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Real-time oxygen saturation measurement in blood-filled vascular structures

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MOTIVATION

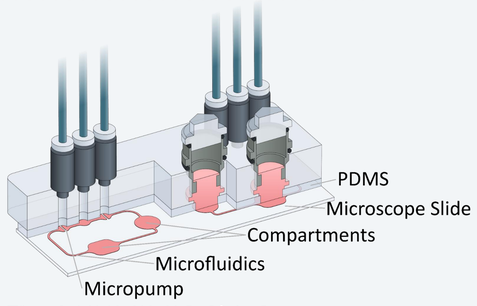

Fig. 1 HUMIMIC Chip2

Animal experiments and conventional cell culture techniques often fall short in replicating complex human systemic interactions.Multi-Organ-Chip (MOC) systems address these limitations by providing human-relevant, physiologically integrated models for biomedical research.

A key requirement for the functionality of these microphysiological systems is proper vascularization, enabling the development of organ models with realistic tissue architecture and function.However, physiologically accurate oxygen transport has not been possible in most systems to date, as they lack erythrocytes or whole blood. In this study, a microscope is therefore being developed that can be used to photolithographically print vascular structures in a two-organ chip (Fig. 1) and simultaneously measure oxygen saturation in the blood in an analogous way to pulse oximetry.

HEMOGLOBIN PROPERTIES

At 98%, the majority of the oxygen contained in the blood is bound to hemoglobin. Oxygen saturation describes the ratio of oxygenated hemoglobin to (HbO_2) to total hemoglobin. The relationship between oxygen bound to hemoglobin and oxygen dissolved in plasma is described by the oxygen dissociation curve (Fig. 2).

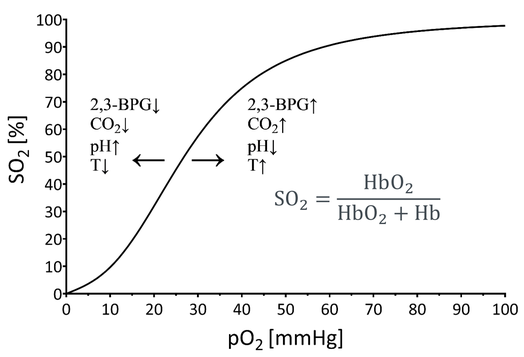

Fig. 2 Oxygen dissociation curve (standard conditions)

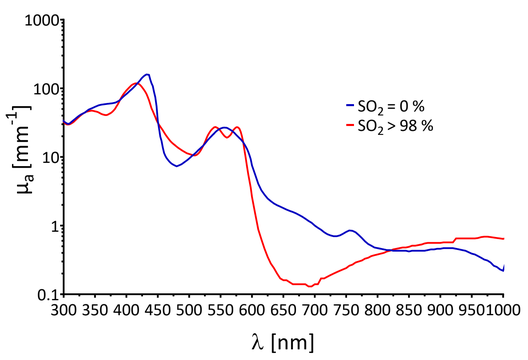

Fig. 3 Absorption spectra of HbO_2 and Hb

If the oxygen saturation in the blood is measured, important information about the oxygen supply and metabolic processes can be derived from this. In this study, the oxygen saturation of whole blood is therefore measured in a multi-organ chip using a specially developed microscope analogous to reflection pulse oximetry. This method makes use of the different absorption spectra (Fig. 3) of oxygenated hemoglobin and deoxygenated hemoglobin (Hb). The oxygen saturation can be determined from the ratio R of the two reflection signals.

OXYGEN SATURATION CALIBRATION CURVE

The functional relationship between the measured value R and the oxygen saturation must be determined empirically. For this purpose, the oxygen partial pressure pO_2 was continuously varied in a multi-organ chip filled with blood (shown in Fig. 4) and R was measured simultaneously (Fig. 5).

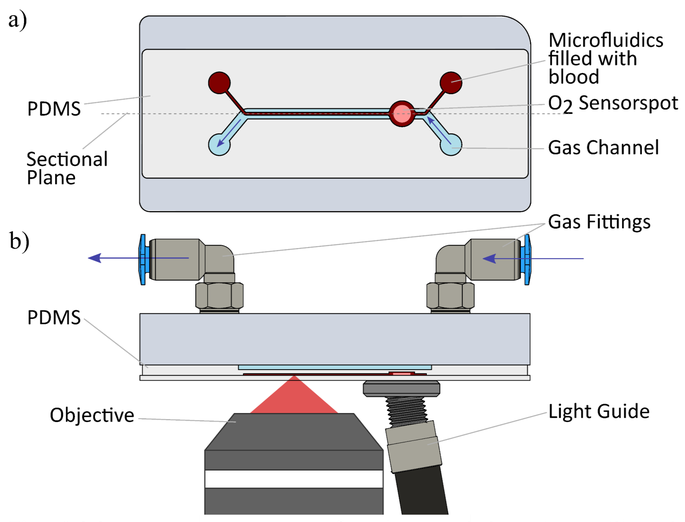

Fig. 4 Measurement setup for determining the calibration curve a) Structure and channel layout with a view of the chip from below b) Section through the sectional plane shown in a)

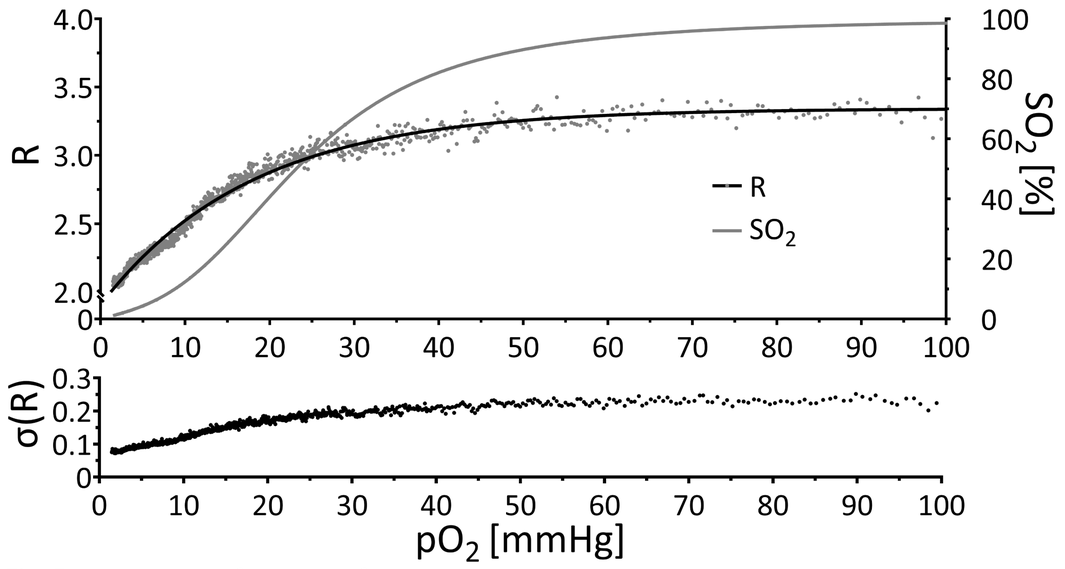

Fig. 5 R and SO_2 as function of pO_2

If this measurement is then combined with the oxygen dissociation curve, the calibration curve $SO_2 = f(R)$ can be determined. Using this calibration curve, oxygen saturation can now be measured non-invasively directly in the multi-organ chip.

PRINTING OF PREVASCULATURE

To produce the prevascularization, a photolithographic process is used to print channels directly in the chip. This new method was designed to be easily integrated into automated processes to allow pipetting robots to be used. The procedure consists of five process steps (Fig. 6).

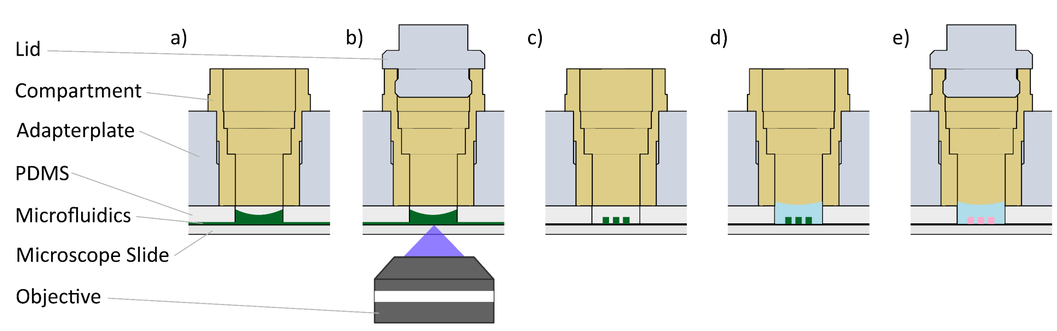

Fig. 6 Workflow for preparation of the prevascularization a) filling the compartment with HAMA-based photosensitive ink b) selective cross-linking of the ink c) removing the excess ink d) Filling the compartment with the fibrin-collagen gel e) dissolving the sacrificial structure and subsequent endothelialization

First, sacrificial structures made of methacrylated hyaluronic acid (HAMA) are printed into the chip. The height of the printed structures is limited by the addition of an optical absorber. The compartment is then filled with a fibrin-collagen gel and the HAMA structures are dissolved enzymatically.

ENDOTHELIALIZATION

Before the multi-organ chip was filled with blood to measure oxygen saturation, six parallel channels were printed into the chip as a pre-vascularization using the method described above. The channels were then endothelialized with HDMECs (Fig. 7).

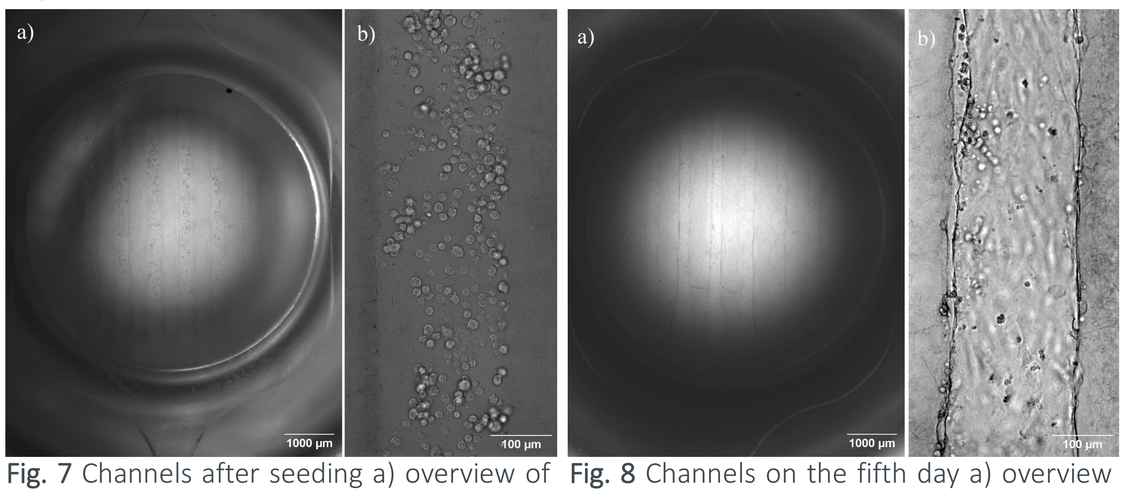

Fig. 7 Channels after seeding a) overview of the compartment b) single channel with round shaped endothelial cells

Fig. 8 Channels on the fifth day a) overview of the compartment b) single channel with elongated endothelial cells

The pump of the chip was then switched on with a pressure of +/-450 mbar and a frequency of 0.5 Hz. The chips were cultured with these conditions for five days (Fig. 8). On the fifth day, the chips were filled with blood to measure oxygen saturation.

OXYGEN SATURATION DISTRIBUTION

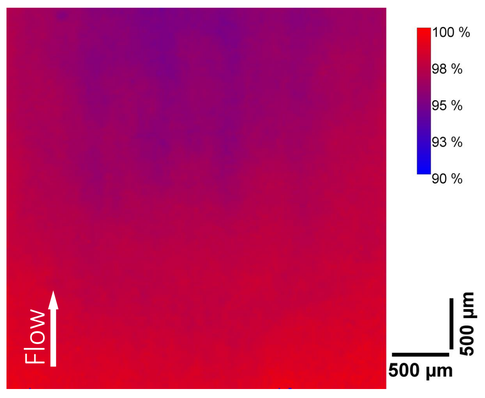

Fig. 9 Distribution of oxygen saturation in the compartment

At the end of this study, the oxygen saturation was measured in the blood-filled chip. As expected, the oxygen saturation at the entrance of the compartment is in the upper physiological range and decreases in the direction of flow (Fig. 9). Although the oxygen saturation decreases, the compartment is still in the arterial oxygen saturation range. The results show that, analogous to pulse oximetry, oxygen saturation can be measured spatially resolved in a multi-organ chip.

SUMMARY

The results show that the developed photolithographic method can be used to print channels directly into a multi-organ chip. It has also been shown that these channels are functional in terms of fluid flow and wall shear stress, and that they can be seeded with endothelial cells. An oxygen saturation gradient within the multi-organ-chip could be measured and demonstrates oxygen transport and aerobic metabolism within the vascularized chip. With the help of the developed methods it will be possible in the future to create more complex vascularized organ models and to characterize their oxygen supply at the same time.

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