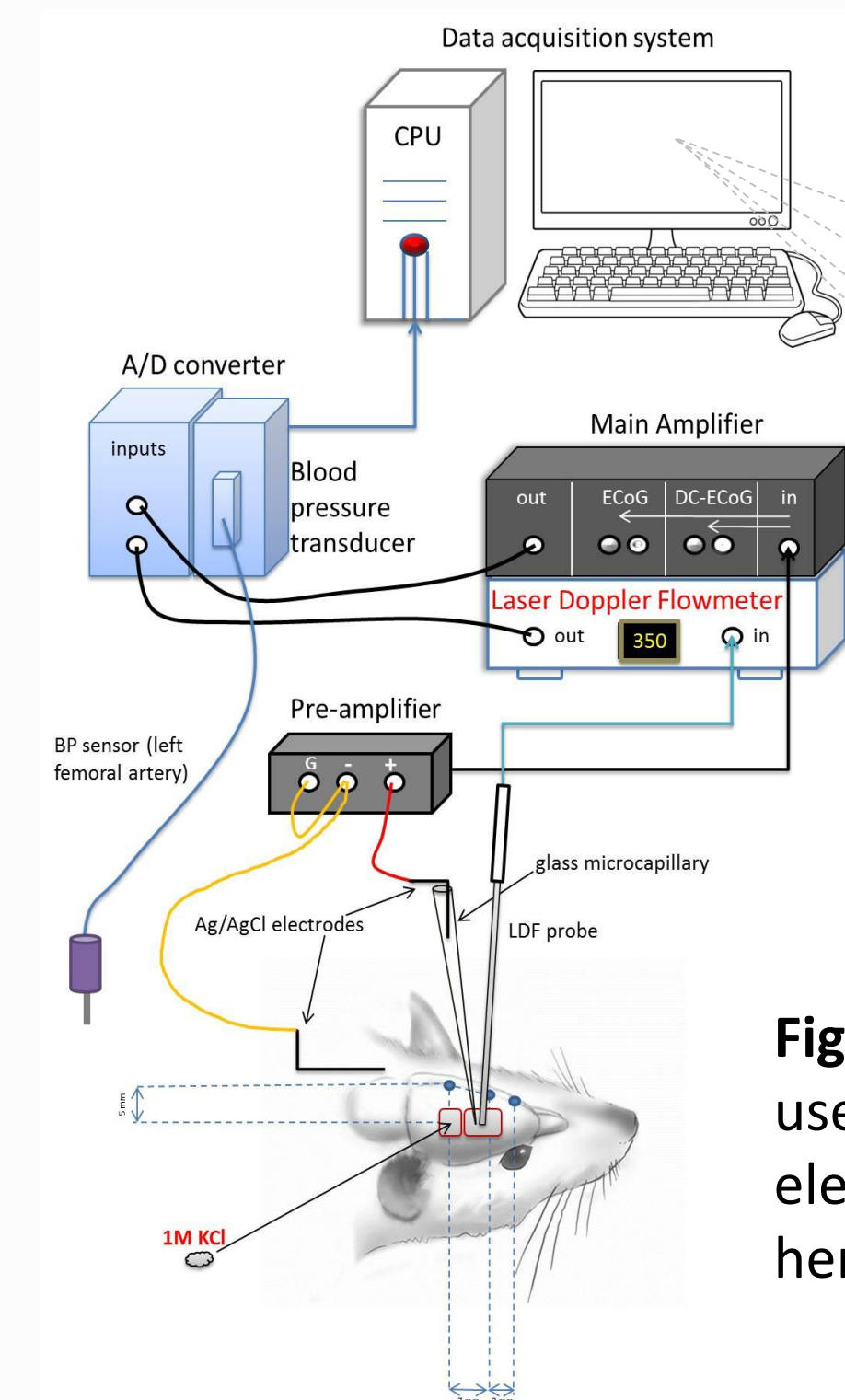


Figure 1. Experimental setup used for simultaneous recording of electrophysiological and hemodynamic parameters.

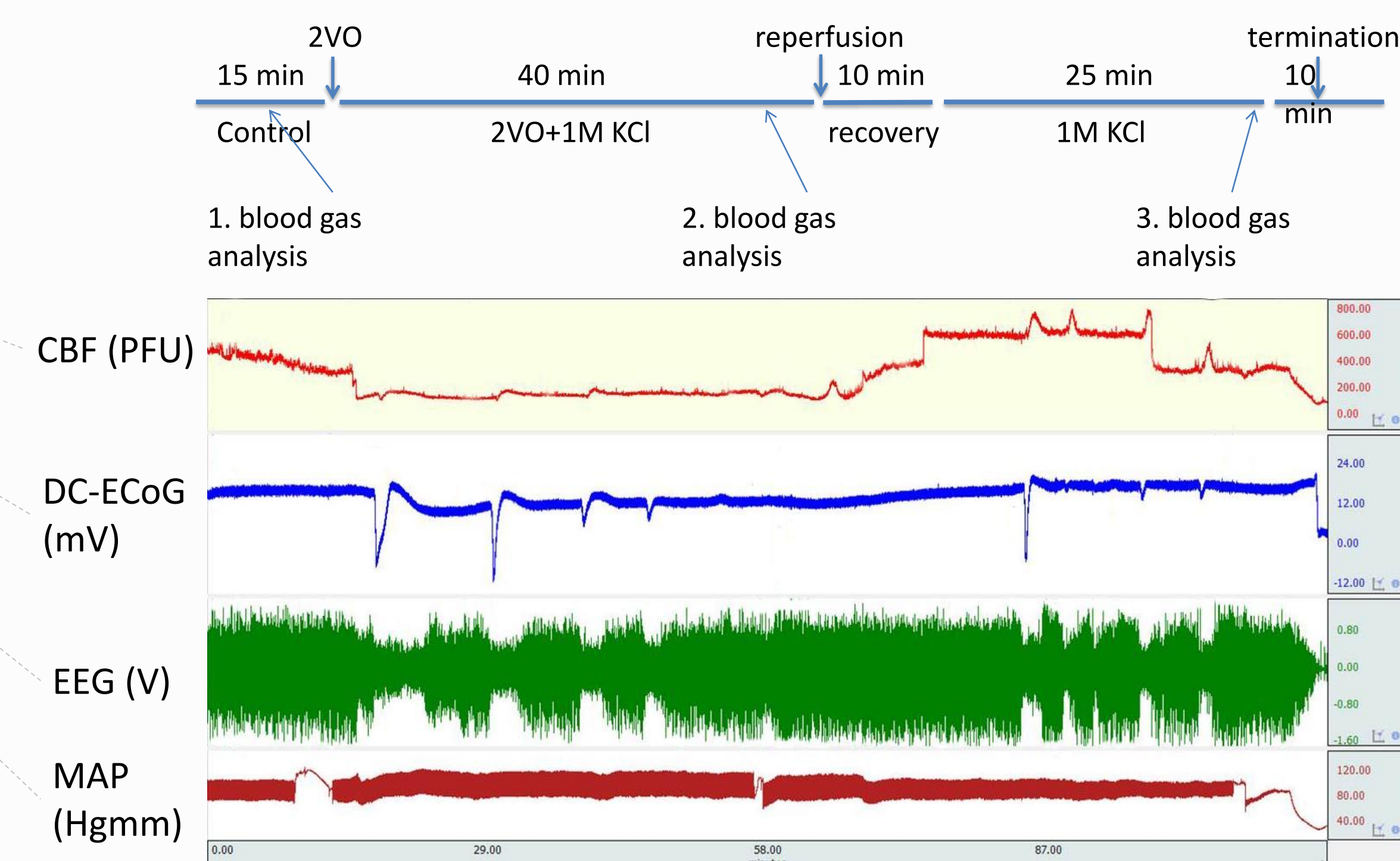
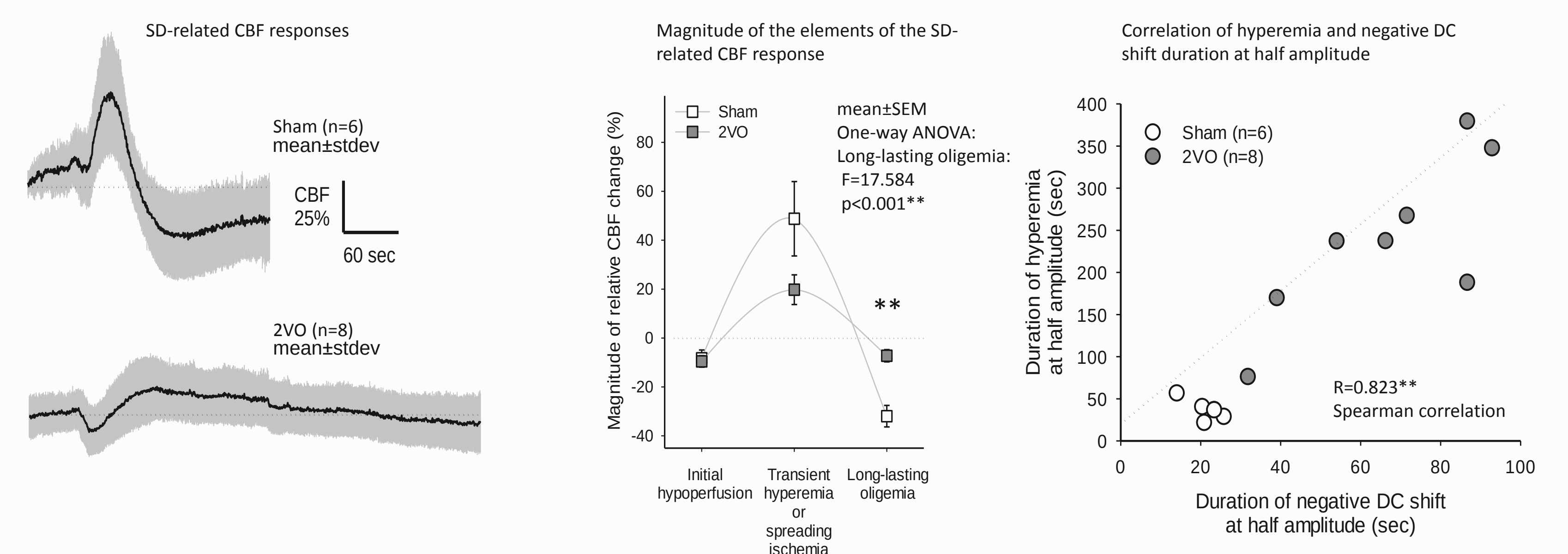
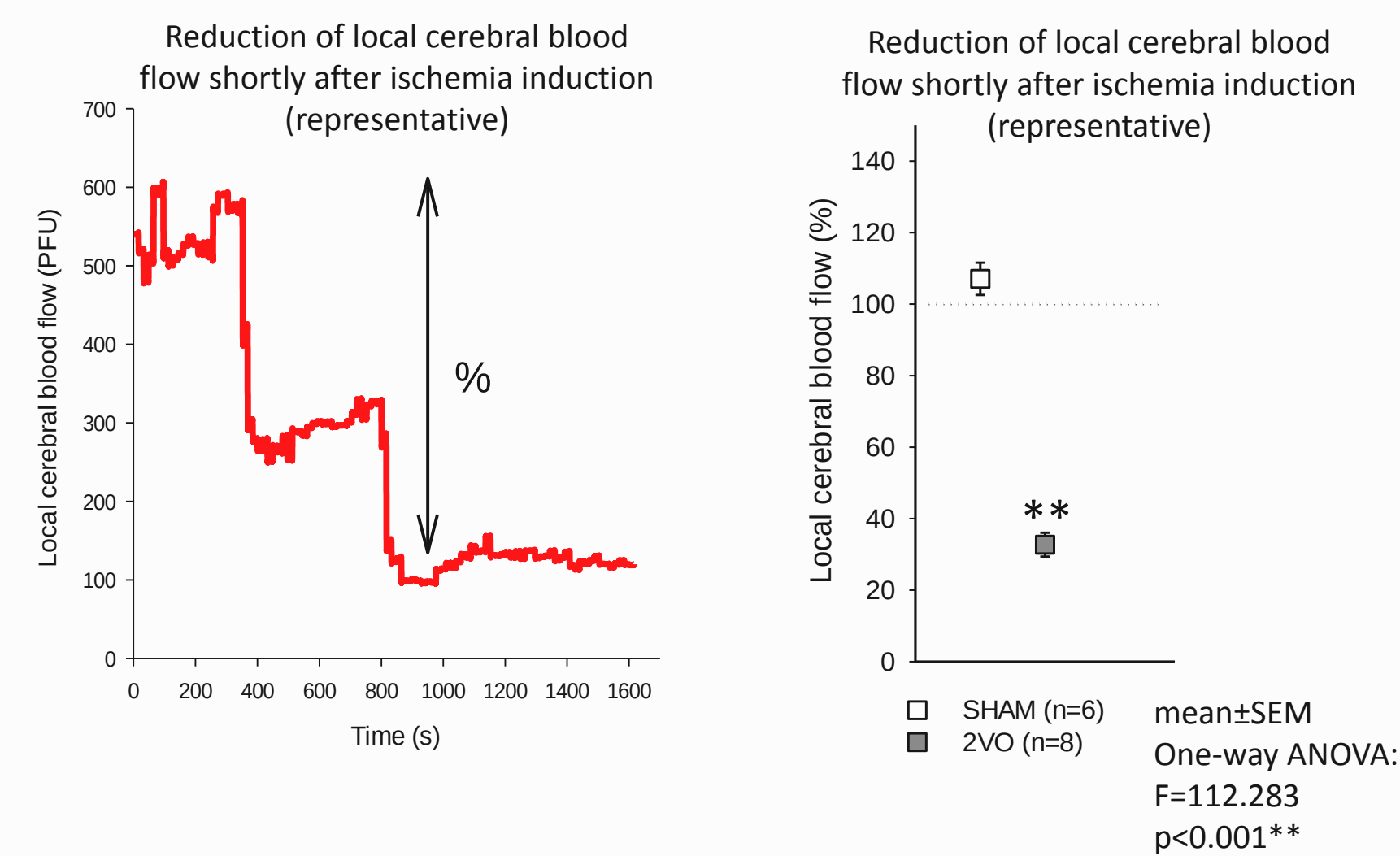
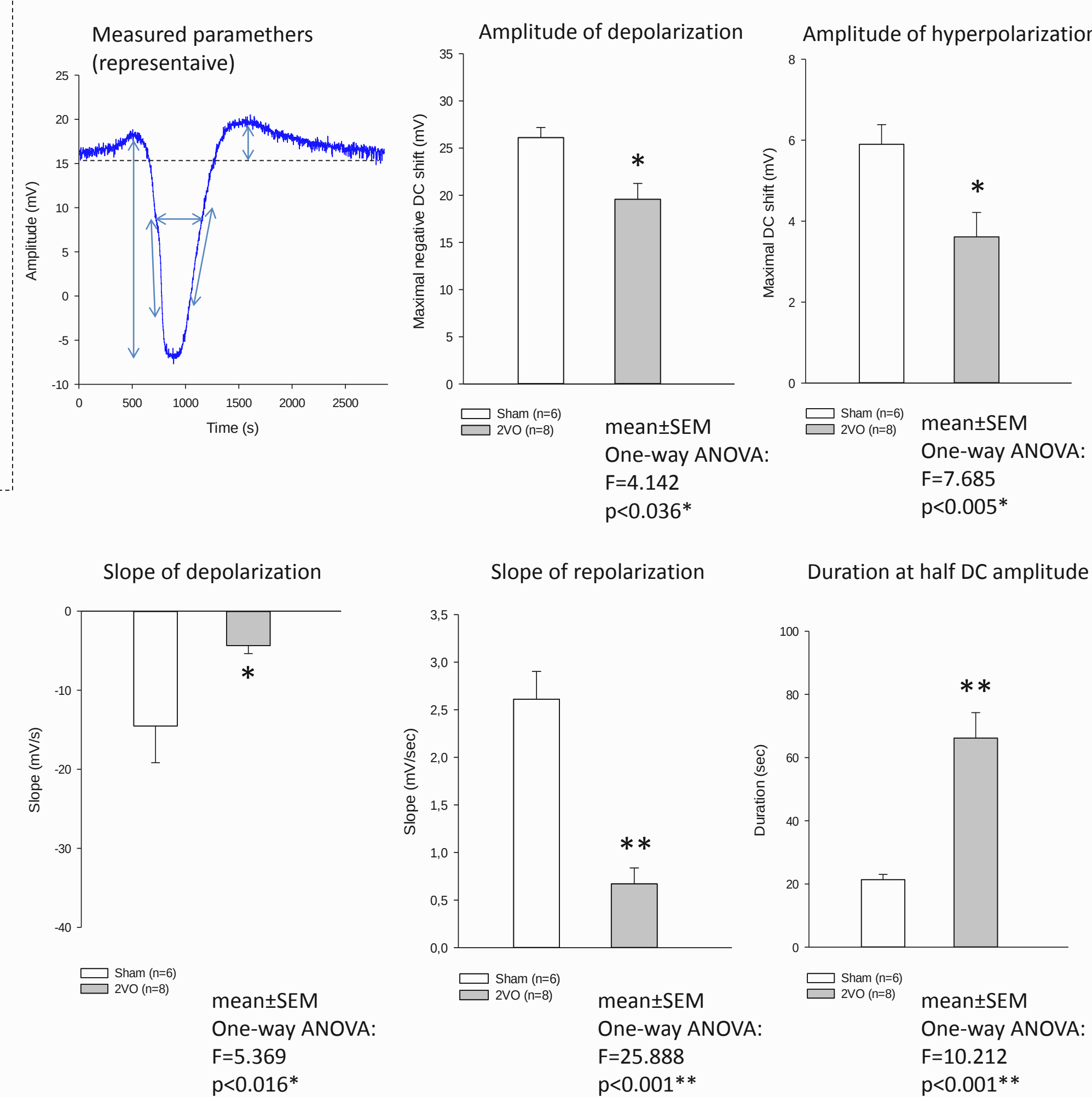


Figure 2. Experimental protocol.

Figure 3. Representative recordings of the four variables under study. 1. Channel (top, red): Laser Doppler Flow measured with a stainless steel doppler probe. 2. Channel (blue): DC-ECOG was measured via glass microcapillary with differential amplifier in DC-coupled mode. 3. Channel (green): EEG was measured via same glass capillary with differential amplifier in AC-coupled mode. 4. Channel (bottom, drone): MAP was measured via a left femoral arterial catheter.

RESULTS

Ischemia reduced the amplitude of the SD-related negative shift in DC potential (19.58 ± 1.67 vs. 26.1 ± 1.1 mV), the slope of depolarization (-4.34 ± 1.02 vs. -14.52 ± 4.64 mV/s), while it increased the DC shift duration at half amplitude (66.18 ± 8.07 vs. 21.36 ± 1.66 s). Ischemia reduced the maximal deflection of the long lasting oligemia phase of the CBF response (7.26 ± 2.51 vs. 31.95 ± 4.4 %), and increased the duration of hyperemic phase (237.66 ± 34.39 vs. 36.66 ± 4.82 s).



DISCUSSION

Global forebrain ischemia modified the general characteristics of SD-s and caused an overall reduction in the coupled CBF response. In cerebrovascular disorders, such as stroke, SD-s with delayed cell membrane repolarization and attenuated hyperemia further deteriorate the severity of tissue damage, leading to impairment of the neurovascular unit. The model used is suitable for the reliable reproduction of the ischemic SD-related CBF response, with accurate comparison to corresponding, non-ischemic SDs.

FUNDING

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