Next genetration neuromonotoring

SCIENTIFIC AND SOCIETAL IMPLICATIONS

The main incentive of this thesis is the unmet need for an improved assessment, therapy, and clinical outcome in a critically ill patient with a focus on traumatic brain injury patients. From the clinical side, this need is exemplified by the limited availability of information and therapies to treat or protect the injured brain. In addition, families and the clinical team have uncertainties about the clinical outcome. This goes along with (prolonged) intensive care unit (ICU) stay as well as remaining post-ICU disabilities and consequently high social and financial costs.

Professionals working in the ICU care for patients who require continuous monitoring and treatments to maximize the chance of surviving critical illness. An organ like the heart can be supported by machines and/or medication. The brain function is usually assessed by bedside questions and tests for the 'awake' patient. In other words, their behavior is assessed. However, in the ICU, most patients with acute brain injuries are comatose or sedated, so a continuous behavioral assessment of the brain functioning is not possible. Alternatively, the brain can be monitored using signal monitoring devices inserted into the brain (invasive) or devices that do not require insertion through the skull (non-invasive monitoring). This monitoring information could contribute to the development of new therapies or outcome prediction of brain-injured patients.

Unique for the brain as an organ is that an incompressible skull encloses it. After a trauma, such as a fall on the head, the brain of the patient can swell after which the volume increases and the pressure in the skull increases. Too high-pressure results in tissue compression and eventually loss of brain tissue. The pressure is invasively measured via a meter inserted through a hole in the skull. Not only is the pressure in the skull relevant, but also the pressure to supply the tissue with sufficient blood, called cerebral perfusion pressure. Up to now, patients are treated according to the critical thresholds based on group values i.e., 'one size fits all' principle. However, there is an increasing interest in changing the treatment from this concept towards a therapy based on the individual patient. This is called precision medicine.

In our research, we study examples of precision medicine by performing neuromonitoring measurements in more than 100 patients with mainly a brain injury after trauma, also called traumatic brain injury (TBI). The patients received either invasive intracranial pressure monitoring or non-invasive monitoring by applying a simple sensor on the forehead. Both devices can measure a complex mechanism in the brain that regulates cerebral perfusion

pressure. This mechanism, called cerebral autoregulation, is often impaired in patients with TBI but also in some other critically ill patients.

With our research, we focus on the feasibility and safety of an individualized treatment that aims to optimize the perfusion pressure by using information from this complex mechanism. Our research results show that it is possible to start an individual treatment driven by neuromonitoring data. Although the current patients do not profit from these results, one of the next steps is to study if the therapy results in an improvement in outcome in patients with TBI. When these results are promising, the therapy will be integrated in treatment guidelines for TBI patients.

For the general ICU population is only non-invasive monitoring available, whereas we are for these patients interested in information from this complex mechanism too. Therefore, we used the non-invasive sensor to evaluate the degree of impairment of this mechanism in a typical critically ill ICU population. Our results show that the mechanism is more often impaired in patients who passed away within six months after their acute illness. By using a non-invasive assessment method for the general ICU population, more information from the brain becomes available. For future patients, this might contribute to individualizing care and/or decision making and finally outcome improvements.

Patients who discharged from the ICU alive are often not yet fully recovered but instead require a long recovery phase. That is why an important question is what the outcome is after an ICU stay. In our last research, we focused on such clinical outcome. However, outcome measures are often only rough measures. For example, patients with a favorable outcome (able to work and take care of themselves) versus patients with an unfavorable outcome (unable to work and unable to take care of themselves). Of course, there are also patients with a range of milder symptoms and impairments such as fatigue, concentration problems etc. which may be very disabling to people in their daily lives. These outcome measures generally receive only minor attention in an acute intensive care perspective. We obtained a detailed insight into the long-term outcome of ICU patients that included a range of symptoms and impairments such as fatigue and concentration problems. Therefore, these surviving TBI patients were interviewed by a neuropsychologist at home. More than half of the 52 patients suffered from cognitive impairments such as memory problems, fatigue and/or restrictions in participating domains (mostly work or education and going out). Also, about a third of the caregivers experienced a high workload by taking care of the former patients with TBI. Although the current patients do not profit from our results, the societal implications of our results

are that a detailed outcome assessment of the patients could contribute to the evaluation of new individualized therapies that are developed for ICU patients.

We started this paragraph with the need for therapies and the need to obtain insight into brain functioning. Our research questions contributed to solutions for this need. However, we also showed in our studies that measuring signals in an ICU environment can be challenging as the signals can be disturbed by several external or internal factors. For example, we observed in some data an unwanted frequent in- and decrease in the pressure signals. This simple observation resulted from the bed mattress that in- and deflated to overcome bedsores. Indeed, we actually often do not fully understand the exact meaning of the signals due to e.g., heterogeneity in injury location and injury severity. This is even further complicated when invasive, non-invasive, local, and global signals are combined.

On the other hand, when we want to obtain information from the brain's mechanism that regulates the cerebral perfusion pressure, we need to challenge the mechanism. A translation to a more daily example is when we want to evaluate somebodies hearing. We need a sound (is challenge) to test the system (hearing) However, in the ICU challenging the cerebral autoregulation mechanism is difficult as patients are sedated and comatose. Therefore, often no challenge is performed. In this thesis, we applied an innovative methodology – adapted from an animal study - by turning on the 'sigh' function on the ventilator. A 'sigh' results in a change in the blood pressure and hence a challenge for the brain's mechanism to respond to.

Throughout our research we show a dual meaning of precision medicine. On the one hand, we aim for individual therapies and a refined clinical outcome. However, on the other hand, we show the complexity of monitoring as external factors can adversely affect the signals and we show a way to improve measurements, so precision defined by the Cambridge dictionary as: 'the qualities of being careful and accurate'. Simply said, it is a matter of time and quality. Improving measurements might delay the introduction of new therapies for clinical use but continuing research towards the effectiveness of new therapies limits the ability to first improve the quality of the measurements. In other words, do we aim for the best or for the fastest way to improve outcome (prediction) for neurocritical care patients?