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Quantitative and localized spectroscopy for non-invasive bilirubinometry in neonates

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Summary

Due to underdeveloped organ functions at birth, preterm neonates have an increased risk on developing jaundice. Jaundice (hyperbilirubinemia) is related to elevated bilirubin concentrations in blood and may result in brain damage (kernicterus) if bilirubin levels rise to levels that cause extravasation of bilirubin through the blood-brain barrier. It is therefore essential to accurately monitor bilirubin levels in jaundiced neonates.

The current gold standard to measure bilirubin levels is invasive blood sampling, commonly by a heel stick, which may be needed up to 3 times a day. Subsequent laboratory analysis of the blood sample provides the total blood, or serum bilirubin concentration (TSB). Naturally, this is a very painful and stressful procedure for the neonate. In addition, the method is laborious and time consuming, lacking the possibility for immediate diagnosis.

A possible alternative for invasive blood sampling is transcutaneous bilirubinometry, which is a non-invasive and painless method that provides an instantaneous read-out of the cutaneous bilirubin concentration (TcB). Transcutaneous bilirubinometry is based on optical spectroscopy, which relates the amount of light absorption around 460 nm by bilirubin in the skin (i.e. the yellow color of the skin) to the concentration of bilirubin in blood. Although bilirubinometers based on this principle have been developed since 1980, no device has been found accurate enough to completely replace the heel stick. The focus of this thesis is therefore 1) to investigate the reasons for the limited accuracy of current bilirubinometers and 2) to design a bilirubinometer that can replace invasive blood sampling.

To investigate the reasons for the limited accuracy of current bilirubinometers, we built a transcutaneous bilirubinometer that determines not only the TcB, but also the blood volume fraction (BVF) in the investigated skin volume. In an exploratory patient study, we found that the TcB consists primarily (>99%) of bilirubin in the tissue *surrounding* the blood vessels in the skin, instead of bilirubin inside the blood vessels themselves. Since the bilirubin concentration in the surrounding tissue is difficult to relate to the concentration in blood (TSB), this introduces an inevitable inaccuracy in the comparison of existing bilirubinometers to the heel stick determination (Chapters 1 and 2).

One way to solve this problem is by designing a transcutaneous bilirubinometer that excludes the influence of the surrounding skin tissue, i.e. a bilirubinometer that can confine its probing volume to the inner lumen of a blood vessel only. Current spectroscopic techniques are unable to do such a determination, since light scattering from the surrounding tissue always contributes to the measured value. Therefore, we developed a new spectroscopic technique – low coherence spectroscopy (LCS) – which, based on low coherence interferometry, allows for very careful control over the size and location of the investigated tissue volume (axial x lateral resolution: 22 μm x 9 μm).

When designing a new optical technique for measurements on neonatal skin, knowledge on the optical properties of neonatal skin is required. Therefore, we used

the bilirubinometer from our patient study also for the determination of the optical properties of neonatal skin, as described in Chapter 3.

The remaining Chapters 4 to 7 of this thesis describe the development and validation of LCS. This validation involves the demonstration of 1) that we can use LCS for the *quantitative* determination of absorption coefficient spectra μ_a , which is needed to derive chromophore concentrations such as bilirubin and 2) that we can use LCS for the *localized* determination of μ_a , which is needed for confining the measurement volume to a single blood vessel.

In Chapter 4, we demonstrate that LCS can quantitatively measure μ_a in tissue simulating phantoms from which the exact optical properties are known. Since LCS measures the total attenuation coefficient of the sample – which is the sum of the scattering and absorption coefficient – knowledge of the contribution of scattering to the LCS signal is important for accurate measurements of μ_a . Therefore, scattering contributions to the LCS signal are investigated in Chapter 5.

The localized determination of μ_a is validated in Chapter 6 on layered tissue simulating phantoms. In addition to these phantom measurements, the first *in vivo* results for LCS are demonstrated on human skin, from which the μ_a and chromophore concentrations are determined within distinct skin volumes (the dermal and the epidermal layer). The measured concentration of the chromophore hemoglobin in the dermis is comparable to normal hemoglobin concentrations found in human skin, as is the oxygen saturation that was derived from the hemoglobin absorption.

To enhance the clinical value of LCS, improvements on the acquisition speed and accuracy may be needed. Therefore, Chapter 7 describes the possibility of replacing the time domain detection scheme of our current LCS system by spectroscopic detection, which provides a theoretical speed and/or sensitivity advantage.

In summary, this thesis describes the essential first steps in the design, development and validation of LCS as a potential non-invasive alternative for invasive bilirubin measurements. Before LCS can be clinically applied for this purpose, future research is needed, primarily on the optimization of the suggested configuration for spectroscopic detection. Nevertheless, even at this early stage of development, we can already show that the current time domain LCS system can be used for measuring the μ_a within a single blood vessel in human skin, and that the derived hemoglobin concentration is well within the range of normal human whole blood hemoglobin concentrations (Chapter 8). Therefore, LCS is a very promising technique that deserves further development and can potentially lead to less pain and complications for preterm neonates.