The source of the early-negative blood oxygenation signal

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Background Optical intrinsic signal (OIS) imaging is often used to explain BOLD fMRI because of their dependence on common physiological sources. In OIS imaging, wavelengths absorbed preferentially by deoxyhemoglobin (610 – 700 nm) are commonly used for functional mapping since the initial darkening of OIS, or "early dip" is localized well to increased neural active sites. Despite its frequent use, the physiological source of the early dip is highly controversial; one can associate the early dip with a decrease in blood oxygen saturation (SO2) to elevation in oxygen consumption, while it can also be associated with an increase in total hemoglobin due to increases in cerebral blood volume (CBV). In the present study, we performed concurrent measurements of CBF, blood oxygen tension (PO2) and OIS on the visual cortical surface in anesthetized animals to reconcile the contradicted interpretation of the early dip source. When oxygen consumption increases in the active parenchyma, it causes oxygen saturation levels to decrease (i.e., a decrease in blood PO2) and increases deoxyhemoglobin content in blood. These changes are expected to be observed in emerging pial veins because of blood draining. Since the early dip is not usually observed in most BOLD studies, our direct measurements of the partial pressure of oxygen in emerging veins are crucial for interpreting the sources of the OIS early dip and its implications for BOLD fMRI.

Methods A total of 11 anesthetized (0.6 – 1.0% isoflurane) and paralyzed (1.5 mg/kg/hr pancuronium bromide) Long Evans rats (mean ± SD: 0.384 ± 0.056 kg) were used. OIS with both 620 nm (i.e., deoxyhemoglobin weighted) and 570 nm (i.e., CBV weighted) wavelengths, blood oxygen tension (Po2) with a polarographic oxygen sensor (tip diameter, 10 um) and cerebral blood flow (CBF) with laser Doppler flowmetry were concurrently recorded from cortical surface. The polarographic oxygen sensing method utilizes oxygen reduction reaction; when the sensor cathode is polarized against the internal reference between at 0.6- 0.9 V, the current between them is linearly related to the PO2 surrounding the sensor tip. The spatial resolution of the sensor is supposed to be the same as the tip diameter. The blood Po2 was measured on an emerging pial vein (diameter: 20 - 80 um, median 50.5 um, distance from emerging point: 85-1060 um, median 210 um). The blood PO2 data was converted to absolute PO2 using calibration curves from each experiment. Then, blood PO2 was converted into SO2 using the Hill equation (Hill coefficient of 2.6 and P50 of 36 mmHg). The PO2 measurement lag due to sensors' response time was not corrected, but they were typically less than 1.0 s to 90% of the peak magnitude. To evoke visual response, a 2-s duration of a full-field moving square wave grating with spatial frequency of 0.05 cycle/degree and temporal frequency of 3.5 Hz was presented monocularly. Inter-stimulus interval was 42 sec. One session consists of 10 runs and 5 – 11 (typically 10) sessions were repeated for signal averaging to obtain sufficient SNR. To evaluate whether CBF response is fast or slow, the slope of CBF response was determined by measuring a slope of a line connecting between 10% and 90% of the response peak. OIS traces were obtained from averaging pixels (excluded vessels and the sensor) within a 1-mm diameter circle at the center of the venous PO2 sensor tip.

Results We observed a good correspondence between light absorption changes in emerging vein and SO2 changes in it. The brightening of veins was observed when SO2 was increased, while the darkening of veins was observed when SO2 was decreased. No vessel dilation was detected from the recording veins, suggesting that absorption changes and the blood PO2 changes in the emerging veins are caused by blood oxygenation level changes rather than CBV increases. To examine relationship of the presence and absence of the early decrease in SO2 (SO2 dip) to CBF response, CBF slope was plotted against SO2 dip amplitude for initial 2 s (Fig. 1A). The SO2 dip was more prominent when CBF response was slower and no recognizable SO2 dip was observed when CBF response was fast (Fig. 1A). Interestingly, regardless of the presence and absence of SO2 dip, 620-nm OIS early dip and 570-nm OIS was always observed (Fig., 1, B and C).

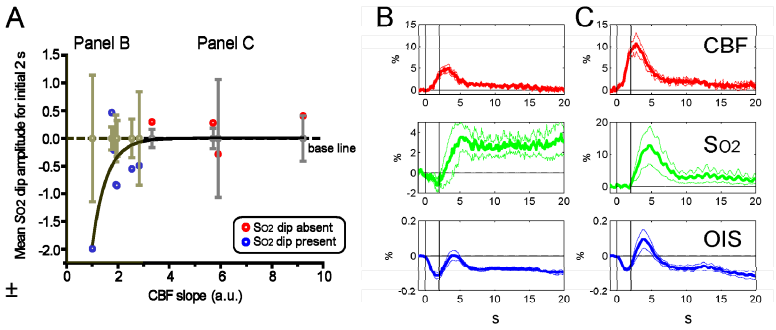

Fig. 1. Relationship between CBF, SO2 and 620-nm OIS. A) The CBF slope is plotted against the mean SO2 dip amplitude for initial 2 s for each rats (n = 11). Based on the CBF slope, data were subjectively divided into to two groups. **B)** Average data for CBF slope smaller than 3 are shown (n = 7, Mean ± SE). **C)** Average data for CBF slope larger than 3 (n = 4, Mean ± SE). Mean arterial blood pressure (MABP) and blood gas measures were similar between these two groups. MABP = 107.2 ± 0.16 vs. 96.5 ± 0.08 mmHg, pco2 = 38.6 ± 2.7 vs. 39.3 ± 3.3 mmHg, po2 = 128.3 ± 10.7 vs.119.8 18.2 mmHg (B vs. C, Mean ± SD).

Conclusion The early dip likely comprises an increase in CBV when CBF response is fast while the early dip consists of both a decrease in blood oxygen saturation level due to an increase in tissue oxygen consumption and an increase in CBV when CBF response is slow. A relative contribution of the SO2 decrease and CBV increase to the early dip will be varied by several factors, such as local and global physiological conditions altered by invasive procedures and anesthesia, species differences, recording areal differences, type of stimulation differences etc.

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