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In this study, we investigated the feasibility of separating intra- and extracerebral tissue by using a cw HR-DOT imaging system which is normally used to determine concentration changes of oxy- (HbO) and deoxygenated (HbR) hemoglobin [12,17] due to brain activation. We were able to reproduce previous results [6,7] with a less demanding system in all three subjects. Three-dimensional result volumes of absorption changes were reconstructed within a few seconds due to the use of pre-calculated forward solutions. The images show a high lateral and good depth resolution and allow the separation of intra- and extracerebral tissue.

The used wavelengths are close to the maximal absorption spectrum of ICG in plasma. We are aware of the fact that there are three chromophores that mainly contribute to the measured signal, but the impact of changes in HbO and HbR concentration (which can be seen in fluctuations of the baseline) is relatively small and stable over time compared to the high amplitude changes in light attenuation caused by the ICG. For example, referring the measurement with  $\lambda = 760$  nm (subject 1, bolus 1, intracerebral ROI) we found an almost 10-fold increased amplitude of the ICG response ( $1.1 \cdot 10^{-5}$  mol/l) compared to the standard deviation of a 45s pre-bolus baseline ( $1.2 \cdot 10^{-6}$  mol/l). For  $\lambda = 830$  nm (same measurement) we found a more than 20-fold increase.

Nevertheless, hemodynamics can be observed in the signal; especially within the 830 nm time courses, to which HbO is the predominantly contributing hemoglobin species, we see oscillations that are part of systemic signals [18]. For further studies, we consider the implementation of a third wavelength, allowing for a better separation of the signals. However, the typical bolus kinetics with different bolus arrival times within the different compartments and the fast decline of the signal within cerebral tissue and can clearly be seen using a single wavelength. The distinct border of the early arrived bolus at 12 mm tissue depth indicates the cerebral boundary.

In this study we succeeded in the attempt of showing the separation of intra- and extracerebral tissue by using a cw HR-DOT imaging system in combination with the injection of a safe dye. In our results, we see the early arrival of the ICG for larger SD-separations in the raw data and the expected bolus kinetics in different layers of the reconstructed volume. This work can help to promote the use of DOT for monitoring patients undergoing brain trauma or stroke. It could be highly useful to detect changes in brain perfusion in time without expensive measurements and difficult transport of the patient. We highly recommend further studies using a more complex system that takes changes of all important chromophores into account.

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