Neonatal brain temperature monitoring based on broadband near-infrared spectroscopy

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Abstract We present here the initial development of a novel algorithm based on broadband Near-Infrared Spectroscopy (bNIRS) data to estimate the changes in brain temperature (BT) in neonates. We first explored the validity of the methodology on a simple numerical phantom and reported good agreements between the theoretical and retrieved values of BT and hemodynamic parameters changes, which are the parameters usually targeted by bNIRS. However, we noted an underestimation of the absolute values of temperature and haemoglobins' concentration changes when large variations of tissue saturation were induced, probably due to a crosstalk between the species in this specific case. We then tested this methodology on data acquired on 2 piglets during a protocol that induces seizures. We showed that despite a decrease in rectal temperature (RT) over time (-0.1048°C 1.5 hours after seizure induction, 95% CI: -0.1035 to -0.1061°C), BT was raising (0.3122°C 1.5 hours after seizure induction, 95% CI: 0.3207 to 0.3237°C). We also noted that the piglet displaying the largest decrease in RT also displays the highest increase in BT, which could be a marker of the severity of the seizure induced brain injury. These initial results are encouraging and show that having access to the changes in BT non-invasively could help to better understand the impact of BT on injury severity and to improve the current cooling methodologies in the neonatal neurocritical care following neonatal encephalopathy.

1 Introduction

Brain tissue temperature is a dynamic balance between heat generation from metabolism, passive loss of energy to the environment, and thermoregulatory processes such as perfusion. Perinatal brain injuries, particularly neonatal encephalopathy (NE) and seizures, have a significant impact on the metabolic and haemodynamic state of the developing brain, and thereby likely induce changes in

brain temperature (BT). The brain and/or body temperature elevation is indeed often associated with brain injury [1]. Moreover, therapeutic hypothermia (TH) is now a well-established standard to treat infants with moderate to severe hypoxic–ischemic encephalopathy (HIE) but this method is only partially effective[2]. In that context, having a tool allowing to follow the brain temperature non-invasively at the bedside can help to optimize the TH treatments and further benefit the care of infants in the neonatal intensive care unit (NICU).

Indeed, magnetic resonance spectroscopy (MRS) has been used as a viable, non-invasive tool to measure temperature in the newborn brain [3]. However, MRS thermometry requires transport to an MRI scanner and a lengthy single-point measurement. On the other hand, optical monitoring using near-infrared spectroscopy (NIRS), has the promise to overcome this limitation and be able to monitor the newborn's brain tissue temperature continuously at the bedside.

To answer this need, we propose a novel algorithm based on broadband NIRS fitting to monitor BT in real-time, together with parameters related to tissue oxygenation and metabolism. This algorithm can be deployed on our research instrument, named FLORENCE, currently in use in the NICU, that combines bNIRS and Diffuse Correlation Spectroscopy (DCS). This would allow to complement the current monitoring of the hemodynamic and metabolic brain parameters of infants.

This algorithm is based on the linear temperature-dependent changes in NIR water absorption spectra to estimate the tissue temperature. Previous algorithms have been developed in order to estimate the tissue temperatures using this feature, however, they required the use of an extra calibration step based on principal component analysis [4]. Here, we directly used the absorptivity temperature coefficients from the literature [5]. Briefly, this two-steps algorithm is based on (1) the initial fit of the optical properties based on the second derivative methods and (2) the fit of the changes in absorption considering only the oxy- and deoxyhaemoglobin ([HbO_2] and [HHb] respectively) and temperature changes.

In this work, we present the algorithm and demonstrates its capacities on a basic numerical phantom. Then, we applied it to data collected on 2 piglets in preclinical studies looking at seizures, which are known to induces BT [6].

2 Methods

The algorithm presented here is based on the broadband fitting method [7]. This method allows to retrieve the spectral absorption and reduced scattering coefficients of the tissue by spectrally constraining the possible solutions, both for the absorption, i.e., only considering the absorption spectra of specific chromophore, typically the haemoglobins and water, and for the scattering, by assuming it follows the Mie equation, reducing it to two parameters: a and b.

In order to estimate the temperature changes of the tissue, a two-step method is used. Firstly, the standard broadband fitting optimisation routine is applied on the baseline spectra. The fitting procedure uses the solution to the diffusion approximation for a semi-infinite medium as a reference function and is split into three steps to target individual spectral features of the chromophores: (i) the water content (WC) is found by fitting the second derivative of the reflectance spectra (R) in the range of prominent water absorption features, between 825 and 850 nm, (ii) after fixing the found WC, [HHb] is found by fitting the second derivative of R, between 700 and 800 nm, as this range has a distinct 760 nm HHb feature, (iii) for the last step, [HHb] is also set constant and [HbO2], a and b are determined from fitting the first spectral derivative of R, between 680 to 845 nm.

This constitutes an initial fit of the optical parameters of the tissues. Then, in order to measure the temperature changes of the tissues, the information acquired by the initial fit is used to fit the differential reflectance spectra (Rdiff) from the initial point. To do so, R_{diff} is calculated as: $R_{diff_{\Delta\mu_a,\Delta\mu_s'}}(t) = R_{\mu_a,\mu_s'}(t) - R_{\mu_a,\mu_s'}(t_0)$. The parameters of $R_{\mu_a,\mu_s'}(t_0)$ are known from the initial fit, as the scattering parameters from $R_{\mu_a,\mu_s'}(t)$ that are assumed constant over time. The absorption parameters of $R_{\mu_a,\mu_s'}(t)$ are calculated as $\mu_a\,(t) = \mu_a(0) + \Delta\mu_a$, with $\mu_a(0)$ known from the initial fit and $\Delta\mu_a = \Delta T * \varepsilon_T + \Delta[HbO_2] * \varepsilon_{[HbO_2]} + \Delta[HHb] * \varepsilon_{[HHb]}$. Here ε_x is the extinction coefficient spectra of chromophore x. Thus, in that step, $\Delta T, \Delta[HbO_2]\ and\ \Delta[HHb]$ are the fitted parameters. This fitting procedure is performed between 720 and 880 nm.

In order to investigate the accuracy of the method and potential crosstalk between the fitting parameters, simulated spectra of various tissue parameters were generated using the solution to the diffusion approximation for a semi-infinite medium [8]. Here, we will report the simulation of a concurrent change in BT and brain oxygen tissue saturation (StO_2). Here, StO_2 is defined as StO_2 = [HbO_2] / [HBT], with [HBT] = [HbO_2] + [HHb]. We thus induce changes in temperature, [HbO_2] and [HHb] but keep [HBT] constant (100uM). This will enable us to investigate the potential crosstalk between these parameters. Maximum temperature variations of +/-2 °C were induced and the StO_2 values were varied in a range 50 to 85%. The theoretical values of these variables are display as solid lines in figure 1.

Finally, optical data was collected with FLORENCE on piglets monitored during a preclinical study looking at seizures. We only focused on the bNIRS data here which were recorded between 700 and 900 nm, with a 1nm resolution, and a source/detector distance of 3cm (reflectance mode). Briefly, the seizures were induced using bicuculine (4mg/kg) in 2 white male piglets and were continuously monitored with a combined optical platform and continuous video EEG for 2.5 hours. Systemic parameters were also recorded, and particularly the rectal temperature of the animal which was compared to the brain temperature estimated using the novel algorithm.

3 Results

Figure 1 presents the retrieved changes in BT, [HbO_2] and [HHb] using the novel algorithm. The simulation emulates a large desaturation event (StO_2 drops from 75% to 50%), a plateau at low saturation (50%) and a return to normal with an overshoot to 85%. In the meantime, the temperature change was simulated in a range +2 to -2 °C, with plateau values set at different time compared to saturation plateau. This allows to investigate the crosstalk between the temperature and haemoglobins concentration changes.

We can see that the trend of both BT and haemoglobins' concentrations are retrieved with reasonable agreement. However, the maximum change in the raising temperature is underestimated by a maximum of 1°C and, at the saturation plateau, the changes in haemoglobins' concentrations are also underestimated by a maximum of 4µMol. We can note than the maximum of these discrepancies appears for large haemoglobins' concentration changes. Below a 10µMol haemoglobin's concentration change, the maximum mismatch between theoretical and calculated temperature values is 0.5°C.

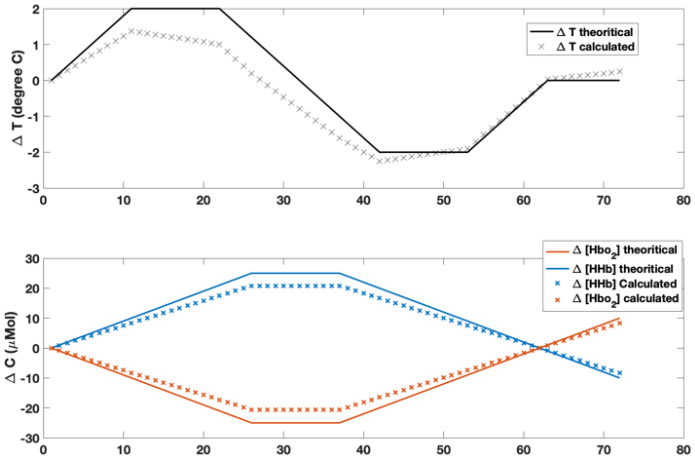

Fig.1. Results of the simulation. Upper Panel – Temperature changes estimation together with theoretical values. Lower Panel – Haemoglobins' concentrations changes estimation together with theoretical values.

Figure 2 focuses on the measured values of rectal and brain temperature (RT and BT respectively) changes for the 2 piglets. Both RT and BT dropped soon after seizure induction for the 2 piglets. Subsequently, a significant increase in BT was noted (0.3122°C at 1.5h after seizure induction, 95% CI: 0.3207 to 0.3237°C), while RT decreased followed by a recovery and a mild increase from baseline with a trend to decrease over time. 1.5h after the seizure induction, RT was significantly reduced by -0.1048°C (95% CI: -0.1035 to -0.1061°C). Finally, oscillations can be seen in the BT changes in piglet 1. These oscillations were also present in the other variables monitored (like [HbO_2] and [HHb], heart rate; data not shown). We have

noticed this behaviour in several piglets monitored by our system in this study and are currently exploring the possible reasons for this phenomenon to occur. However, since these oscillations are present in all the variables (both brain and systemic), we are confident that this is a real physiological signal, and not an artefact from the BT algorithm.

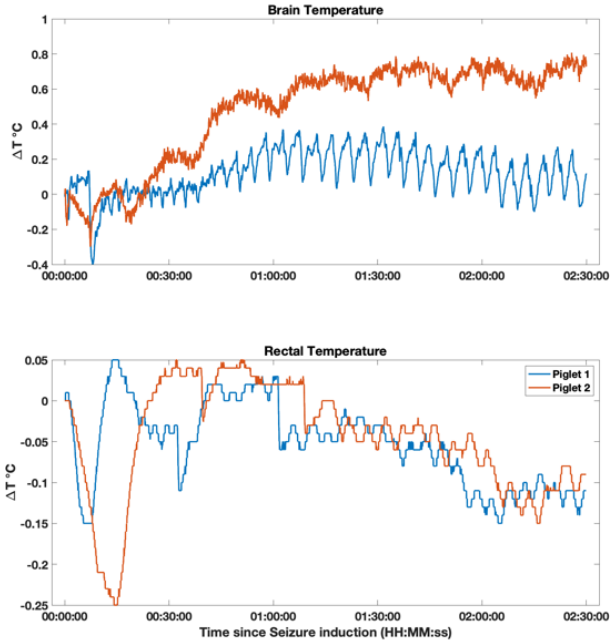

Fig.2 Brain Temperature (upper) and rectal temperature (lower) for the 2 piglets. Time 0 is the time of seizure induction.

4 Discussion

We report here the initial development of a novel algorithm designed to measure BT in neonates. This algorithm has been evaluated through numerical simulations emulating large changes in haemoglobins' concentrations and moderated temperature changes. This extreme scenario allows us to check for potential crosstalk between temperature and haemoglobin concentration changes. We have shown that both the temperature and haemoglobins' concentrations changes could be retrieved with reasonable agreement. However, an underestimation of the temperature and haemoglobins' concentrations changes was noted, with the maximum discrepancies between the theoretical and measured values found when haemoglobin concentrations changes were superior to 10µMol (for [HBT]=100µMol), which corresponds to high values of StO_2 changes. This

inaccuracy is likely due to a crosstalk between the variables when hemoglobins changes becomes significant. Thus, a more precise evaluation of this phenomena will be required if the present algorithm needed to be used in such cases. However, for moderate variation of StO_2, we can expect to retrieve accurate values of BT. This would correspond to most long-term monitoring scenarios in which we are interested, were large desaturation events are only transitory.

The current algorithm has then been tested on real datasets acquired during preclinical studies looking at the effect of seizures on the piglet brain. We could see that despite a decrease in RT induces by the seizure, the BT was increasing. This increase in BT with seizures was previously reported in the literature [6]. We can also note that the piglet displaying the largest decrease in RT temperature also displays the highest increase in BT, which could be a marker of the severity of the seizure induced brain injury. Although these are only case studies, these initial results are encouraging. However, more validation work is required at that stage. Indeed, invasive temperature monitoring would be required in order to fully validate the accuracy of the measurement of the BT using this algorithm. Unfortunately, this data was not available for the datasets processed here. Alternatively, more complex numerical simulation, based on Monte-Carlo simulation, allowing to take into account the effect of the anatomy [9], and incorporating noise level comparable to the one of our instruments could be used to validate further our results. Nevertheless, our initial numerical simulations showed that the estimation of the BT changes could be retrieve with reasonable accuracy, and our first test on preclinical data could retrieve values of BT changes in line with values previously reported in the literature. This constitutes a good first step into the validation of the BT measurement using our methods.

In conclusion, we report the initial development of a novel algorithm based on bNIRS data to measure concurrently the BT and oxygenation changes. The initial validations steps displayed encouraging results, and we believe that providing the clinicians with such information would help them to better understand the impact of brain temperature on injury severity and to improve the current cooling methodologies in the neonatal neurocritical care following NE.

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