Cerebral and cardiac signal monitoring in fetal sheep with hypoxic-ischemic encephalopathy

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Summary
The personal and societal burden of hypoxic-ischemic encephalopathy (HIE) is immense. HIE is expressed as persistent brain injury induced by severe perinatal hypoxia (low blood oxygen levels) and/or ischemia (severely reduced blood flow). Brain injury occurs in two stages. The first stage is acute and takes place during hypoxic-ischemic conditions. The second stage of brain injury starts several hours after hypoxia-ischemia has been resolved. Infants with HIE will often experience lifelong effects, e.g., motor and learning disabilities, cerebral palsy, and blindness. Neonatal encephalopathy globally leads to 50 million disability-adjusted life-years (DALY). In comparison, the entire spectrum of cancer was estimated to lead to 169 million DALY globally. Though part of the burden can be reduced through general improvements to obstetric care in regions where public health care is less developed, additional reduction can only be realised through new and innovative improvements in perinatal care. Computer-assisted analysis has the potential of aiding physicians in assessing complex and challenging physiological signals, thus improving patient care. In this thesis we focussed on computer-assisted signal analysis in the two stages of HIE-related brain injury with the aim of improving the diagnostic tools available to physicians.

First, more accurate and earlier detection of conditions leading to the first stage of brain injury is essential to prevent or limit the extent of HIE. Fetal ECG contains characteristics that can be used to assess the hypoxic and acidotic conditions during birth that might lead to HIE. Heart rate and changes in the ST waveform of the fetal ECG have been implemented in clinical devices as markers to assess the fetal metabolic compromise related to severe hypoxia. Recent meta-analyses of clinical trials demonstrate that aforementioned devices effect little—if any—improvement in primary outcomes, e.g., a reduction in HIE. The cause for these findings is unknown. We hypothesised that these findings might be due to the choice of markers used in the devices. Several ECG based markers were reported in literature. We compared these markers within a fetal ovine model for standardized severe hypoxia-ischemia to identify which of these markers might be suitable for assessment of fetal hypoxia and acidosis. We found that the length of ventricular activation and repolarisation time, as well as heart rate may be useful interval-based markers for assessing fetal hypoxia. In contrast, waveform analysis of the ST segment was not useful as an early marker of fetal hypoxia. When compared to interval-based ECG markers, waveform-based markers are less reliable due to dependency on ECG lead and heart vector orientation. We found similar results with respect to ST waveform analysis using clinical Neoventa STAN S31 device in the fetal ovine model. Despite the basic observation that the ST waveform does change during prolonged hypoxia, the device was unable to adequately provide alarms. We speculated that this was mostly due to algorithm formulation.

Secondly, we investigated several markers on their suitability to assist clinicians in making treatment decisions for infants that potentially develop the second stage of brain injury. Currently, treatment of HIE needs to start before the onset of the second stage of brain injury for it to be effective. This means that assessment and treatment prognosis is required before the second stage begins. One issue here is that current markers that would enable physicians to reliably base their treatment decisions on are only effective after onset of the second phase of brain injury. Identification of suitable markers for basing outcome prognosis on is thus necessary. Beyond prognosis, the ability to monitor the effect of HIE and treatment on the functional level may help...
physicians make further decisions. In this thesis we investigated markers that are related to cortical, subcortical and autonomic function, and could be used for monitoring purposes and/or prognostic purposes.

In hypoxic-ischemic encephalopathy seizures not only indicate cortical dysfunction due to neuronal damage in hypoxic-ischemic encephalopathy, but they also may contribute to further brain injury. In preterm infants, seizures are often of short duration (<1 min) and difficult to detect using existing seizure detection algorithms. We developed and evaluated a method that facilitated detection of short seizures in preterm infants by assessing the transition to and from seizure state in the EEG. This method can be used to provide improved detection of seizures and thus affects clinical treatment decisions.

Interhemispheric synchrony of EEG burst activity may be used as a marker for interhemispheric neuronal connectivity and subcortical function. In literature qualitative decreases of interhemispheric neuronal activity in HIE have been reported. Knowledge on baseline values for interhemispheric connectivity in healthy individuals is essential to allow quantitative descriptions of changes therein. Up to now, baseline values for interhemispheric burst synchrony in healthy preterm infants are not well established. Though various, slightly different methods enable manual estimation of interhemispheric burst synchrony, this estimation is a laborious task and subject to error. We developed an algorithm that enabled automated calculation of interhemispheric EEG burst synchrony. Using the algorithm we demonstrated a high degree of interhemispheric burst synchrony in healthy preterm infants (28-36 weeks postmenstrual age) that was not related to postmenstrual age. This finding indicates the early fetal presence of functional cortico-cortical (e.g. corpus callosum) and thalamocortical connections. The algorithm facilitates further quantitative investigation of interhemispheric burst synchrony in HIE.

Baroreceptor reflex associated cardiovascular fluctuations were assessed as marker for autonomic function. The baroreceptor reflex is a regulatory mechanism that maintains arterial blood pressure at a relatively constant level. Disruption of baroreceptor reflex function exposes the brain to periods of hypertension and hypotension. Disruption of baroreceptor reflex function thus threatens the still maturing vasculature of the infant brain and limits sufficient cerebral perfusion. HIE clearly attenuated operation of the baroreceptor reflex. However, baroreceptor reflex function was preserved after stem cell treatment. Hence the baroreceptor reflex may be used as a marker for identifying HIE treatment effects.