Pulse Spectrophotometric Determination of Plasma Bilirubin in Newborns

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ABSTRACT

In neonatal jaundice, plasma bilirubin has to be measured repeatedly in order to direct phototherapy. Invasive determination is standard. The authors delineate a concept for the non-invasive spectrophotometric determination of absolute plasma bilirubin concentration. By referencing the pulsatile spectrophotometric signal component of the metabolite of interest (MOI, here: bilirubin) to the pulsatile spectrophotometric signal component of a reference metabolite (MOR, here: water) of known plasma concentration, the absolute MOI concentration can be calculated. Based on Beer-Lambert’s law and some reasonable assumptions, the authors developed a theoretical concept for the calculation of MOI concentration. They suggest light of 1200 nm wavelength to measure MOR, 795 nm and 570 nm to measure hemoglobin as correction signal, and 450 nm to measure the MOI. To enhance data quality one could assign several wavelengths to each metabolite. Since in tissue spectrophotometry Beer-Lambert’s law does not reflect physiology accurately, it will be necessary to empirically fine-tune the computer algorithms.

KEYWORDS
Absorption, Bilirubin, Jaundice, Measurement, Neonate, Non-invasive, Pulsatile, Spectrophotometry

INTRODUCTION

In neonatal jaundice there is need for the repeated determination of plasma bilirubin to check the indication for, or the efficacy of, phototherapy (Maisels et al., 2012; Maisels & Newman, 2012). Standard method is the invasive measurement, depending on a painful needlestick. So far, the methods available for the non-invasive estimation of plasma bilirubin, i.e. visual assessment of jaundice (Riskin et al., 2008) or the extent of cephalocaudal jaundice progression (Keren et al., 2009), spectral reflectance analysis measuring transcutaneous bilirubin (Blutani et al., 2000; Ho et al., 2006; Penhaker et al., 2013), or both (Mishra et al., 2009), may help identify those neonates
requiring phototherapy but are too inaccurate or of no proven value for this indication in extremely premature neonates, or for monitoring patients undergoing phototherapy or thereafter (Nagar et al., 2013). Noninvasive detection of bilirubin using pulsatile light absorption is similar to our concept but needs intraindividual calibration with ‘true’ plasma bilirubin (McEwen et al., 2006).

**Problem Definition**

There is need for a *non-invasive* method of plasma bilirubin determination with an accuracy similar to pulse oximetry, the non-invasive spectrophotometric measurement of the ratio of oxygenated and total hemoglobin (= oxygen saturation) that has become a routine procedure (Hutton & Fletcher, 1994; Jubran, 1999; Ross et al., 2014; Zijlstra, 1991). However, our application does not target the molar ratio of two metabolites that is independent of the length of the light pathway (length of pathway mathematically cancelling out) (Hutton & Fletcher, 1994; Zijlstra, 1991) but rather the *absolute metabolite plasma concentration*. But, measuring the length of the light pathway is a technical challenge and obviated at best.

**Aim of the Study**

We delineate a concept for the *non-invasive* spectrophotometric determination of *absolute* plasma bilirubin concentration *without the need to measure the length of the light pathway*. The method should be both feasible and accurate enough for the application on jaundiced premature or mature neonates to guide phototherapy.

**METHODS AND RESULTS**

**Basic Assumptions**

Arteries show some pulse synchronous fluctuation in diameter. In in-vivo spectrophotometry this results in a fluctuating length of the light-pathway (furtheron referenced to as “pathlength”) and hence -- if light of an appropriate wavelength is used -- in a metabolite-specific pulsatile signal. Isolating the pulsatile signal component from the total light signal detected allows for the determination of the arterial metabolite concentration, provided the corresponding pathlength is known.

**Proposed New Principle**

By referencing the pulsatile spectrophotometric signal of the metabolite of interest (MOI, here: bilirubin) to the pulsatile spectrophotometric signal of a reference metabolite (MOR) of known plasma concentration, the *absolute* MOI concentration can be calculated without knowing the pathlength. We propose water as MOR. In humans, plasma water concentration is about 51.66 mol/L (0.93 g/mL) and fairly constant (Nguyen et al., 2007).

**General assumptions**: For definitions see Table 1:

1. Light of intensity $I$ is travelling first along a path $a$ of a constant but unknown pathlength, altering its intensity to $I_0$, and then along a path of pulsatile fluctuating pathlength $b$. Finally it is measured as intensity $I_x$ (Figure 1);
2. There are two (or more, see Discussion) separate measurements done using light of different wavelengths corresponding to the metabolite of interest (MOI), or the reference metabolite (MOR);
3. At first approximation, except for extinction, light spreading conditions (i.e. scattering) are similar for the wavelengths used.
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