Aus der Klinik für Anästhesiologie mit Schwerpunkt operativer Intensivmedizin
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

# Intensive Care Unit-acquired weakness and its relationship with glycemic parameters

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Rudolf Mörgeli
aus Niquelandia, Brasilien

Datum der Promotion: 04.03.2022

# Table of Contents

# 1 Abstracts

Intensive Care Unit (ICU)-acquired weakness (ICUAW) is a serious complication of intensive care treatment, leading to severe muscle weakness and failure to wean. ICUAW is the clinical presentation of distinct underlying pathologies, namely Critical Illness Myopathy (CIM), Critical Illness Polyneuropathy (CIP), or a combination of both syndromes (CIM/CIP). CIM is the most common condition, developing first and predisposing the development of CIP. A clinical differentiation is not possible, but electrophysiological evaluations, even in unresponsive patients, can detect anomalies associated with these entities and predict ICUAW. Our analysis (Publication #1) demonstrated that an early differentiation is associated with outcome one year after discharge, in that patients with an isolated CIM were more likely to recover completely, in contrast to those with concurrent neuropathy.

Hyperglycemia has often been described as a risk factor for the development of CIM. Nevertheless, guideline recommendations instruct us to accept a moderate hyperglycemia to reduce the occurrence of hypoglycemia- which is independently associated with higher mortality. The underlying issue is that glucose management in the ICU is primarily intermittent, and our inability to promptly identify dangerous glucose fluctuations has forced us to hazard the consequences of hyperglycemia, including higher rates of CIM. Continuous glucose monitoring systems are promising, as they would alert clinicians to dangerous glucose levels in real-time. The accuracy and reliability of such systems, however, are major prerequisites for their implementation in the ICU. An analysis (Publication #2) of such a device shows that their performance remains inadequate, and that currently they do not meet the necessary requirements to guarantee patient safety in the ICU.

In addition to hypo- and hyperglycemia, glucose variability has emerged as a third relevant domain, having an independent association with ICU mortality. The mechanism has not been sufficiently explained, and an association with muscle pathologies is likely, but ultimately unknown. Our investigation (Publication #3) aimed to find an association between glucose variability and early electrophysiological signs of CIM. As CIM is known to develop within the first days of critical illness, glucose readings were analyzed using several variability scores throughout the first week of

ICU treatment. An association was observed in all metrics investigated. Significant dysglycemia, however, was not observed in the first days, concurrent with the development of CIM, but only late in the first week, suggesting that myopathy may precede glycemic dysregulation in ICU patients.

## Zusammenfassung

Die Intensive Care Unit-acquired weakness (ICUAW) ist eine ernste Komplikation der Intensivbehandlung, die zu schwerer Muskelschwäche und Weaningversagen führen kann. ICUAW ist die klinische Präsentation verschiedener zugrundeliegender Pathologien, dazu gehören die Critical Illness Myopathy (CIM), Critical Illness Polyneuropathy (CIP) oder eine Kombination beider Syndrome (CIM/CIP). Die CIM ist von den beiden die häufigere Erkrankung. Sie entwickelt sich zuerst und stellt, wenn sie aufgetreten ist, eine Prädispositon für die Entwicklung der CIP dar. Eine klinische Differenzierung ist nicht möglich, aber elektrophysiologische Untersuchungen, auch bei nicht ansprechbaren Patienten, können Merkmale der verschiedenen Entitäten erkennen und die Entwicklung von ICUAW vorhersagen. Unsere Analyse (Publikation #1) zeigte, dass sogar eine frühe Differenzierung mit dem Outcome ein Jahr nach Entlassung assoziiert ist. Patienten mit einer isolierten CIM erholten sich mit höherer Wahrscheinlichkeit vollständig, im Gegensatz zu Patienten mit gleichzeitig vorliegender Neuropathie.

Hyperglykämie wurde oft als Risikofaktor für die Entwicklung einer CIM beschrieben. Dennoch wird in den Leitlinien empfohlen, eine moderate Hyperglykämie zu akzeptieren, um das Auftreten von Hypoglykämien zu reduzieren, welche unabhängig betrachtet bereits mit einer höheren Mortalität verbunden sind. Das zugrundeliegende Problem ist, dass das Glukosemanagement auf der Intensivstation primär intermittierend erfolgt. Da wir aktuell noch nicht in der Lage sind, gefährliche Glukoseschwankungen rechtzeitig zu erkennen, sind wir gezwungen, die Folgen einer Hyperglykämie, einschließlich höherer Raten von CIM, in Kauf zu nehmen. Kontinuierliche Glukoseüberwachungssysteme sind vielversprechend, da sie den Kliniker in Echtzeit auf gefährliche Glukosewerte aufmerksam machen. Die Genauigkeit und Zuverlässigkeit solcher Systeme ist jedoch eine wichtige Voraussetzungen für deren Einsatz auf der Intensivstation. Eine Analyse (Publikation #2) eines solchen Gerätes zeigte, dass ihre Leistung weiterhin ungenügend ist, um die Patientensicherheit auf der Intensivstation zu gewährleisten.

Neben der Hypo- und Hyperglykämie hat sich die Glukosevariabilität als dritter relevanter Bereich herauskristallisiert. Sie weist einen unabhängigen Zusammenhang

mit der Mortalität auf. Wie sie zu einer höheren Sterblichkeit beiträgt, ist nicht ausreichend geklärt, und ein Zusammenhang mit Muskelpathologien ist wahrscheinlich, aber letztlich unbekannt. Unsere Untersuchung (Publikation #3) zielte darauf ab, eine Assoziation zwischen Glukosevariabilität und frühen elektrophysiologischen Zeichen von CIM zu identifizieren. Da bekannt ist, dass sich CIM innerhalb der ersten Tage der kritischen Erkrankung entwickelt, wurden die Glukosemesswerte anhand verschiedener Variabilitäts-Scores während der ersten Woche der Intensivbehandlung analysiert. Bei allen untersuchten Scores wurde ein Zusammenhang beobachtet. Da signifikante Dysglykämien nicht in den ersten Tagen der Intensivbehandlung, beobachtet wurden, sondern erst gegen Ende der ersten Behandlungswoche, geht eine Myopathie einer glykämischen Dysregulation möglicherweise ursächlich voraus.

# 2 Introduction

## 2.1 Intensive Care Unit-acquired Weakness and its underlying Disorders

Intensive care unit (ICU)-acquired weakness (ICUAW) is a common and serious complication of intensive care treatment, leading to a severe loss of skeletal muscle mass and strength. Although nearly all patients in the ICU setting experience some level of weakness due to immobility and pharmacological intervention, ICUAW has no identifiable causes other than nonspecific inflammation [1]. This weakness is generalized, can affect both limb and respiratory muscles, and displays major differences to the well-known disuse muscle atrophy [2–4], as the muscular function is not impaired simply by a reduction in mass, but also by changes in muscular structure and physiology. The impact of this condition has been increasingly recognized, as it promotes metabolic disorders, organ failure, failure to wean from mechanical ventilation, prolonged hospital stays, and increased mortality [5–8]. Besides the significant financial burden to health care systems [5,9], the condition has a severe effect on the quality of life of ICU survivors [10].

ICUAW is a clinical manifestation of distinct underlying disorders, namely Critical Illness Myopathy (CIM), Critical Illness Polyneuropathy (CIP), or Critical Illness Myopolyneuropathy (CIM/CIP), which is a combination of both syndromes [11,12].

## 2.2 Diagnosis and Prognosis

Provided the patient is awake and cooperative, the ICUAW diagnosis can be achieved clinically using the Medical Research Council (MRC) score, which grades muscle strength between 0 (complete paralysis) and 5 (normal muscle strength) [4,6]. In this case, failure to wean or problems with mobilization are often the first indications of the condition [1,9].

Alternatively, electrophysiological testing can detect neuromuscular abnormalities in unconscious patients, long before the assessment of an MRC score becomes viable [13–16]. While conventional nerve conduction studies can detect CIP, traditional electromyogram provide only non-specific results that cannot be used to differentiate the conditions, such as spontaneous activity in the form of positive sharp waves and fibrillation potentials [13,14]. Extended testing is required to detect signs of CIM or the combination of both entities (CIM/CIP), which is achieved by measuring the amplitude

of the compound muscle action potentials (CMAP) generated by direct muscle evoked stimulation (dmCMAP). Direct muscle stimulation assesses membrane excitability by using needle electrodes to stimulate the muscle, where a dmCMAP amplitude < 3 mV is considered abnormal and indicative of CIM. Nevertheless, it is important to note that this does not always correspond to a clinical ICUAW diagnosis [13,15]. As these tests are not standard in the ICU setting, the subclassification of ICUAW is often disregarded by clinicians [17].

Following discharge, ICU survivors suffering from ICUAW have an uncertain prognosis, with some recovering within weeks while other face years of disability [18,19]. Although evidence suggests that CIM patients tend to recover earlier [17,20], it is unknown whether early electrophysiological differentiation is associated with long-term outcome.

## 2.3 Risk Factors

As the current literature describes specific populations and varying diagnostic methods, general incidence levels for ICUAW range from 25 to 83% [21]. While the specific pathomechanisms of ICUAW are still poorly understood, a range of risk factors has been identified. The most significant risk factors are the manifestation of a sepsis or a Systemic Inflammatory Response Syndrome (SIRS), either of which result in the development of ICUAW in nearly 100% of the cases [22], as well as patients suffering from multi-organ failure [5,23]. Furthermore, the mechanical ventilation over 7 days represents another major risk, where at least 25% of patients proceed to acquire the condition [6]. A systematic review by Stevens et al reported that nearly 50% of all adult ICU patients with any of these risk factors will develop ICUAW [24].

Though additional risk factors have been recognized, further studies are required to corroborate their significance in the etiology of ICUAW. Chief among these factors is an impaired glucose metabolism, which is frequently encountered in the ICU setting in the form of uncontrolled hyperglycemia and/or insulin resistance [25–27].

## 2.4 Glycemic Control in the ICU

There have been reports about the beneficial effects of strict glycemic control (SGC) on the incidence of ICUAW, length of mechanical ventilation, ICU stay, and mortality [28–30]. SGC was designed to control hyperglycemia via intensive insulin therapy (IIT),

maintaining blood glucose levels within a target range of 80-110 mg/dL. This is a sound strategy, as uncontrolled hyperglycemia has been linked to higher incidences of ICUAW and mortality rates [31,32]. Similar studies, however, were unable to replicate these findings [33–37], possibly due to differing diagnostic methods. An important concern is that SGC is not without danger, as reflected by strong recommendations from the American College of Physicians to abstain from the therapy in the ICU setting [37]. SGC with IIT excessively increases the incidence of hypoglycemic episodes, and even mild episodes have been directly linked to higher mortality rates [37–41]. This impasse stems from the fact that glucose management in the ICU is primarily intermittent, and the inability to promptly identify and correct blood sugar fluctuations has forced clinicians to hazard the consequences of hyperglycemia, including higher rates of neuromuscular complications. Continuous glucose management (CGM) systems could potentially provide a solution to this predicament [42,43]. Real-time glucose readings would offer clinicians the ability to recognize dangerous glucose levels without delay and intervene accordingly. The accuracy and reliability of such systems, however, are major prerequisites for their implementation in the ICU setting [43], and trials have so far been inconsistent [44–46].

### 2.5 Glycemic Variability

Besides hyperglycemia and hypoglycemia, glucose variability emerged as a third critical domain of glycemic control. Promoted by Krinsley et al, the analysis of blood glucose fluctuations became a novel parameter, being independently linked to mortality in the ICU [47]. Reducing variability may provide significant benefits, irrespective of mean blood glucose values [39,47–50]. While standard deviation (SD) is the most widely used measurement, there is a lack of standardization in the assessment of glucose variability, with differing scores emphasizing the time and/or order of the readings. It is important to note that not all scores are associated with mortality [43,49,51–53]. By adjusting IIT to a higher blood glucose range, reducing variability could offer the protective effects of a SGC while avoiding recurring hypoglycemic episodes. Further research is needed to assess the potential of glucose variability measurements, as well as suitable metrics for possible associations. This new parameter has thus far been neglected in ICUAW studies.

## 2.6 Study Objectives

### 2.6.1 CIM & CIP Prognosis Study (Publication # 1)

The primary goal of this study was to evaluate whether differential diagnosis of CIM and CIP during the early course of critical illness could predict long-term outcomes [54].

### 2.6.2 Continuous Glucose Monitoring Study (Publication # 2)

This study aimed to evaluate the accuracy and reliability of a minimally-invasive interstitial device, Medtronic's Sentrino® CGM, in the critical care setting. Feasibility of their use and nurse acceptance were also investigated [55].

### 2.6.3 CIM and Glycemic Variability Study (Publication # 3)

The primary aim of this clinical study is to evaluate the relationship between blood glucose variability and the incidence of CIM [56].

# 3 Materials and Methods

## 3.1 CIM & CIP Prognosis Study Protocol

### 3.1.1 Setting & Patient Selection

This prospective observational study recruited adult patients admitted to a surgical ICU of the Campus Virchow Klinikum, Charité Universitätsmedizin Berlin between October 2007 and April 2009. Inclusion criteria were defined as SAPS-II ≥ 20 at admission and mechanical ventilation > 3 days, whereas patients with preexisting neuromuscular conditions, as well as cerebral or spinal injuries were excluded [54]. The project was reviewed and approved by Charité Ethics Commission (EA2/061/06) and in accordance with the Declaration of Helsinki, written informed consent was obtained from all study participants or their respective legal proxies.

### 3.1.2 Outcome Variables & Assessments

The patients were subject to electrophysiological examinations during the early course of critical illness, allowing differentiation among CIM, CIP and CIM/CIP. Using a 2-channel Medtronic Keypoint® Portable, the test battery assessed nerve compound action potential (neCMAP), and sensory nerve action potential (SNAP), while quantitative electromyography was used to assess quantified motor unit action potentials (Q-MUAP) and dmCMAP. A dmCMAP under 3 mV or reduced Q-MUAP duration were deemed indicative of CIM, while reduced SNAP amplitudes were regarded as indicative of CIP [13,15,57,58]. Abnormal spontaneous activity or reduced neCMAP amplitudes can occur in both conditions and were deemed unspecific if SNAP and dmCMAP were normal [54]. Patients with normal results in all tests were assigned to a control group. Richmond Agitation and Sedation (RASS) scores were documented daily, whereas a score ≤ -1 was considered a marker for immobility. The maximum Sepsis-related Organ Failure Assessment (SOFA) score was documented as a marker for severity of illness. Prior to ICU discharge, an assessment of muscle strength according to MRC scores took place. Here, ICUAW is diagnosed when the cumulative score of 12 muscles/muscle groups (bilaterally: wrist extension, elbow flexion, shoulder abduction, dorsiflexion of the foot, knee extension, and hip flexion) fails to reach 48, or if the mean score among testable muscles fails to reach a score of 4 [4].

Follow-up visits took place at 2 weeks, 1, 2, 3, 6 and 12 months after discharge, evaluating subjective functional capacity using a questionnaire ranking their physical abilities from 0 (not able to stand alone) to 5 (full recovery, no limitations), MRC scores and full electrophysiological testing [54].

### 3.1.3 Statistical Analyses

The study was exploratory, so that no group size analysis or alpha adjustment was done. Categorical data was presented as median with interquartile ranges, and ordinal and binary data was shown as frequencies and percentages. Differences among groups were deemed statistically significant if a p-value was below 0.05. Mann-Whitney-U tests were used for independent samples with 2 variables, and Kruskal-Wallis test for 3 or more variables. Qualitative data was examined using the Exact Fischer's Test. Descriptive analyses and statistical tests were carried out with software from IBM SPSS Statistics (version 19, SPSS Inc., Chicago, Illinois, USA).

## 3.2 Continuous Glucose Monitoring Study Protocol

### 3.2.1 Setting & Patient Selection

This prospective study took place in 2 interdisciplinary ICUs of the Campus Virchow Klinikum, Charité Universitätsmedizin Berlin between December 2014 and June 2015. Adult patients with an expected ICU stay of at least 72 hours were recruited, excluding pregnant women and terminal patients. The project was reviewed and approved by Charité Ethics Commission (EA2/095/14) and in accordance with the Declaration of Helsinki, written informed consent was obtained from all study participants or their respective legal proxies.

### 3.2.2 Outcome Variables & Assessments

Participants had a Medtronic Sentrino® CGM device inserted into the subcutaneous tissue of their upper leg. The device provides glucose readings every minute for up to 72 hours, which were accompanied by values provided by intermittent blood gas analyses (BGA) every 2 to 4 hours (Radiometer ABL FLEX 800, Copenhagen, Denmark). The target glucose was set to 80-149 mg/dL, and although staff were instructed to observe the displayed trends, corroboration of values with BGA was

required prior to any treatment adjustment [55]. All values were automatically recorded in the electronic patient file. Calibration readings were conducted by study staff every 8 hours, and these readings were excluded from the analyses. In order to complete a suitable accuracy evaluation, at least 12 comparative readings were required, corresponding to 48 hours of monitoring [55].

Outcome variables included [55]:

- *Accuracy*: percentage of readings within an acceptable margin of reference standards (12.5% or ± 10 mg/dL for readings under 100 mg/dL), as well as the mean absolute relative difference (MARD) between sensor and reference values, whereas a MARD < 14% is desirable (values based on published consensus recommendations [43]). Likely confounders were investigated, including SIRS, vasopressors, history of diabetes mellitus, arterial pO2, temperature, lactate, pH values, hemoglobin, potassium, and SOFA scores.
- *Reliability*: frequency and duration of device-related data gaps. The consensus recommendations require a continuous display of data for > 95% of the sensor lifetime (in this case, 72 hours) and data gaps of no more than 30 minutes [43].
- *Feasibility*: time required for insertion, rate of accidental catheter displacement, non-device-related interruptions, such as inadvertent disconnection and delays in calibration by personnel, as well as rate of adverse events (i.e., bleeding or infection at insertion site).
- *Nurse acceptance*: questionnaire investigation subjective advantages and disadvantages of the device, along with a personal recommendation for implementation (yes or no)
- *Longitudinal intra-individual analyses*: glycemic control was analyzed for 72 hours prior, during, and after use of the device.
- *Parallel intra-individual analyses*: glycemic control was analyzed based on values from BGA and CGM device with acceptable accuracy (MARD < 14%)

### 3.2.3 Statistical Analyses

Categorical data was presented as median with interquartile ranges, and ordinal and binary data was shown as frequencies and percentages. Bland-Altman plot [59], Clarke and Surveillance Error-Grids were used to illustrate clinical accuracy, and non-parametric tests were used, whereas differences were deemed statistically significant if a p-values were below 0.05. Descriptive analyses and statistical tests were carried

out with software from IBM SPSS Statistics (version 21, SPSS Inc., Chicago, Illinois, USA), Microsoft Excel© 2010, and R 3.2.0 (R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria) [55].

## 3.3 CIM and Glucose Variability Study Protocol

### 3.3.1 Setting & Patient Selection

This retrospective analysis compiled data from two prospective observational studies [14,31], and the control group of an interventional project investigating interventions to reduce the occurrence of ICUAW [60]. All projects were reviewed and approved by Charité Ethics Commission (EA181/2002, EA2/061/06, EA2/041/10). In accordance with the Declaration of Helsinki, written informed consent was obtained from all study participants or their respective legal proxies. All studies took place in the same setting (intensive care units of the Campus Virchow Klinikum, Charité Universitätsmedizin Berlin), and although inclusion and exclusion criteria of the three trials were similar, a retrospective adjustment was necessary to eliminate known dysglycemia confounders (e.g. diabetes, obesity). Ultimately, the analysis included adult patients with an initial SOFA ≥ 8 that were mechanically ventilated, excluding those with more than 72h of ventilation prior to screening, pre-existing neuromuscular disorders, diabetes mellitus, BMI > 35 kg/m2, terminal patients, and pregnant women [56].

### 3.3.2 Outcome Variables & Assessments

The primary outcome of this exploratory analysis was differences in glycemic variability observed in patients with and without electrophysiological signs of CIM during the first week of ICU treatment. This period was set to encompass the period where CIM develops [15,61]. Since glucose variability is a relatively new parameter, there is no gold standard for its assessment, and differing formulas have been used to assess specific outcomes. As this is the first attempt to find an association between glucose variability and CIM, several scores were investigated according to the suitability of the available data, including standard deviation (SD) [47], coefficient of variation (CV) [62], mean absolute glucose (MAG) [49], mean amplitude of glycemic excursions (MAGE) [63], and means of daily differences (MODD) [64].

For each patient, blood glucose readings were collected four times daily using a blood gas analyzer (Radiometer ABL FLEX 600/800, Copenhagen, Denmark). The readings took place at regular intervals, i.e. 0200hrs, 0800hrs, 1400hrs, and 2000hrs (or closest match) for the first week of ICU treatment. Although the glucose target range during the ICU stay was conservatively set at 100 to 150 mg/dL, a range of 70 to 179 mg/dL was retrospectively defined as acceptable, in light of guideline recommendations to avoid both hypoglycemia or severe hyperglycemia [43]. Standard glycemic parameters (mean, minimum and maximum) and time on target range were also described, along with insulin and caloric requirements during that period [56].

All patients received specific electrophysiological CIM diagnostics during the first week of their ICU stay, which were performed by a trained neurologist. With the exception of Q-MUAP measurements, which were not performed in this study, all electrophysiological tests were analogous to those previously described in Section 3.1.2, including dmCMAP analyses with a cutoff of < 3 mV as a predictor of CIM [12,15,54]. When possible, patients received a clinical assessment with MRC to confirm diagnosis as soon as they were deemed sufficiently awake.

### 3.3.3 Statistical Analyses

A sample size calculation powered to detect a one standard deviation among groups through inference of means was performed, as Krinsley [47] could show that such a difference already impacted mortality rates. Hill [65] defined mean standard deviation in healthy volunteers to be 27.0 ± 12.6, so that a 2-sided test ($\alpha = 0.05$, power = 0.8) yielded 16 patients per group. Nonetheless, this analysis is to be seen strictly as exploratory. Categorical data was presented as mean standard deviation for normally distributed data, otherwise as median with interquartile ranges. Ordinal and binary data was shown as frequencies and percentages. Differences among groups were deemed statistically significant if a p-value was below 0.05. Mann-Whitney-U tests were used for independent samples with 2 variables. Qualitative data was examined using the Exact Fischer's Test. Descriptive analyses and statistical tests were carried out with software from IBM SPSS Statistics (version 24, SPSS Inc., Chicago, Illinois, USA).

# 4 Results

## 4.1 CIM & CIP Prognosis Study Results

### 4.1.1 Participants & Descriptive Data

The study examined 26 patients 12 months after ICU discharge, including 7 controls, 8 CIM patients, and 11 patients with CIM/CIP, according to Figure 1 [54]. No group differences were observed in terms of age, gender, BMI, or MRC at discharge. Compared to controls, CIM and CIM/CIP patients more frequently suffered from sepsis at admission ($p = 0.016$), and had higher initial SAPS-II and maximum SOFA scores throughout the stay ($p = 0.033$ and $p = 0.002$, respectively). CIM and CIP/CIM patients also had longer periods of immobility, defined as a RASS ≤ -1 ($p = 0.002$), and longer ICU stays ($p = 0.002$). Detailed patient characteristics is shown in Table 1 [54].

### 4.1.2 Outcome Data and Main Results

One year after ICU discharge, subjective physical capacity was still reduced in 12 patients. Of these, 4 were initially diagnosed with CIM (50%) and 7 with CIM/CIP (63.6%), while all control patients recovered fully. Based on electrophysiological examinations, 1 CIM patient (12.5%) and 5 CIP/CIM patients (45.5%) still exhibited abnormal electrophysiology along with physical impairment. All 5 CIP/CIM patients showed only mild to moderate reduction in recruitment patterns while exhibiting a persisting polyneuropathy, and 3 of them suffered from neuropathic pain. Patients reporting residual deficits continued to have lower MRC scores 12 months after discharge (see Supplemental Table 1 [54]), and 4 of the 5 CIM/CIP patients still required assistance with daily activities. Accordingly, subjective physical capacity showed that the recovery of patients with an early CIM or CIM/CIP diagnosis was delayed in comparison to controls (see Figure 2 [54]).

A univariate analysis comparing patients with and without a full recovery confirmed that an early CIM/CIP diagnosis was significantly associated with long-term disability ($p = 0.021$). Other early factors associated with long-term disability included advanced age ($p = 0.009$), higher insulin requirements during the first 2 weeks of ICU treatment ($p = 0.033$), sepsis on admission ($p = 0.001$) and higher SAPS-II scores ($p = 0.013$). Throughout the ICU stay, higher SOFA scores ($p = 0.015$), longer periods of immobilization ($p = 0.002$) and at the ICU ($p = 0.002$), as well as lower MRC scores at

discharge (p = 0.001) were also associated with long-term disability. Additional details are available in Table 2 [54].

## 4.2 Continuous Glucose Monitoring Study Results

### 4.2.1 Participants & Descriptive Data

Of 20 patients enrolled, 19 could complete the trial with the minimum number of readings (see Figure 1, [55]). A total of 68655 readings were collected by the sensors, with 532 corresponding BGA readings. The majority of BGA readings (89.3%) were arterial, no significant differences in accuracy were detected when compared to venous readings. Patient characteristics are shown in Table 1 [55], and key glycemic variables and events are shown in Table 2 [55].

### 4.2.2 Outcome Data and Main Results

*Accuracy*

Only 60.3% of the data was in an acceptable range, in comparison to the recommended 98%, and MARD was found to be 15.3% (95% CI 13.5-17.0%). Results for the Bland-Altman plot, Clarke and Surveillance Error Grids are shown in Figure 3 [55], showing a mean bias of 0.53 mg/dL (95% limit of agreement +64.6 to -63.5 mg/dL) and potentially dangerous discrepancies between sensor and BGA glucose readings [55]. 104 out of 188 (55.5%) of dysglycemic events recorded by the sensors were incorrect, missing all 3 episodes of hypoglycemia and misclassifying 71 out of 155 (45.8%) of hyperglycemic excursions (see Table S2 [55]).

Sensor accuracy deteriorated with increasing glucose variability (median MARD of 8.8% within 1 SD of mean vs. 24% within 2 SD of mean), as well as in hypoglycemic and severe hyperglycemic range (median MARD of 65.8% and 16%, respectively, vs. 8.8% in euglycemic range). Among possible confounders, the application of vasopressors increased MARD values (18% [95% CI 14-22] with vasopressors vs. 13.7% [95% CI 12.1-15.3] without, p= 0.001), and higher SOFA scores slightly correlated with higher MARD (Spearman-Rho k 0.088, p= 0.043). No other confounders were found to be significant [55].

*Reliability*

The sensors properly displayed data for an average of 32.5h (84.8%) of the monitoring time. The majority of data gaps were very brief, with 43.9% <15 min, while 33.5% were over the recommended 30 minutes. Detailed results are shown in Table 3 [55].

*Feasibility*

The insertion time of the sensor was under 10 minutes. Only 10 sensors completed the expected 72h, while 21 sensors were removed prematurely, 15 of which due to device-related reasons (7 accidentally, 8 due to device failure). Non-device-related data gaps accounted for 7.4% of gaps in monitoring time. No infections took place, and only 4 patients (20%) developed minor bleeding at the insertion site. Detailed results are shown in Table 3 [55].

*Nurse acceptance*

Only 43 (34%) of the distributed questionnaires were returned, and 79.1% of nurses did not consider the device to be beneficial and were opposed to its implementation. Main disadvantages listed included additional device (23.3%) and inadequate alarm performance (23.3%) [55].

*Longitudinal intra-individual analyses*

There were no significant improvements in glycemic control in 9 consecutive days (n = 10). Details on Table 4 [55].

*Parallel intra-individual analyses*

When the device was working properly (MARD < 14%), sensor devices identified hypo- and hyperglycemic events significantly more often than intermittent measurements. Details on Table 4 [55].

## 4.3 Glycemic Variability and its Association with CIM

### 4.3.1 Participants & Descriptive Data

74 patients could be included in the analysis, and 50 of them showed electrophysiological abnormalities associated with CIM. At enrollment, patients in the CIM group were significantly older (53.5 vs 42.5 years old), and had more often a

sepsis/acute respiratory distress syndrome (ARDS) diagnosis (60% vs 21%). No group differences were observed in regard to gender, body-mass index, or severity of disease (SOFA, SAPS II, APACHE). Detailed patient characteristics is shown in Table 1 [56].

### 4.3.2 Outcome Data and Main Results

CIM and non-CIM patients were kept inside the glucose target range for the majority of the time (91.1% vs 91.9%, respectively). In the cumulative analysis (day 1 through 7), no differences between CIM and non-CIM groups were observed in relation to mean, maximum, or minimum blood glucose levels, nor in insulin or caloric requirements [56]. Furthermore, no significant variations in the cumulative assessment of the analyzed glycemic variability measurements were detected.

Daily analyses revealed no significant differences in glycemic parameters until the 5$^{th}$ day of ICU treatments. Starting then, CIM patients exhibited the following significant changes in glucose parameters when compared to non-CIM patients [56]:

- Day 5: higher maximum glucose ($p = 0.015$), SD ($p = 0.011$), CV ($p = 0.013$), MAG ($p = 0.003$), MAGE ($p = 0.007$), and less time on target ($p = 0.017$)
- Day 6: higher mean glucose ($p = 0.042$) and MODD ($p = 0.041$)
- Day 7: higher maximum glucose ($p = 0.021$), SD ($p = 0.006$), CV ($p = 0.008$), MAG ($p = 0.003$), and less time on target ($p = 0.042$)

As expected, CIM patients had longer ICU stays (25 vs 21 days, $p = 0.011$), delayed regain of consciousness (day 13 vs 9 $p = 0.047$), and higher mortality rates (26% vs 4% $p = 0.025$). Details are listed in supplemental table 1 [56]. Ultimately, 56 patients were sufficiently awake to be assessed via MRC, and 5 of them did not develop ICUAW despite pathological electrophysiological findinds.

# 5 Discussion

## 5.1 Early Electrophysiological Differentiation and Prognoses

### 5.1.1 Interpretation

This explorative analysis demonstrates that an early electrophysiological examination indicative of CIM or CIM/CIP is associated with worse long-term outcomes, and that physical capacity of CIP/CIM patients was worse than that of with CIM alone after one year. Contrary to CIP, CIM exhibits a well-documented reduction in membrane excitability [14,15], and this study analyses SNAP to confirm nerve involvement, as well as Q-MUAP and dmCMAP to evaluate myopathy [16,66]. Q-MUAP duration was no longer abnormally reduced in the follow-up period, so the dmCMAP examination was critical for diagnosing an ongoing myopathy, supporting the notion that an early assessment might be more accurate and relevant to the prognosis.

Although a combination of polyneuropathy and myopathy is frequently observed, an isolated polyneuropathy is rare [14,67], and none was observed in this cohort. The two previous studies analyzing long-term patient outcome in patients with CIM and CIP [17,20] did not use direct muscle stimulation, and performed examinations at discharge or later, at a neurorehabilitation facility. The result was a far greater proportion of patients diagnosed with an isolated CIP, although patients likely suffered from a combined pathology. Despite discrepancies regarding incidences, these results agree that recovery of CIM patients is nearly complete one year after discharge, while only 63-75% of CIP patients and 50-66% of CIM/CIP patients can recover in the same period. It is important to note that on all 5 patients with ongoing CIM/CIP one year after admission, all displayed only mild to moderate reduction in recruitment patterns, indicating that neuropathy was the leading cause of the persisting weakness [54]. In addition, persisting spontaneous activity and reduced dmCMAP suggest that the muscle membrane in CIM/CIP patients remains unstable and depolarized, likely due to denervation [68,69], ultimately preventing recovery.

In this cohort, immobility, length of ICU stay, and severity of illness were associated with poorer long-term outcomes, which is in line with other reports [70,71].

### 5.1.2 Limitations

Among the limitations of this work is the single ICU setting and the small group sizes, which is responsible for the complete lack of CIP-only patients. Also, the subjective functional capacity assessments were based on patient self-reports.

### 5.1.3 Conclusions

In conclusion, patients without neuromuscular involvement or isolated CIM have a better prognosis than patients with CIP/CIM, and early differential assessment can help provide a more reliable prognosis [54].

## 5.2 Accuracy, Reliability, Feasibility and Acceptance of CGM in the ICU

### 5.2.1 Interpretation

The Medtronic Sentrino® CGM device did not meet the minimum accuracy requirements stipulated by the consensus recommendations [43]. Although the Bland-Altman plot showed no systematic bias, the wide 95% limit of agreement (95% of values within 128 mg/dL of reference) indicated a significant random error, which was confirmed by dangerous discrepancies in the Clarke and Surveillance Error Grid, including an event displayed hyperglycemia during actual hypoglycemia [55,59]. Even as a supportive tool, conflicting readings can potentially disrupt and delay treatment decisions.

Glucose diffusion times from plasma to interstitial compartments may play a role, and factors affecting this rate (e.g., microcirculation, blood flow) are frequently altered in critically-ill patients [72]. In line with this hypothesis is the observation that SOFA score and vasopressor use adversely affected sensor accuracy, although there are conflicting reports in this regard [73]. Nevertheless, similarly high inter-sensor variability has been observed when evaluating two sensors concurrently in the same patient [74].

Insufficient GLUT-4 translocation to the sarcolemmal membrane of skeletal muscle cells has been demonstrated in critically ill patients, as well as in adipocytes of septic rats [31,75]. Therefore, it is conceivable that similar processes may impair glucose uptake in subcutaneous tissue, causing significant discrepancies in blood glucose values. If this is the case, calibrating the sensors with blood glucose values, especially

when rapid fluctuations are at play (e.g. increased glucose variability), may indeed amplify discrepancies [55,72].

Reliability was poor, with data gaps exceeding recommended limits and several instances of premature sensor removal or failure. Data gaps may have been enhanced by the fact that calibration and troubleshooting was performed exclusively by study staff. However, nurse acceptance was low without further involvement, and device-related gaps alone already exceeded recommended limits. High rates of accidental removal underline the vulnerability of these devices in the ICU setting, and although familiarization might improve acceptance and feasibility, device-related issues remain unacceptably high [43,55].

The use of a CGM device did not improve intra-individual longitudinal glycemic control, and glycemic variability did not differ significantly from intermittent measurements. It is important to note, however, that the high rate of time on target hampers an improvement analysis [55].

#### 5.2.2 Limitations

An important limitation of this study is the restriction of analyses to point accuracy due to a limited number of BGA readings. Additionally, it cannot be ruled out that BGA readings were subject to delays in clinical routine. The low number of hypoglycemic events in the study limits a robust performance analysis during such events. Nurse acceptance analyses were conducted despite low response rates, which may reflect a bias [55].

#### 5.2.3 Conclusions

In conclusion, the accuracy, reliability, feasibility and nurse acceptance of the Medtronic Sentrino® CGM device are low. As is, the device is not suitable for guiding insulin therapy in the acute phase [55].

### 5.3 Glycemic Variability and its Association with CIM

#### 5.3.1 Interpretation

The goal of this study was to find an association between glycemic variability and the incidence of CIM, the most common ICUAW underlying condition. A positive association was found, at least transiently, in all investigated metrics [56], although

MAG and SD appear to be more sensitive. Since uncontrolled hyperglycemia increases the risk of CIM and augments glucose variability, the fact that both CIM and non-CIM patients were kept inside the target range for over 90% of the time eliminates an important confounder.

There is evidence that CIM develops by the 5$^{th}$ day of critical illness [61], and hyperglycemia is a known risk factor [30,76,77], with evidence suggesting that intensive insulin treatment can limit development of the condition [41,78]. Therefore, if any association was present at all, the expectation was to find high glucose variability early in the week, predisposing the development of CIM. Contrary to these expectations, significant differences were only observed later in the first week of treatment, suggesting that dysglycemia might not be a risk factor, but a consequence of CIM [56].

Excessive glucose can damage tissues by increasing oxidative stress and mitochondrial disruption, which has been shown to cause apoptosis in neurons [79,80]. Hyperglycemia can therefore lead to neuropathy, but as postulated by Callahan [25], glucose uptake in muscles must first be impaired in order to allow hyperglycemia to develop. This is in line with observations that CIM develops earlier and precedes neuropathy in cases of CIM/CIP [15]. Reduced glucose uptake in muscles is likely caused by an impaired GLUT-4 translocation [31], leading to an uncontrolled hyperglycemia that can potentially damage neurons and lead to neuropathy. This supports the notion that myopathy precedes dysglycemia.

### 5.3.2 Limitations

Limitations of this study include significant group differences at admission in regards to age and diagnosis (CIM patients more frequently had sepsis and ARDS). No CGM systems were utilized in this study, as they were previously shown to be inadequate for the acute setting. Nevertheless, this limited the number of variability metrics that could be analyzed. Finally, electrophysiological signs of CIM does not always correspond to a clinical ICUAW diagnosis, and although pathophysiological processes may be at play, these may be clinically unapparent. As not all patients could be assessed with MRC, those with abnormal electrophysiology were kept in their initial group [56].

### 5.3.3 Conclusions

This exploratory analysis found an association between electrophysiological signs of CIM and glycemic dysregulation, including hyperglycemia and higher glucose variability, late in the first week of ICU treatment. This suggests that myopathy preceeds glycemic dysregulation [56].

# 6 References

1. Vincent J-L, Norrenberg M. Intensive care unit-acquired weakness: framing the topic. Crit Care Med. Oktober 2009;37(10 Suppl):S296-298.
2. Eikermann M, Koch G, Gerwig M, Ochterbeck C, Beiderlinden M, Koeppen S, Neuhäuser M, Peters J. Muscle force and fatigue in patients with sepsis and multiorgan failure. Intensive Care Med. Februar 2006;32(2):251–9.
3. Ochala J, Ahlbeck K, Radell PJ, Eriksson LI, Larsson L. Factors underlying the early limb muscle weakness in acute quadriplegic myopathy using an experimental ICU porcine model. PloS One. 2011;6(6):e20876.
4. Latronico N, Rasulo FA. Presentation and management of ICU myopathy and neuropathy. Curr Opin Crit Care. April 2010;16(2):123–7.
5. Bloch S, Polkey MI, Griffiths M, Kemp P. Molecular mechanisms of intensive care unit-acquired weakness. Eur Respir J Off J Eur Soc Clin Respir Physiol. April 2012;39(4):1000–11.
6. De Jonghe B, Sharshar T, Lefaucheur J-P, Authier F-J, Durand-Zaleski I, Boussarsar M, Cerf C, Renaud E, Mesrati F, Carlet J, Raphaël J-C, Outin H, Bastuji-Garin S. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA J Am Med Assoc. 11. Dezember 2002;288(22):2859–67.
7. Judemann K, Lunz D, Zausig YA, Graf BM, Zink W. [Intensive care unit-acquired weakness in the critically ill : critical illness polyneuropathy and critical illness myopathy]. Anaesthesist. Oktober 2011;60(10):887–901.
8. Needham DM. Mobilizing patients in the intensive care unit: improving neuromuscular weakness and physical function. JAMA J Am Med Assoc. 8. Oktober 2008;300(14):1685–90.
9. Schefold JC, Bierbrauer J, Weber-Carstens S. Intensive care unit-acquired weakness (ICUAW) and muscle wasting in critically ill patients with severe sepsis and septic shock. J Cachexia Sarcopenia Muscle. Dezember 2010;1(2):147–57.
10. Fan E. Critical illness neuromyopathy and the role of physical therapy and rehabilitation in critically ill patients. Respir Care. Juni 2012;57(6):933–44; discussion 944-946.
11. Latronico N, Fenzi F, Recupero D, Guarneri B, Tomelleri G, Tonin P, De Maria G, Antonini L, Rizzuto N, Candiani A. Critical illness myopathy and neuropathy. Lancet Lond Engl. 8. Juni 1996;347(9015):1579–82.
12. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol. Oktober 2011;10(10):931–41.
13. Trojaborg W, Weimer LH, Hays AP. Electrophysiologic studies in critical illness associated weakness: myopathy or neuropathy--a reappraisal. Clin Neurophysiol Off J Int Fed Clin Neurophysiol. September 2001;112(9):1586–93.
14. Koch S, Spuler S, Deja M, Bierbrauer J, Dimroth A, Behse F, Spies CD, Wernecke K-D, Weber-Carstens S. Critical illness myopathy is frequent: accompanying neuropathy protracts ICU discharge. J Neurol Neurosurg Psychiatry. März 2011;82(3):287–93.
15. Weber-Carstens S, Koch S, Spuler S, Spies CD, Bubser F, Wernecke KD, Deja M. Nonexcitable muscle membrane predicts intensive care unit-acquired paresis in mechanically ventilated, sedated patients. Crit Care Med. September 2009;37(9):2632–7.
16. Rich MM, Bird SJ, Raps EC, McCluskey LF, Teener JW. Direct muscle stimulation in acute quadriplegic myopathy. Muscle Nerve. Juni 1997;20(6):665–73.
17. Guarneri B, Bertolini G, Latronico N. Long-term outcome in patients with critical illness myopathy or neuropathy: the Italian multicentre CRIMYNE study. J Neurol Neurosurg Psychiatry. Juli 2008;79(7):838–41.
18. Fletcher SN, Kennedy DD, Ghosh IR, Misra VP, Kiff K, Coakley JH, Hinds CJ. Persistent neuromuscular and neurophysiologic abnormalities in long-term survivors of prolonged critical illness. Crit Care Med. April 2003;31(4):1012–6.

19. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, Kudlow P, Cook D, Slutsky AS, Cheung AM. Functional Disability 5 Years after Acute Respiratory Distress Syndrome. N Engl J Med. 7. April 2011;364(14):1293–304.
20. Intiso D, Amoruso L, Zarrelli M, Pazienza L, Basciani M, Grimaldi G, Iarossi A, Di Rienzo F. Long-term functional outcome and health status of patients with critical illness polyneuromyopathy. Acta Neurol Scand. März 2011;123(3):211–9.
21. Shepherd S, Batra A, Lerner DP. Review of Critical Illness Myopathy and Neuropathy. The Neurohospitalist. Januar 2017;7(1):41–8.
22. Tennilä A, Salmi T, Pettilä V, Roine RO, Varpula T, Takkunen O. Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. Intensive Care Med. September 2000;26(9):1360–3.
23. Witt NJ, Zochodne DW, Bolton CF, Grand'Maison F, Wells G, Young GB, Sibbald WJ. Peripheral nerve function in sepsis and multiple organ failure. Chest. Januar 1991;99(1):176–84.
24. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. Intensive Care Med. November 2007;33(11):1876–91.
25. Callahan LA, Supinski GS. Hyperglycemia and acquired weakness in critically ill patients: potential mechanisms. Crit Care. 2009;13(2):125.
26. Preiser J-C, Ichai C, Orban J-C, Groeneveld ABJ. Metabolic response to the stress of critical illness. Br J Anaesth. Dezember 2014;113(6):945–54.
27. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. Crit Care Clin. Januar 2001;17(1):107–24.
28. Hermans G, Schrooten M, Van Damme P, Berends N, Bouckaert B, De Vooght W, Robberecht W, Van den Berghe G. Benefits of intensive insulin therapy on neuromuscular complications in routine daily critical care practice: a retrospective study. Crit Care Lond Engl. 2009;13(1):R5.
29. Fan E, Zanni JM, Dennison CR, Lepre SJ, Needham DM. Critical illness neuromyopathy and muscle weakness in patients in the intensive care unit. AACN Adv Crit Care. September 2009;20(3):243–53.
30. Van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology. 26. April 2005;64(8):1348–53.
31. Weber-Carstens S, Schneider J, Wollersheim T, Assmann A, Bierbrauer J, Marg A, Al Hasani H, Chadt A, Wenzel K, Koch S, Fielitz J, Kleber C, Faust K, Mai K, Spies CD, Luft FC, Boschmann M, Spranger J, Spuler S. Critical Illness Myopathy and GLUT4 - Significance of Insulin and Muscle Contraction. Am J Respir Crit Care Med. 4. Januar 2013;
32. Krinsley JS, Egi M, Kiss A, Devendra AN, Schuetz P, Maurer PM, Schultz MJ, van Hooijdonk RT, Kiyoshi M, Mackenzie IM, Annane D, Stow P, Nasraway SA, Holewinski S, Holzinger U, Preiser J-C, Vincent J-L, Bellomo R. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. Crit Care Lond Engl. 1. März 2013;17(2):R37.
33. COIITSS Study Investigators, Annane D, Cariou A, Maxime V, Azoulay E, D'honneur G, Timsit JF, Cohen Y, Wolf M, Fartoukh M, Adrie C, Santré C, Bollaert PE, Mathonet A, Amathieu R, Tabah A, Clec'h C, Mayaux J, Lejeune J, Chevret S. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. JAMA J Am Med Assoc. 27. Januar 2010;303(4):341–8.
34. Arabi YM, Dabbagh OC, Tamim HM, Al-Shimemeri AA, Memish ZA, Haddad SH, Syed SJ, Giridhar HR, Rishu AH, Al-Daker MO, Kahoul SH, Britts RJ, Sakkijha MH. Intensive

versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. Crit Care Med. Dezember 2008;36(12):3190–7.
35. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY-S, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 26. März 2009;360(13):1283–97.
36. Wieske L, Harmsen RE, Schultz MJ, Horn J. Is critical illness neuromyopathy and duration of mechanical ventilation decreased by strict glucose control? Neurocrit Care. Juni 2011;14(3):475–81.
37. Qaseem A, Humphrey LL, Chou R, Snow V, Shekelle P, Clinical Guidelines Committee of the American College of Physicians. Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 15. Februar 2011;154(4):260–7.
38. Krinsley JS, Schultz MJ, Spronk PE, Harmsen RE, van Braam Houckgeest F, van der Sluijs JP, Mélot C, Preiser JC. Mild hypoglycemia is independently associated with increased mortality in the critically ill. Crit Care Lond Engl. 2011;15(4):R173.
39. Meyfroidt G, Keenan DM, Wang X, Wouters PJ, Veldhuis JD, Van den Berghe G. Dynamic characteristics of blood glucose time series during the course of critical illness: effects of intensive insulin therapy and relative association with mortality. Crit Care Med. April 2010;38(4):1021–9.
40. NICE-SUGAR Study Investigators, Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, McArthur C, Mitchell I, Foster D, Dhingra V, Henderson WR, Ronco JJ, Bellomo R, Cook D, McDonald E, Dodek P, Hébert PC, Heyland DK, Robinson BG. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 20. September 2012;367(12):1108–18.
41. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. Cochrane Database Syst Rev. 2009;(1):CD006832.
42. Wernerman J, Desaive T, Finfer S, Foubert L, Furnary A, Holzinger U, Hovorka R, Joseph J, Kosiborod M, Krinsley J, Mesotten D, Nasraway S, Rooyackers O, Schultz MJ, Van Herpe T, Vigersky RA, Preiser J-C. Continuous glucose control in the ICU: report of a 2013 round table meeting. Crit Care Lond Engl. 13. Juni 2014;18(3):226.
43. Finfer S, Wernerman J, Preiser J-C, Cass T, Desaive T, Hovorka R, Joseph JI, Kosiborod M, Krinsley J, Mackenzie I, Mesotten D, Schultz MJ, Scott MG, Slingerland R, Van den Berghe G, Van Herpe T. Clinical review: Consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults. Crit Care Lond Engl. 14. Juni 2013;17(3):229.
44. van Hooijdonk RTM, Leopold JH, Winters T, Binnekade JM, Juffermans NP, Horn J, Fischer JC, van Dongen-Lases EC, Schultz MJ. Point accuracy and reliability of an interstitial continuous glucose-monitoring device in critically ill patients: a prospective study. Crit Care Lond Engl. 5. Februar 2015;19:34.
45. Kosiborod M, Gottlieb RK, Sekella JA, Peterman D, Grodzinsky A, Kennedy P, Borkon MA. Performance of the Medtronic Sentrino continuous glucose management (CGM) system in the cardiac intensive care unit. BMJ Open Diabetes Res Care. 2014;2(1):e000037.
46. Punke MA, Decker C, Wodack K, Reuter DA, Kluge S. Continuous glucose monitoring on the ICU using a subcutaneous sensor. Med Klin Intensivmed Notfallmedizin. 14. Februar 2015;
47. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med. November 2008;36(11):3008–13.

48. Ali NA, O'Brien JM Jr, Dungan K, Phillips G, Marsh CB, Lemeshow S, Connors AF Jr, Preiser J-C. Glucose variability and mortality in patients with sepsis. Crit Care Med. August 2008;36(8):2316–21.
49. Hermanides J, Vriesendorp TM, Bosman RJ, Zandstra DF, Hoekstra JB, Devries JH. Glucose variability is associated with intensive care unit mortality. Crit Care Med. März 2010;38(3):838–42.
50. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology. August 2006;105(2):244–52.
51. Meynaar IA, Eslami S, Abu-Hanna A, van der Voort P, de Lange DW, de Keizer N. Blood glucose amplitude variability as predictor for mortality in surgical and medical intensive care unit patients: a multicenter cohort study. J Crit Care. April 2012;27(2):119–24.
52. Braithwaite SS. Glycemic variability in hospitalized patients: choosing metrics while awaiting the evidence. Curr Diab Rep. Februar 2013;13(1):138–54.
53. Selam JL. [How to measure glycemic instability?]. Diabetes Metab. April 2000;26(2):148–51.
54. Koch S, Wollersheim T, Bierbrauer J, Haas K, Mörgeli R, Deja M, Spies CD, Spuler S, Krebs M, Weber-Carstens S. Long-term recovery In critical illness myopathy is complete, contrary to polyneuropathy. Muscle Nerve. September 2014;50(3):431–6.
55. Wollersheim T, Engelhardt LJ, Pachulla J, Moergeli R, Koch S, Spies C, Hiesmayr M, Weber-Carstens S. Accuracy, reliability, feasibility and nurse acceptance of a subcutaneous continuous glucose management system in critically ill patients: a prospective clinical trial. Ann Intensive Care [Internet]. 21. Juli 2016;6. Verfügbar unter: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4954792/
56. Mörgeli R, Wollersheim T, Engelhardt LJ, Grunow JJ, Lachmann G, Carbon NM, Koch S, Spies C, Weber-Carstens S. Critical illness myopathy precedes hyperglycaemia and high glucose variability. J Crit Care [Internet]. 29. Januar 2021 [zitiert 3. Februar 2021]; Verfügbar unter: http://www.sciencedirect.com/science/article/pii/S0883944121000125
57. Buchthal F, Kamieniecka Z. The diagnostic yield of quantified electromyography and quantified muscle biopsy in neuromuscular disorders. Muscle Nerve. April 1982;5(4):265–80.
58. Bednarík J, Vondracek P, Dusek L, Moravcova E, Cundrle I. Risk factors for critical illness polyneuromyopathy. J Neurol. März 2005;252(3):343–51.
59. Bland JM, Altman DG. Comparing methods of measurement: why plotting difference against standard method is misleading. Lancet Lond Engl. 21. Oktober 1995;346(8982):1085–7.
60. Wollersheim T, Grunow JJ, Carbon NM, Haas K, Malleike J, Ramme SF, Schneider J, Spies CD, Märdian S, Mai K, Spuler S, Fielitz J, Weber-Carstens S. Muscle wasting and function after muscle activation and early protocol-based physiotherapy: an explorative trial. J Cachexia Sarcopenia Muscle. August 2019;10(4):734–47.
61. Wollersheim T, Woehlecke J, Krebs M, Hamati J, Lodka D, Luther-Schroeder A, Langhans C, Haas K, Radtke T, Kleber C, Spies C, Labeit S, Schuelke M, Spuler S, Spranger J, Weber-Carstens S, Fielitz J. Dynamics of myosin degradation in intensive care unit-acquired weakness during severe critical illness. Intensive Care Med. April 2014;40(4):528–38.
62. Lanspa MJ, Dickerson J, Morris AH, Orme JF, Holmen J, Hirshberg EL. Coefficient of glucose variation is independently associated with mortality in critically ill patients receiving intravenous insulin. Crit Care Lond Engl. 2014;18(2):R86.
63. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes. September 1970;19(9):644–55.

64. Molnar GD, Taylor WF, Ho MM. Day-to-day variation of continuously monitored glycaemia: a further measure of diabetic instability. Diabetologia. November 1972;8(5):342–8.
65. Hill NR, Oliver NS, Choudhary P, Levy JC, Hindmarsh P, Matthews DR. Normal reference range for mean tissue glucose and glycemic variability derived from continuous glucose monitoring for subjects without diabetes in different ethnic groups. Diabetes Technol Ther. September 2011;13(9):921–8.
66. Rich MM, Teener JW, Raps EC, Schotland DL, Bird SJ. Muscle is electrically inexcitable in acute quadriplegic myopathy. Neurology. März 1996;46(3):731–6.
67. Lefaucheur J, Nordine T, Rodriguez P, Brochard L. Origin of ICU acquired paresis determined by direct muscle stimulation. J Neurol Neurosurg Psychiatry. April 2006;77(4):500–6.
68. Rich MM, Pinter MJ. Sodium channel inactivation in an animal model of acute quadriplegic myopathy. Ann Neurol. Juli 2001;50(1):26–33.
69. Teener JW, Rich MM. Dysregulation of sodium channel gating in critical illness myopathy. J Muscle Res Cell Motil. 2006;27(5–7):291–6.
70. Leijten FS, Harinck-de Weerd JE, Poortvliet DC, de Weerd AW. The role of polyneuropathy in motor convalescence after prolonged mechanical ventilation. JAMA. 18. Oktober 1995;274(15):1221–5.
71. de Sèze M, Petit H, Wiart L, Cardinaud JP, Gaujard E, Joseph PA, Mazaux JM, Barat M. Critical illness polyneuropathy. A 2-year follow-up study in 19 severe cases. Eur Neurol. 2000;43(2):61–9.
72. Cengiz E, Tamborlane WV. A tale of two compartments: interstitial versus blood glucose monitoring. Diabetes Technol Ther. Juni 2009;11 Suppl 1:S11-16.
73. Holzinger U, Warszawska J, Kitzberger R, Herkner H, Metnitz PGH, Madl C. Impact of shock requiring norepinephrine on the accuracy and reliability of subcutaneous continuous glucose monitoring. Intensive Care Med. August 2009;35(8):1383–9.
74. Boyne MS, Silver DM, Kaplan J, Saudek CD. Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. Diabetes. November 2003;52(11):2790–4.
75. Igarashi M, Yamatani K, Fukase N, Daimon M, Ohnuma H, Takahashi H, Manaka H, Tominaga M, Sasaki H. Sepsis inhibits insulin-stimulated glucose transport in isolated rat adipocytes. Diabetes Res Clin Pract. März 1992;15(3):213–8.
76. Bercker S, Weber-Carstens S, Deja M, Grimm C, Wolf S, Behse F, Busch T, Falke KJ, Kaisers U. Critical illness polyneuropathy and myopathy in patients with acute respiratory distress syndrome. Crit Care Med. April 2005;33(4):711–5.
77. Zhou C, Wu L, Ni F, Ji W, Wu J, Zhang H. Critical illness polyneuropathy and myopathy: a systematic review. Neural Regen Res. 1. Januar 2014;9(1):101.
78. Hermans G, Wilmer A, Meersseman W, Milants I, Wouters PJ, Bobbaers H, Bruyninckx F, Van den Berghe G. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. Am J Respir Crit Care Med. 1. März 2007;175(5):480–9.
79. Nishikawa T, Edelstein D, Du XL, Yamagishi S, Matsumura T, Kaneda Y, Yorek MA, Beebe D, Oates PJ, Hammes HP, Giardino I, Brownlee M. Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature. 13. April 2000;404(6779):787–90.
80. Vincent AM, McLean LL, Backus C, Feldman EL. Short-term hyperglycemia produces oxidative damage and apoptosis in neurons. FASEB J Off Publ Fed Am Soc Exp Biol. April 2005;19(6):638–40.

## Statutory Declaration

“I, Rudolf Mörgeli, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic “*Intensive Care Unit-acquired weakness and its relationship to glycemic parameters*” independently and without the support of third parties, and that I used no other sources and aids than those stated.
All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Berlin, Signature:

## Declaration of your own contribution to the publications

Rudolf Mörgeli contributed the following to the below listed publications:

*Publication 1:*

Koch S, Wollersheim T, Bierbrauer J, Haas K, **Mörgeli R**, Deja M, Spies CD, Spuler S, Krebs M, Weber-Carstens S. Long-term recovery In critical illness myopathy is complete, contrary to polyneuropathy. Muscle & Nerve. September 2014; 50(3):431–6.

Detailed contribution: Rudolf Mörgeli participated in data curation, particularly for data used on Figure 1, Table 1 and Table 2. He also conducted literature research and critically revised the original draft and all subsequent versions of the manuscript for content and language.

*Publication 2:*

Wollersheim T, Engelhardt LJ, Pachulla J, **Moergeli R**, Koch S, Spies C, Hiesmayr M, Weber-Carstens S. Accuracy, reliability, feasibility and nurse acceptance of a subcutaneous continuous glucose management system in critically ill patients: a prospective clinical trial. Annals of Intensive Care. July 2016; 6:70

Detailed contribution: Rudolf Mörgeli was involved in the literature research and provided guidance regarding calculation, interpretation, and reporting of glycemic variability parameters, in particular Table 2, Table 4, Figure 4 and Supplemental Figure 1. He also critically revised the original draft and all subsequent version of the manuscript for content and language.

*Publication 3:*

**Mörgeli R***, Wollersheim T*, Engelhardt LJ, Grunow JJ, Lachmann G, Carbon NM, Koch S, Spies C, Weber-Carstens S. Critical illness myopathy precedes hyperglycaemia and high glucose variability. Journal of Critical Care. January 2021; 63:32–9.

* Shared first-authorship

Detailed contribution: Rudolf Mörgeli conducted preliminary literature research, participated in the development of the hypothesis and study design, as well as in data collection, databank generation and validation. He independently conducted the data analyses and the calculation of all glycemic parameters presented. Together with Dr. Tobias Wollersheim, Rudolf Mörgeli conducted all statistical evaluations, and prepared all tables and figures. Rudolf Mörgeli independently wrote the original draft and guided all subsequent manuscript versions until publication. Under my supervision, Rudolf Mörgeli and Tobias Wollersheim were responsible for the manuscript submission.

_____

Signature, date and stamp of first supervising university professor

_____

Signature of doctoral candidate

## Selected Publications

Koch S, Wollersheim T, Bierbrauer J, Haas K, **Mörgeli R**, Deja M, Spies CD, Spuler S, Krebs M, Weber-Carstens S. Long-term recovery In critical illness myopathy is complete, contrary to polyneuropathy. Muscle & Nerve. September, 2014;50(3):431–6.

https://doi.org/10.1002/mus.24175

Wollersheim T, Engelhardt LJ, Pachulla J, **Moergeli R**, Koch S, Spies C, Hiesmayr M, Weber-Carstens S. Accuracy, reliability, feasibility and nurse acceptance of a subcutaneous continuous glucose management system in critically ill patients: a prospective clinical trial. Annals of Intensive Care . 21. Juli 2016;6:70

Wollersheim *et al. Ann. Intensive Care (2016) 6:70*
DOI 10.1186/s13613-016-0167-z

Annals of Intensive Care

RESEARCH Open Access

# Accuracy, reliability, feasibility and nurse acceptance of a subcutaneous continuous glucose management system in critically ill patients: a prospective clinical trial

Tobias Wollersheim[1,2†], Lilian Jo Engelhardt[1†], Jeanne Pachulla[1], Rudolf Moergeli[1], Susanne Koch[1], Claudia Spies[1], Michael Hiesmayr[3] and Steffen Weber-Carstens[1,2*]

**Abstract**

**Background:** Continuous glucose monitoring (CGM) has not yet been implemented in the intensive care unit (ICU) setting. The purpose of this study was to evaluate reliability, feasibility, nurse acceptance and accuracy of the Medtronic Sentrino® CGM system in critically ill patients.

**Methods:** Sensors were inserted into the subcutaneous tissue of the patient's thigh, quantifying interstitial glucose concentration for up to 72 h per sensor. Reliability and feasibility analysis included frequency of data display, data gaps and reasons for sensor removal. We surveyed nurse acceptance in a questionnaire. For the accuracy analysis, we compared sensor values to glucose values obtained via blood gas analysis. Potential benefits of CGM were investigated in intra-individual analyses of factors, such as glycemic variability or time in target range achieved with CGM compared to that achieved with intermittent glucose monitoring.

**Results:** The device generated 68,655 real-time values from 31 sensors in 20 critically ill patients. 532 comparative blood glucose values were collected. Data were displayed during 32.5 h [16.0/62.4] per sensor, which is 45.1 % of the expected time of 72 h and 84.8 % of 37.9 h actual monitoring time. 21 out of 31 sensors were removed prematurely. 79.1 % of the nursing staff rated the device as not beneficial; the response rate was one-third. Mean absolute relative difference was 15.3 % (CI 13.5–17.0 %). Clarke error grid: 76.9 % zone A, 21.6 % zone B, 0.2 % zone C, 0.9 % zone D, 0.4 % zone E. Bland–Altman plot: mean bias +0.53 mg/dl, limits of agreement +64.6 and −63.5 mg/dl. Accuracy deteriorated during elevated glycemic variability and in the hyperglycemic range. There was no reduction in dysglycemic events during CGM compared to 72 h before and after CGM. If CGM was measuring accurately, it identified more hyperglycemic events when compared to intermittent measurements. This study was not designed to evaluate potential benefits of CGM on glucose control.

**Conclusions:** The subcutaneous CGM system did not perform with satisfactory accuracy, feasibility, or nursing acceptance when evaluated in 20 medical-surgical ICU patients. Low point accuracy and prolonged data gaps

*Correspondence: steffen.weber-carstens@charite.de
†Tobias Wollersheim and Lilian Jo Engelhardt contributed equally to this work
[1] Department of Anesthesiology and Operative Intensive Care Medicine, Campus Charité Mitte and Campus Virchow Klinikum, Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany
Full list of author information is available at the end of the article

significantly limited the potential clinical usefulness of the CGM trend data. Accurate continuous data display, with a MARD < 14 %, showed potential benefits in a subgroup of our patients.

*Trial registration* NCT02296372; Ethic vote Charité EA2/095/14

**Keywords:** Continuous glucose monitoring, Subcutaneous, Interstitial, Critically ill patients, ICU, Medtronic Sentrino®, Accuracy, Reliability, Feasibility, Nurse acceptance, Evaluation

## Background

Critically ill patients frequently experience stress-induced alterations in glucose homoeostasis resulting in hyperglycemia [1]. Peripheral insulin resistance and an enhanced hepatic glucose production, caused by a release of counter-regulatory hormones and cytokines, are contributing mechanisms [1, 2]. Insufficient GLUT4 translocation in skeletal muscle of critically ill patients is related to glucose dysregulation [3]. Hyperglycemia, elevated glycemic variability and hypoglycemia, were associated with an increased mortality risk in critically ill patients [4–6]. Randomized controlled trials showed that insulin therapy and management of glycemic control in the ICU remains challenging [6–10].

Continuous glucose monitoring (CGM) in the ICU, combined with an appropriate insulin protocol, may improve management of glycemic control and consequently impact patient outcome [11–13]. Wernerman et al. provided an overview of CGM technologies, including glucose oxidase, mid-infrared spectroscopy and fluorescence, ranging from invasive intravascular devices to minimally invasive interstitial and noninvasive transcutaneous systems [11]. Interstitial devices designed for use in diabetic patients have already been applied in critically ill patients [13–16]. Despite promising attempts, these systems have not yet been implemented to daily routine in the ICU and improvements are desirable. The subcutaneous Medtronic Sentrino® CGM system was designed for use in ICU patients. The displayed real-time glucose trend line allows the ICU staff to observe glucose excursions at an earlier stage when compared to the established intermittent measurements. Patients may benefit from increased time in target range and improved glycemic variability. In addition, nurse workload may be reduced.

The purpose of this study was to evaluate reliability, feasibility, nurse acceptance and accuracy of this subcutaneous CGM system, as well as to identify potential weaknesses of the device in severely ill patients. In addition to previous studies [17–19], we retrospectively assessed potential benefits of CGM in comparison with intermittent glucose monitoring in our medical-surgical ICU.

## Methods

### Inclusion criteria and study participants

Inclusion criteria included an expected length of stay in the ICU of at least 72 h, age ≥18 years and written informed consent given by patient or legal proxy. We recruited critically ill patients during a time period of seven months in 2014. Patient inclusion started immediately after the local ethics committee, Ethikkommission Charité Universitätsmedizin Berlin, approved the study protocol (Charité-EA2/095/14). The protocol was registered under https://clinicaltrials.gov, trial registration number NCT02296372.

### Glycemic control in the study setting

The single-center study was set in two interdisciplinary mixed medical-surgical ICUs of a university hospital. The glucose target levels for insulin therapy were 80–149 mg/dl. Dysglycemic events were defined as follows: ranges above 149 mg/dl represented moderate hyperglycemia, and glucose levels above 179 mg/dl represented severe hyperglycemia. Moderate hypoglycemia was defined in a range from 41 to 70 mg/dl, and severe hypoglycemia as ≤40 mg/dl [11, 20]. Due to general ICU routine, nurses took blood samples from an arterial catheter in 2- to 4-h intervals, depending on the patient's condition. In the absence of an arterial line, blood was collected from a central or peripheral venous catheter. Blood glucose was determined by glucose oxidase reaction using a Radiometer ABL 800 FLEX (Copenhagen, Denmark) blood gas analyzer. Depending on the identified blood glucose value, the nursing staff regulated the intravenous insulin therapy according to the local insulin protocol (Additional file 1: Table S1). All patient data, including blood gas analyses, were documented within the patient data management system (PDMS).

### CGM sensor

According to manufacturer's information, the sensors of the interstitial CGM device consist of four independently working electrodes, which are embedded in two cannulas. This multisensory system provides enhanced signal stability and accuracy in critically ill patients. The electrodes are coated by glucose oxidase. In the enzymatic reaction, electrons are released and create an electrical gradient, which is proportional to the interstitial glucose concentration. Based on the electrical signal, the CGM algorithm calculates out of the four data signals one blood glucose value, which is displayed on a bedsided monitor. The device provides one real-time glucose

measurement per minute, with an insignificant lag time for signal processing, for up to 72 h (for more details, see Additional file 1: CGM Device).

### Study procedure

We inserted the sensors into the subcutaneous tissue of patient's upper leg. After initialization, the sensors required one initial blood glucose entry, followed by two further calibrations after the first and second running hour. Subsequently, the study team performed calibrations every 8 h, as proposed by the manufacturer. The ward staff were not required to perform further calibrations. We instructed nurses to observe the continuous glucose trend line and perform blood glucose measurements to adapt insulin therapy in case of excursions above or below the target range (defined in the local insulin protocol Additional file 1: Table S1). Glucose values determined by the blood gas analyzer were used as reference. Blood glucose measurements used for initial calibrations and calibrations after data gaps (>15 min) were excluded from the point accuracy analysis. Further blood glucose measurements were included and compared to the latest CGM value immediately before calibration. As specified in the study protocol (Fig. 1), the accuracy analysis required a minimum monitoring time of 48 h or at least 12 comparative readings.

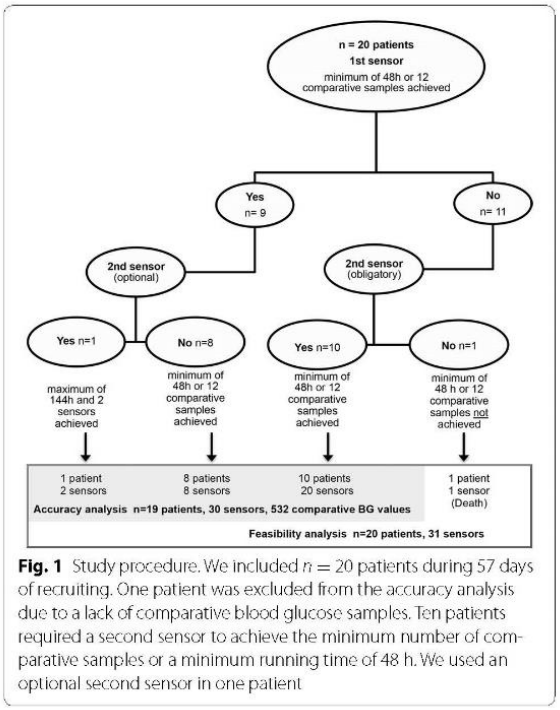



**Fig. 1** Study procedure. We included $n = 20$ patients during 57 days of recruiting. One patient was excluded from the accuracy analysis due to a lack of comparative blood glucose samples. Ten patients required a second sensor to achieve the minimum number of comparative samples or a minimum running time of 48 h. We used an optional second sensor in one patient

### Analysis criteria

Figure 2 illustrates detailed endpoints for the analysis of reliability, feasibility, nurse acceptance, accuracy and potential benefits of CGM. The analysis is based on the 2013 consensus recommendations, published by Finfer et al. defining criteria for continuous glucose control in critically ill patients [20]. Desirable reliability criteria include a continuous data display during >95 % of time and device-related data gaps <30 min [20]. We calculated frequency of data gaps and analyzed the gaps subdivided as very brief (<15 min), brief (15–30 min), prolonged (>30 min) and very prolonged (>2 h), so as to better describe the clinical significance of the missing trend data. The feasibility analysis considered the capacity of the device to perform within the busy ICU setting. This was supplemented by a survey of nurse acceptance assessed by brief questionnaires given to the nurses in charge of each shift (Additional file 1: Fig. S3). To determine accuracy, sensor values were compared to the simultaneously recorded blood glucose values from PDMS. We calculated point accuracy according to criteria specified within the consensus recommendations [20], which can be summarized as follows

- 98 % of device readings should be within 12.5 % of a reference standard (or within ±10 mg/dl for readings <100 mg/dl)
- The remaining 2 % of readings should be within 20 % of a reference standard
- Mean absolute relative difference (MARD) should be <14 % (M)ARD = $|$(blood glucose − sensor glucose)$|$/blood glucose × 100
- MARD > 18 % represents poor accuracy.

In addition, we analyzed possible confounding factors on MARD, such as arterial $pO_2$, temperature, hemoglobin, potassium, lactate, pH value, sequential organ failure assessment (SOFA) Score, systemic inflammatory response syndrome (SIRS), history of diabetes, blood glucose variability and glucose ranges (<80 mg/dl, 80–179 mg/dl, >179 mg/dl). We retrospectively calculated MARD after time-shifting the reference a fixed amount (1 up to 30 min), so as to investigate a time delay as a possible confounding factor. To investigate potential benefits of CGM in our ICU, we report glycemic control achieved with CGM compared to that achieved with intermittent glucose monitoring. This was accomplished by performing intra-individual analyses, longitudinal and parallel, of factors such as mean blood glucose level, blood glucose variability, number of dysglycemia events and time in blood glucose target range (Fig. 2). Glycemic variability was determined using standard deviation of blood glucose and glycemic lability index (Table 4b), as a

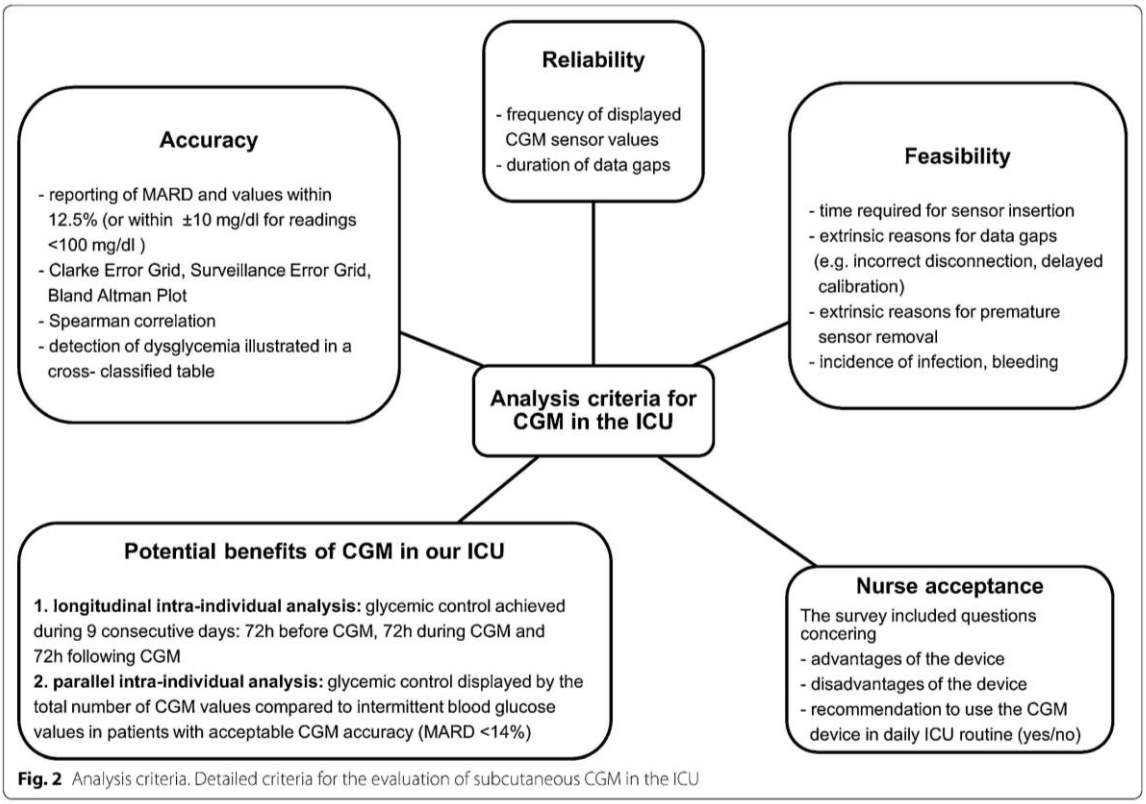



**Fig. 2** Analysis criteria. Detailed criteria for the evaluation of subcutaneous CGM in the ICU

time-weighted index [21]. To evaluate safety, we reported local complications and discussed patient risks due to inaccurate CGM measurements in a safety statement.

### Statistical analysis

Results were shown as median with interquartile range or as absolute numbers with percentages. Clinical accuracy was illustrated using Bland–Altman plot [22], Clarke error grid [23] and Surveillance Error-Grid [24]. We calculated glycemic lability index using EasyGV© software [21]. Nonparametric tests were performed (Mann–Whitney *U* Test, Wilcoxon Test, Kruskal–Wallis Test, Friedman Test and Spearman's correlation). We used IBM© SPSS© Statistics version 21, Microsoft Excel© $^{2010}$ and R for the statistical analysis.

## Results

We included 20 critically ill patients in this prospective trial using a total of 31 sensors (Fig. 1). Table 1 shows patient characteristics. In total, the device generated 68655 (1144.3 h) real-time glucose values during 1337.1 h of monitoring. The median monitoring time per patient was 70.5 h [57.2/72.7]. For the accuracy comparison, we collected 532 blood glucose values in 19 patients, of which 475 (89.3 %) were obtained from arterial and 57 (10.7 %) from venous catheters. There was no significant difference in accuracy between the 475 arterial blood glucose values compared to all 532 glucose values ($p = .799$). Table 2 shows a summary of glycemic control metrics.

### Reliability, feasibility and safety

The reliability analysis showed a real-time data display during 32.5 h (16/62.4) per sensor, which is 45.1 % of the expected time of 72 h and 84.8 % of the 37.9 h actual monitoring time. During 80223 min (1337.1 h) of monitoring, we observed in total 11568 min (192.8 h) of missing values. The number of data gaps was 155, of which 68 (43.9 %) were very brief (<15 min), 35 (22.6 %) were brief (15–30 min), 27 (17.4 %) were prolonged (30–120 min) and 25 (16.1 %) were very prolonged. The sensor insertion itself was easily performed and required less than 10 min. The complication rate at the site was low. Minor bleeding after insertion occurred in four patients. We observed no local infection. The main feasibility issue was premature sensor removal. Detailed device reliability and feasibility is shown in Table 3.

**Table 1 Patient characterization**

| | |
|---|---|
| Age | 61 [54/69] |
| Gender (female/male) | 14 (70 %)/6 (30 %) |
| BMI (kg/m$^{2)}$ | 23 [22/26] |
| Diagnosis leading to ICU stay | |
| ARDS (ECMO, ECLA) | 6 (30 %) |
| ARDS (without ECMO, ECLA) | 8 (40 %) |
| Mediastinitis | 1 (5 %) |
| Peritonitis | 3 (15 %) |
| Intracranial hemorrhage | 1 (5 %) |
| Polytrauma | 1 (5 %) |
| At least one event of SIRS or sepsis during CGM | 20 (100 %) |
| Sequential organ failure assessment (SOFA) Score at inclusion | 8 [4/10] |
| Acute physiology and chronic health evaluation (APACHE) 2 Score at admission | 24 [19/28] |
| History of diabetes mellitus | 5 (25 %) |
| Administration of intravenous insulin therapy during CGM | 14 (70 %) |
| Administration of vasopressors during CGM | 7 (35 %) |
| Mean dose of epinephrine during sensor running time (µg/kg/min) (in seven patients receiving vasopressors) | 0.08 [0.03/0.14] |
| Mortality during ICU stay | 4 (20 %) |

$n = 20$ patients

Results are expressed as median with interquartile range or as absolute numbers with percentages of $n = 20$ patients

*BMI* body mass index, *ARDS* acute respiratory distress syndrome, *ECMO* extracorporeal membrane oxygenation, *ECLA* extracorporeal lung assist, *SIRS* systemic inflammatory response syndrome, *SOFA* sequential organ failure assessment, *APACHE* acute physiology and chronic health evaluation, *ICU* intensive care unit, *CGM* continuous glucose monitoring

**Table 2 Mean glucose level, glycemic variability and glycemic events**

| | Reference blood glucose | Comparative CGM reading | |
|---|---|---|---|
| Number of comparative glucose readings | 532 | 532 | |
| Readings per patient | 28 [18/34] | 28 [18/34] | |
| Mean glucose level per patient (mg/dl) | 133.8 [128.4/147.5] | 133.7 [124.3/150.1]* | |
| Glucose variability per patient measured in SD (mg/dl) | 24.8 [19.9/35.2] | 32.5 [25.2/42.2]§ | |
| Glycemic events: number and percentage of $n = 19$ patients | | | |
| Severe hypoglycemia (≤40 mg/dl) | 1 (5.3 %) | 1 (5.3 %) | |
| Moderate hypoglycemia (41–70 mg/dl) | 1 (5.3 %) | 10 (52.6 %) | |
| Euglycemia (71–149 mg/dl) | 19 (100 %) | 19 (100 %) | |
| Moderate hyperglycemia (150–179 mg/dl) | 18 (94.7 %) | 19 (100 %) | |
| Severe hyperglycemia (>179 mg/dl) | 15 (78.9 %) | 11 (57.9 %) | |
| Glycemic events: number and percentage of $n = 532$ readings | 158 (29.7 %) | 188 (35.3 %) | |
| Severe hypoglycemia (≤40 mg/dl) | 1 (0.2 %) | 1 (0.2 %) | Chi-square test: $p < 0.001$ for crosstabulation see supplement |
| Moderate hypoglycemia (41–70 mg/dl) | 2 (0.4 %) | 15 (2.8 %) | |
| Euglycemia (71–149 mg/dl) | 374 (70.3 %) | 344 (64.7 %) | |
| Moderate hyperglycemia (150–179 mg/dl) | 96 (18.0 %) | 101 (19 %) | |
| Severe hyperglycemia (>179 mg/dl) | 59 (11.1 %) | 71 (13.3 %) | |

$n = 19$ patients

Results are expressed as median with interquartile range or as absolute numbers with percentages

*SD* standard deviation

* $p = 1.0$; § $p = 0.002$

**Table 3 Reliability and feasibility**

| | Per sensor |
|---|---|
| Initialization time | 27 min |
| Total time until first displayed value | 37.5 min [36/42] |
| Expected monitoring time after initialization | 72 h |
| Actual monitoring time after initialization | 37.9 h [23/71.3] |
| Real-time data display | 32.5 h [16/62.4] |
| Percentage of real-time data display/expected monitoring time after initialization | 45.1 % |
| Percentage of real-time data display/actual monitoring time after initialization | 84.8 % [67.9/93.8] |
| Data gaps after initialization | 5 h [1.9/8.3] |
| Percentage of data gaps/actual monitoring time after initialization | 15.2 % [6.2/32.1] |
| Number of performed calibrations | 9.5 [6/13] |

| Reasons for the 11,568 min (192.8 h) of data gaps | Percentage of data gaps 11,568 min (192.8 h) | Percentage of monitoring time 80,223 min (1337.1 h) |
|---|---|---|
| 1 Poor sensor signal (%) | 23.3 | 3.4 |
| 2 Sensor failure (%) | 15.0 | 2.2 |
| 3 Processor line error (%) | 10.9 | 1.6 |
| 4 Disconnection (%) | 15.6 | 2.3 |
| 5 Pending after reconnection (%) | 3.4 | 0.5 |
| 6 Calibration required (%) | 27.8 | 4.0 |
| 7 Others (%) | 4.0 | 0.6 |
| Device-related reasons (1–3) (%) | 49.2 | 7.2 |
| Not device related (4–7) (%) | 50.8 | 7.4 |

| Reasons for 21 prematurely sensor removals | Number of sensors | Percentage of all sensors (%) | Percentage of removed sensors (%) |
|---|---|---|---|
| Sensors 72 h completed | 10 | 32.3 | – |
| Sensors removed prematurely | 21 | 67.7 | 100 |
| 1 Accidentally | 7 | 22.6 | 33.3 |
| 2 Poor sensor signal during measurement | 7 | 22.6 | 33.3 |
| 3 Poor sensor signal immediately after initialization | 1 | 3.2 | 4.8 |
| 4 MRI | 1 | 3.2 | 4.8 |
| 5 Discharge | 1 | 3.2 | 4.8 |
| 6 Death | 2 | 6.5 | 9.5 |
| 7 Others | 2 | 6.5 | 9.5 |
| Device-related reasons (1–3) | 15 | 48.4 | 71.4 |
| Not device related (4–7) | 6 | 19.4 | 28.6 |

$n = 20$ patients, 31 sensors

Results are expressed as median with interquartile range or as absolute numbers with percentages

*MRI* magnetic resonance imaging

### Nurse acceptance

The nurses received 128 questionnaires during the CGM monitoring period. The response rate was one-third ($n = 43$, 34 %). The majority (79.1 %) of the nursing staff rated the device as not beneficial in the daily ICU routine. Advantages, such as the opportunity to observe glucose trends, were reported in 20.9 % of the questionnaires. Disadvantages were described by 53.5 %. Reasons included the inadequate alarm performance (23.3 %), the additional device (23.3 %) and device line (6.9 %) as disturbing factors during bedding and mobilization in the ICU routine.

### Point accuracy

60.3 % of sensor data were within 12.5 % from the reference blood glucose (or were within ±10 mg/dl for readings <100 mg/dl). In total, 76.9 % of sensor readings were within 20, and 23.1 % deviated more than 20 % from the reference. MARD was 15.3 % (95 % CI 13.5–17.0 %). Spearman's correlation coefficient was 0.688, $p < .001$,

$r^2$ = 0.461. The Bland–Altman plot (Fig. 3a) showed a mean bias of 0.53 mg/dl and limits of agreement of +64.6 mg/dl and −63.5 mg/dl. Clarke error grid and Color-Coded Surveillance Error-Grid (Fig. 3b, c) showed potentially dangerous errors. Additional file 1: Table S2 shows the detection of dysglycemic events.

#### Confounding factors on accuracy

We identified that the blood glucose variability, analyzed in standard deviation, was significantly associated with CGM accuracy (Fig. 4a). Confirming this finding, standard deviation per patient was positively correlated with MARD per patient $k = 0.593$, $p = .001$, $n = 19$, $r^2 = 0.298$ (Additional file 1: Fig. S1). MARD deteriorated in the hyperglycemic blood glucose range (Fig. 4a). There was no significant improvement or deterioration of MARD after time-shifting the reference glucose a fixed amount of 1 up to 30 min (Additional file 1: Fig. S2). MARD was worse during application of vasoconstrictors (Additional file 1: Table S3a). Previously known diabetes mellitus and episodes of SIRS did not confound MARD (Additional file 1: Table S3a). The severity of disease, measured via SOFA Score, showed a minor positive correlation with the MARD ($k = 0.088$, $p = .043$, $r^2 = 0.006$, $n = 532$). There was no significant correlation of arterial pO2, temperature, pH value, lactate, hemoglobin, or potassium and MARD (Additional file 1: Table S3b).

#### Potential benefits of CGM in our ICU

In 10 patients with an ICU stay of at least nine consecutive days, the longitudinal analysis showed no significant reduction in dysglycemic events during 3 days of CGM compared to 72 h before and 72 h after CGM (Table 4a). In the parallel analysis, CGM determined significantly lower minimal glucose values and detected more hyperglycemic events compared to intermittent blood glucose values in eight patients, in whom the device displayed accurate results with a MARD < 14 % (Table 4b).

## Discussion

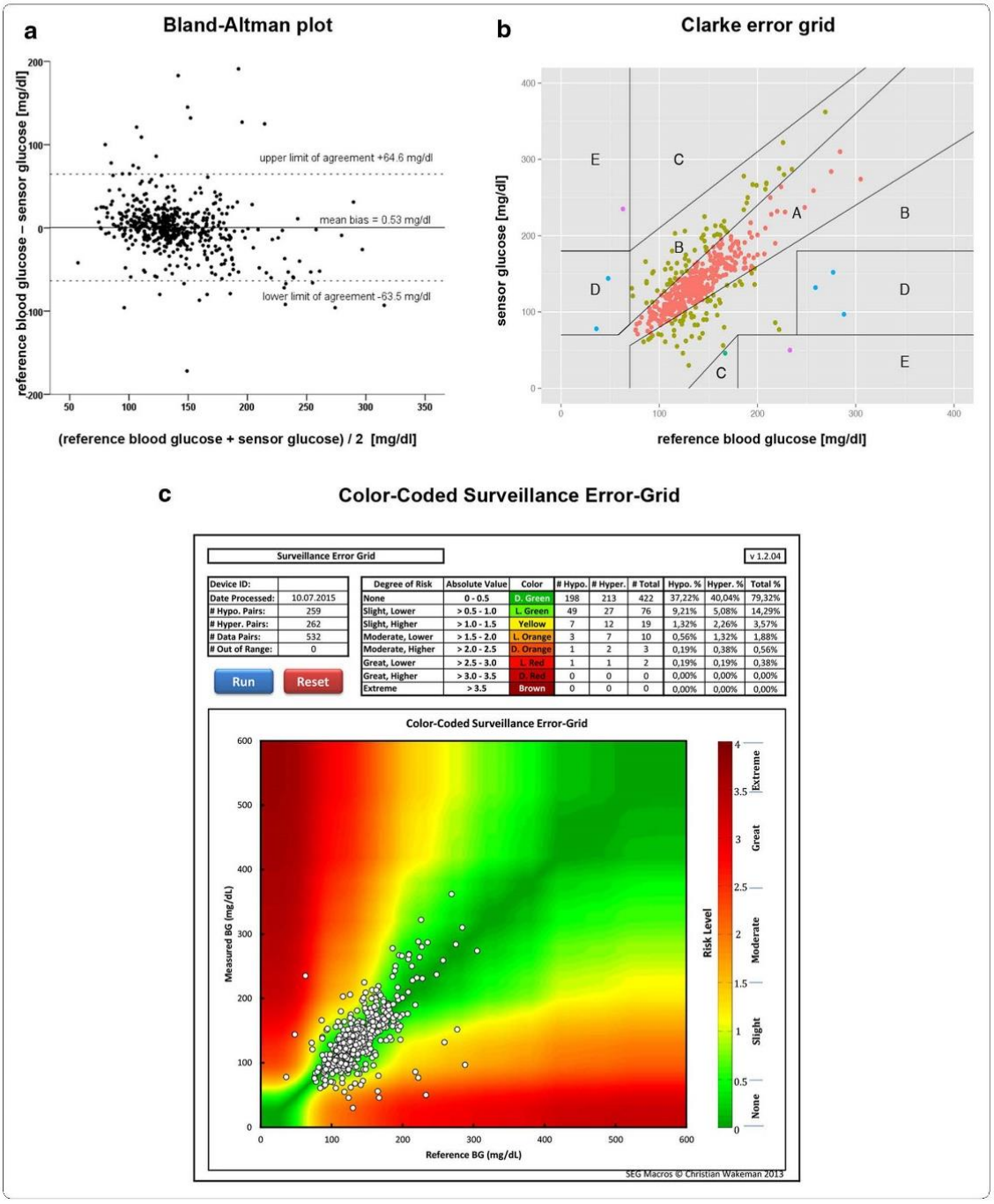
#### Reliability, feasibility and nurse acceptance

This prospective study was initially conducted with the intention of implementing a minimally invasive, simple to use CGM device in our ICU, in order to improve glycemic control. Unfortunately, application and performance were not as reliable as expected. Numerous sensors were removed prematurely, and the percentage of data gaps in relation to the expected sensor running time exceeded the time specified within the consensus recommendations of ICU experts [20]. The fact that we did not demand additional calibrations from the nursing staff and that they were not involved in troubleshooting may have contributed to the extent of data gaps and the poor performance. Since 7.4 % of data gaps were not device related, the data display during 85.6 % of the sensor running time after initialization could be corrected to 93 %. The high rate of accidentally removed sensors underlines the vulnerable use of the subcutaneous device in intensive care. This is supported by the opinion of our ICU nursing staff. More experience with a device may enhance feasibility. However, device-related issues, which are not improvable by experience, occurred frequently. Recently published investigations evaluating the same device reported minimal differences in reliability, but the clinically relevant results were concordant [17–19].

#### Point accuracy and confounding factors

The subcutaneous device did not fulfill the suggested accuracy criteria for CGM in critically ill patients, specified within the consensus recommendations of ICU experts [20]. The distribution in the Clarke error grid [23] was unsatisfactory, as all 532 comparative readings of this analysis should have been located in zone A or B, preferably in zone A. The Surveillance Error-Grid [24], which promises to be closer to clinical routine, showed similar degrees of risk. In the Bland–Altman plot, the mean bias indicated that there was no systematic error [22]. However, 95 % of the values were within 128 mg/dl of the reference glucose. These wide limits of agreement illustrated a high random error [22]. The detection of dysglycemia was critical. The results considering MARD values within the 12.5 % range, and Clarke error grid and Bland–Altman plot are precisely consistent with those reported by Van Hooijdonk et al. [17]. Two further studies showed slightly better accuracy of the same system [18, 19]. Although specifically designed for ICU use, the investigated subcutaneous device failed to achieve comparatively accurate results in all recently published trials [17–19], as opposed to the CGM technologies quantifying glucose concentration in the vascular compartment of critically ill patients [25–28]. This leads to the conclusion that, with the intention to administrate insulin therapy, the subcutaneous glucose determination is not the proper method to estimate blood glucose levels during the acute phase of severe illness.

Inaccuracies may be attributed to a physiological time delay relating to the glucose diffusion from the plasma to the interstitial compartment [29, 30]. In healthy humans and diabetes patients, this time delay has been observed to range from 0 to 40 min in various studies summarized by Scuffi et al. [30]. Rebrin et al. found no evidence that physiological delays exceeded 5–10 min and argued that device-related processes are responsible for longer periods [31]. Moreover, Boyne et al. addressed the issue of random inter-sensor time discrepancies, which were quantitatively similar to physiological time delays, when


a
Bland-Altman plot
upper limit of agreement +64.6 mg/dl
mean bias = 0.53 mg/dl
lower limit of agreement -63.5 mg/dl
reference blood glucose – sensor glucose [mg/dl]
(reference blood glucose + sensor glucose) / 2 [mg/dl]
b
Clarke error grid
sensor glucose [mg/dl]
reference blood glucose [mg/dl]
A
B
C
D
E
c
Color-Coded Surveillance Error-Grid
Surveillance Error Grid
v 1.2.04
Device ID:
Date Processed: 10.07.2015
# Hypo. Pairs: 259
# Hyper. Pairs: 262
# Data Pairs: 532
# Out of Range: 0
Run
Reset
Degree of Risk | Absolute Value | Color | # Hypo. | # Hyper. | # Total | Hypo. % | Hyper. % | Total %
None | 0 - 0.5 | D. Green | 198 | 213 | 422 | 37,22% | 40,04% | 79,32%
Slight, Lower | > 0.5 - 1.0 | L. Green | 49 | 27 | 76 | 9,21% | 5,08% | 14,29%
Slight, Higher | > 1.0 - 1.5 | Yellow | 7 | 12 | 19 | 1,32% | 2,26% | 3,57%
Moderate, Lower | > 1.5 - 2.0 | L. Orange | 3 | 7 | 10 | 0,56% | 1,32% | 1,88%
Moderate, Higher | > 2.0 - 2.5 | D. Orange | 1 | 2 | 3 | 0,19% | 0,38% | 0,56%
Great, Lower | > 2.5 - 3.0 | L. Red | 1 | 1 | 2 | 0,19% | 0,19% | 0,38%
Great, Higher | > 3.0 - 3.5 | D. Red | 0 | 0 | 0 | 0,00% | 0,00% | 0,00%
Extreme | > 3.5 | Brown | 0 | 0 | 0 | 0,00% | 0,00% | 0,00%
Color-Coded Surveillance Error-Grid
Measured BG (mg/dL)
Reference BG (mg/dL)
Risk Level
None
Slight
Moderate
Great
Extreme
SEG Macros © Christian Wakeman 2013

(See figure on previous page.)
**Fig. 3** Bland–Altman plot, Clarke error grid, Color-coded Surveillance Error-Grid. $n = 532$ comparative samples. **a** Bland–Altman plot. The mean bias indicates whether there is a systematic error. Upper and lower limits were calculated by mean bias ±1.96 × standard deviation of the difference between BG and sensor glucose and represent random variations around the mean bias. If there is a Gaussian distribution, 95 % of points are located between these limits. [22, 41]. **b** Clarke error grid. Distribution: $A = 76.9$ %, $B = 21.6$ %, $C = 0.2$ %, $D = 0.9$ %, $E = 0.4$ %. Zones A (CGM data ≤20 % deviation from BG) and *B* are considered as clinically acceptable zones, whereas values in zones *C*, *D* and *E* are increasingly dangerous for the patient, and zone *E* may lead to adverse therapeutic decisions. [23]. **c** Color-coded Surveillance Error-Grid. The Surveillance Error-Grid software is available at http://www.diabetestechnology.org/SEGsoftware/Surveillance-Error-Grid-Analysis.xlsm. Last Accessed: Dec 11 2015 [24]

comparing measurements of two subcutaneous sensors in the same individual [32]. Factors influencing the glucose diffusion rate, such as blood flow, peripheral microcirculation, and metabolic rate of subcutaneous tissue and adjacent cells, are all frequently altered in critically ill patients [11, 33]. We found no indication for a fixed time shift, but time delay and interstitial sensor accuracy may vary depending on the patient's condition. There is evidence to support this hypothesis, since the use of vasopressors and a higher SOFA Score downgraded sensor accuracy in the present trial. In contrast, the accuracy of a subcutaneous CGM device was significantly improved in patients with septic shock compared to patients without sepsis [34]. Further studies cited that circulatory shock requiring norepinephrine therapy and impaired microcirculation had no influence on subcutaneous sensor accuracy [35, 36]. Variable subcutaneous oxygen concentration may interfere with the glucose oxidase. We did not investigate tissue paO2, but arterial paO2, as a correlating factor, had no clinically relevant impact on accuracy.

Glucose homeostasis is affected by the peripheral glucose uptake [33]. Inflammation may lead to an insufficient GLUT 4 translocation to sarcolemmal membrane [3]. This mechanism resulted in an impaired glucose supply in skeletal muscle cells in ICU patients [3]. A decreased glucose uptake was observed in adipocytes of septic rats [37]. We hypothesize that an insufficient GLUT 4 translocation may occur in subcutaneous tissue cells of critically ill patients. This may influence the accuracy of a

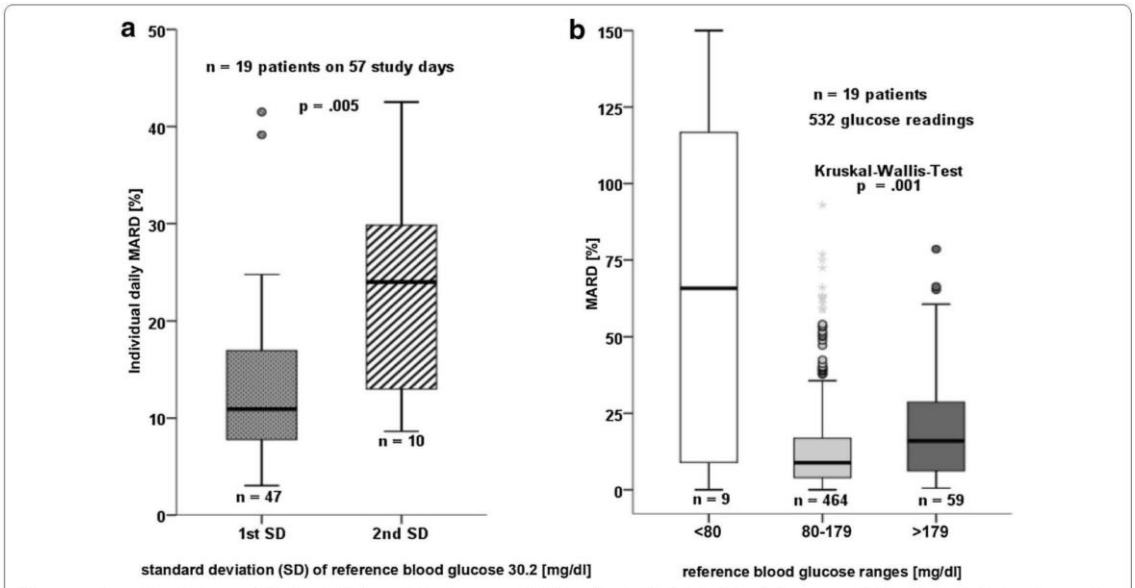



**Fig. 4** Confounding factors on MARD. **a** (*left*): Association between MARD and individual daily blood glucose variability shown in first and second standard deviation of reference glucose. *First boxplot* The CGM device shows acceptable accuracy* (MARD median 10.9 %) if the blood glucose variability is low (first standard deviation). *Second boxplot* Accuracy deteriorates (MARD median 24 %) during increased blood glucose variability (second standard deviation). **b** (*right*): Association between MARD and blood glucose ranges. *Second boxplot* The CGM device shows acceptable accuracy* (MARD median 8.8 %) in blood glucose ranges between 80 and 179 mg/dl. *First* and *Third boxplots* Accuracy deteriorates in the hypoglycemic range (MARD median 65.8 %) and during severe hyperglycemia (MARD median 16 %). **According to criteria specified within the consensus recommendations* [20], *MARD should be* <14 %

**Table 4 Potential benefits of CGM in our ICU**

| Per patient | Blood glucose 3 days before CGM | Blood glucose 3 days during CGM* | Blood glucose 3 days after CGM | *p* value |
|---|---|---|---|---|
| (a) Longitudinal analysis. Blood glucose metrics before/during/after CGM. $n = 10$ patients, 998 blood glucose values | | | | |
| Number of BGA | 30 [25/40] | 35.5 [28/41] | 26.5 [22/34] | $p = .001$[§] |
| Number of hypoglycemia | 0 [0/0] | 0 [0/0] | 0 [0/0] | $p = 1.00$ |
| Number of hyperglycemia | 3 [1/4] | 2.5 [1/5] | 2 [1/3] | $p = .779$ |
| Time in target (in %) | 82.5 [74/98.2] | 81.6 [68.9/95.6] | 88.7 [81.3/94.3] | $p = .452$ |
| Time <71 mg/dl (in %) | 0 [0/0] | 0 [0/0] | 0 [0/0] | $p = 1.00$ |
| Time >149 mg/dl (in %) | 17.5 [1.8/26] | 18.4 [4.4/31.1] | 11.3 [5.7/15.4] | $p = .717$ |
| Blood glucose min (mg/dl) | 89 [80/100] | 85 [73/106] | 97.5 [85/110] | $p = .273$ |
| Blood glucose max (mg/dl) | 173.5 [162/187] | 202 [159/218] | 166 [153/185] | $p = .014$[#] |
| Mean glucose level (mg/dl) | 134 [126.1/137.1] | 130.7 [123.5/139] | 128.5 [120.6/138.4] | $p = .497$ |
| Mean glucose SD (mg/dl) | 18.9 [15.8/22.4] | 20.7 [17.6/36.4] | 16.2 [11.6/24.2] | $p = .741$ |
| **Per patient** | | **Blood glucose values ($n = 239$)** | **CGM sensor glucose ($n = 34056$)** | ***p* value** |
| (b) Parallel analysis. Comparison of intermittent blood glucose to CGM glucose metrics including the total number of CGM readings, $n = 8$ patients MARD < 14 %, 239 blood glucose values, 32,044 CGM values | | | | |
| Number of readings | | 29.5 [26.5/31.5] | 3975 [3780/4109] | $p = .012$ |
| Number of hypoglycemia | | 0 [0/0] | 0.5 [0/2] | $p = .066$ |
| Number of hyperglycemia | | 1 [1/5] | 7 [6/18] | $p = .018$ |
| Time in target range (in %) | | 88.7 [60.7/96.5] | 85.2 [57.9/91.6] | $p = .208$ |
| Time <71 mg/dl (in %) | | 0 [0/0] | 0.3 [0/2.3] | $p = .068$ |
| Time >149 mg/dl (in %) | | 11.3 [3.6/39.3] | 14.3 [6.2/40.6] | $p = .327$ |
| Glucose min (mg/dl) | | 103.5 [87/111.5] | 76 [62/91] | $p = .017$ |
| Glucose max (mg/dl) | | 195 [154.5/211] | 186 [178.5/220.5] | $p = .208$ |
| Mean glucose level (mg/dl) | | 130.2 [124.3/147.9] | 128.7 [120.5/147.4] | $p = .327$ |
| Mean glucose SD (mg/dl) | | 19.9 [14.4/22.7] | 20.6 [16.5/28.4] | $p = .093$ |
| Glycemic lability index | | 38.0 [14/53] | 36.9 [18.5/90.7] | $p = .674$ |

Intra-individual longitudinal and parallel analysis, target range 71–149 mg/dl

Results are expressed as median with interquartile range or as absolute numbers with percentages

Glycemic lability index: time interval 1440 min = 24 h, glucose in mg/dl, sampling interval: blood glucose 120 min = 2 h, sensor glucose 1 min

Number of hypoglycemia or hyperglycemia: only events of newly developed hypoglycemia or hyperglycemia were considered in the analysis

*BGA* blood glucose analysis, *SD* standard deviation, *GLI* glycemic lability index

§ Wilcoxon test before and during $p = .123$; before and after $p = .05$, during and after $p = .005$

# Wilcoxon test before and during $p = .241$, before and after $p = .415$, during and after $p = .013$

* BGAs during CGM data gaps and times of temporary system failure are included

subcutaneous CGM device, when compared to blood glucose. Consequently, it can still be assumed that subcutaneous CGM reflects actual insulin-dependent tissue glucose dynamics, which may be clinically relevant [32].

We identified that the sensor accuracy deteriorated in patients with elevated glycemic variability, as well as in the hyperglycemic range. Unfortunately, inaccuracies of CGM occurred particularly often when the need for CGM would have been most beneficial. Delayed diffusion processes become increasingly significant during rapid glucose oscillations [30, 33] and may contribute to the adverse influence of glucose variability and hyperglycemia on sensor performance. In healthy volunteers, the interstitial glucose was similar to venous glucose during steady-state conditions, but an increased time delay was observed when glucose levels were rapidly elevated by glucose infusion [38]. We could not confirm the findings reported by van Hooijdonk et al. that accuracy was influenced by a history of diabetes [17]. As already assumed in this study, inaccuracies in critically ill diabetic patients were possibly attributable to glucose fluctuations [17]. Although intravascular and interstitial space should be

considered as different glucose compartments, the sensor technology requires blood glucose calibrations [33, 39]. This is a major concern, since sensor calibration during glucose alterations may subsequently cause and amplify inaccuracies [33].

#### Safety statement

The local complication rate was acceptable, but critical safety issues arose as a consequence of inaccurate measurements. Clarke error grid and Surveillance Error-Grid showed potentially dangerous situations for the patients. Clinicians need to be aware of the fact that this device is not safe to guide insulin therapy. Even if used only to support common glucose control, this device can lead to confusing situations in the ICU routine of glucose management. As our experience showed, clinicians should always critically question the displayed CGM data.

#### Potential benefits of CGM in our ICU

Glucose monitoring with the CGM system did not improve glycemic control in the longitudinal, intra-individual analysis. Low accuracy, as well as low nurse acceptance, may be potential reasons. Besides, the time in target of our severely ill patients with and without CGM was high. As a consequence, it may be difficult to demonstrate improved control even with a device that had reasonable accuracy. Conversely, if CGM was accurate, it showed potential benefits. In contrast to the findings of Brunner et al., glycemic variability was not significantly different when calculated from accurate continuous values as compared to less frequent blood glucose values [40]. If accurate CGM systems and adapted insulin protocols are implemented in the ICU, further research is required to evaluate long-term effects on clinical outcomes in RCTs. Insulin therapy guided by CGM did not impact on time in target range and glycemic variability in previous RCTs [13, 14, 40].

#### Potential areas for improvements

- Calibration should only be performed during "steady-state" glucose levels, and not during rapid glucose fluctuations [33, 39] or adapted within a special calibration algorithm
- Improved fixation method or different localization to avoid accidental sensor removal
- Wireless device to avoid data gaps caused by occasional disconnection during bedding or mobilization, as well as accidental removals
- Integration of the continuous glucose display into the established patient monitor to reduce additional equipment
- Inclusion of a suggestion according to the local insulin treatment protocol into monitor

#### Limitations

Firstly, this was a point accuracy analysis, in which only the concurrent blood glucose sample was considered. The reporting of glucose trending is not possible in this trial. Secondly, in the clinical setting we cannot exclude that there is a delay between the taking of a blood sample and the actual analysis via blood gas analyzer, where the time-point is documented [12, 20]. Thirdly, not all nurses were familiar with the device after the initial instructions provided by the manufacturer. Fourthly, the low response rate to the questionnaires may bias the results of the nurse acceptance survey. Fifthly, due to the low number of actual hypoglycemic events, there is a lack of evidence to draw a conclusion concerning the accuracy during hypoglycemia. It has to be stressed that this study was not designed to evaluate potential benefits of CGM on glucose control and there was no variation to the insulin protocol.

## Conclusion

The Medtronic System did not perform with satisfactory accuracy, feasibility or nursing acceptance when evaluated in 20 medical-surgical ICU patients. Low point accuracy and prolonged data gaps significantly limited the potential clinical usefulness of the CGM trend data. Future studies are required to determine the clinical value of the real-time Sentrino® glucose trend data and alarms, using a validated nurse-driven insulin dosing algorithm in order to improve the safety and efficacy of blood glucose control in hospitalized patients.

## Additional file

**Additional file 1:** Supplementary Method. CGM Device. Supplementary Tables. **Table S1.** The local insulin protocol. **Table S2.** Detection of dysglycemic events. **Table S3a.** Confounding factors on MARD. **Table S3b.** Spearman´s correlation of paO2, temperature, lactate, pH-value, hemoglobin, potassium and SOFA-Score and MARD. Supplementary Figures. **Fig. S1.** Correlation of blood glucose variability per patient and MARD per patient. **Fig. S2.** MARD after time-shifting the reference a fixed amount (1 up to 30 minutes). **Fig. S3.** Nurse questionnaire.

#### Abbreviations

ICU: intensive care unit; BG: blood glucose; CGM: continuous glucose monitoring; CI: confidence interval; ICU: intensive care unit; MARD: mean absolute relative difference; PDMS: patient data management system; RCT: randomized controlled trial; SOFA: sequential organ failure assessment.

#### Authors' contributions

TW and LE contributed equally to this work, designed the study, performed data acquisition, analyzed and interpreted data and wrote the manuscript. JP performed data acquisition, analyzed nurse acceptance and critically revised the manuscript for important intellectual content. RM critical revised the manuscript and gave input on calculation of glycemic variability. SK, CS, MH critically revised the manuscript for important intellectual content. SWC revised the manuscript, performed statistical analysis and made substantial contributions to data interpretation. All authors read and approved the final manuscript.

**Author details**
[1] Department of Anesthesiology and Operative Intensive Care Medicine, Campus Charité Mitte and Campus Virchow Klinikum, Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany. [2] Berlin Institute of Health (BIH), Berlin, Germany. [3] Division Cardiac-, Thoracic-, Vascular Anesthesia and Intensive Care, Medical University Vienna, Vienna, Austria.

**Acknowledgements**
Preliminary data of this manuscript were presented at ESICM Lives 2015 as an e-poster [42].

**Competing interests**
The authors declare that they have no competing interests. Medtronic Sentrino® provided two CGM systems for the duration of the study, but had no influence on study design and data analysis.

**Availability of data and materials**
Ethical restrictions prevent public sharing of data. Editors, reviewers and interested researchers should contact the corresponding author or dairesearchdata@charite.de to request data access.

**Consent for publication**
Informed consent included consent for publication.

**Ethics approval and consent to participate**
The local ethics committee, Charité—Universitätsmedizin Berlin Ethikkommission, approved the study (Charité-EA2/095/14). Informed consent was given by the patient or legal proxy.

**Funding**
This investigation was a preliminary study within the European Critical Care Research Network (ECCRN) Grant for Practice Improvement in ICU Nutrition 2013 given to TW. SWC received financial support from Deutsche Forschungsgemeinschaft (DFG) KFO 192 TP3. Medtronic provided two CGM monitor systems for the duration of the study, but had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Received: 24 February 2016 Accepted: 28 June 2016
Published online: 21 July 2016

**References**

1. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. Crit Care Clin. 2001;17:107–24.
2. Preiser J-C, Ichai C, Orban J-C, Groeneveld ABJ. Metabolic response to the stress of critical illness. Br J Anaesth. 2014;113:945–54.
3. Weber-Carstens S, Schneider J, Wollersheim T, Assmann A, Bierbrauer J, Marg A, et al. Critical illness myopathy and GLUT4: significance of insulin and muscle contraction. Am J Respir Crit Care Med. 2013;187:387–96.
4. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc. 2003;78:1471–8.
5. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients*. Crit Care Med. 2008;36:3008–13.
6. NICE-SUGAR Study Investigators, Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, et al. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367:1108–18.
7. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–67.
8. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;354:449–61.
9. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY-S, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
10. Marik PE. Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis. Chest J. 2010;137:544.
11. Wernerman J, Desaive T, Finfer S, Foubert L, Furnary A, Holzinger U, et al. Continuous glucose control in the ICU: report of a 2013 round table meeting. Crit Care. 2014;18:226.
12. Aragon D. Evaluation of nursing work effort and perceptions about blood glucose testing in tight glycemic control. Am J Crit Care. 2006;15:370–7.
13. Boom DT, Sechterberger MK, Rijkenberg S, Kreder S, Bosman RJ, Wester JP, et al. Insulin treatment guided by subcutaneous continuous glucose monitoring compared to frequent point-of-care measurement in critically ill patients: a randomized controlled trial. Crit Care. 2014 [cited 2015 Sep 12];18. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4161875/.
14. Holzinger U, Warszawska J, Kitzberger R, Wewalka M, Miehsler W, Herkner H, et al. Real-time continuous glucose monitoring in critically ill patients. Diabetes Care. 2010;33:467–72.
15. Brunner R, Kitzberger R, Miehsler W, Herkner H, Madl C, Holzinger U. Accuracy and reliability of a subcutaneous continuous glucose-monitoring system in critically ill patients*. Crit Care Med. 2011;39:659–64.
16. Sechterberger MK, van der Voort PHJ, Strasma PJ, DeVries JH. Accuracy of intra-arterial and subcutaneous continuous glucose monitoring in postoperative cardiac surgery patients in the ICU. J Diabetes Sci Technol. 2015;9:663–7.
17. van Hooijdonk RT, Leopold JH, Winters T, Binnekade JM, Juffermans NP, Horn J, et al. Point accuracy and reliability of an interstitial continuous glucose-monitoring device in critically ill patients: a prospective study. Crit Care. 2015 [cited 2015 Sep 12];19. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4382831/.
18. Kosiborod M, Gottlieb RK, Sekella JA, Peterman D, Grodzinsky A, Kennedy P, et al. Performance of the medtronic sentrino continuous glucose management (CGM) system in the cardiac intensive care unit. BMJ Open Diabetes Res Care. 2014 [cited 2015 Sep 12];2. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4212554/.
19. Punke MA, Decker C, Wodack K, Reuter DA, Kluge S. Continuous glucose monitoring on the ICU using a subcutaneous sensor. Med Klin Intensivmed Notfallmedizin. 2015;110:360–3.
20. Finfer S, Wernerman J, Preiser J-C, Cass T, Desaive T, Hovorka R, et al. Clinical review: consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults. Crit Care. 2013;17:229.
21. Hill NR, Oliver NS, Choudhary P, Levy JC, Hindmarsh P, Matthews DR. Normal reference range for mean tissue glucose and glycemic variability derived from continuous glucose monitoring for subjects without diabetes in different ethnic groups. Diabetes Technol Ther. 2011;13:921–8.
22. Bland JM, Altman DG. Comparing methods of measurement: why plotting difference against standard method is misleading. Lancet. 1995;346:1085–7.
23. Clarke WL, Cox D, Gonder-Frederick LA, Carter W, Pohl SL. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. Diabetes Care. 1987;10:622–8.
24. Klonoff DC, Lias C, Vigersky R, Clarke W, Parkes JL, Sacks DB, et al. The surveillance error grid. J Diabetes Sci Technol. 2014;8:658–72.
25. Schierenbeck F, Franco-Cereceda A, Liska J. Evaluation of a continuous blood glucose monitoring system using central venous microdialysis. J Diabetes Sci Technol. 2012;6:1365–71.
26. van Hooijdonk RT, Winters T, Fischer JC, van Dongen-Lases EC, Krinsley JS, Preiser J-C, et al. Accuracy and limitations of continuous glucose monitoring using spectroscopy in critically ill patients. Ann Intensive Care. 2014;4:8.
27. Crane BC, Barwell NP, Gopal P, Gopichand M, Higgs T, James TD, et al. The development of a continuous intravascular glucose monitoring sensor. J Diabetes Sci Technol. 2015;9:751–61.
28. Macken L, Flower OJ, Bird S, Hammond N, Yarad E, Bass F, et al. Continuous intra-arterial blood glucose monitoring using quenched fluorescence sensing in intensive care patients after cardiac surgery: phase II of a product development study. Crit Care Resusc J Australas Acad Crit Care Med. 2015;17:190–6.
29. Basu A, Dube S, Slama M, Errazuriz I, Amezcua JC, Kudva YC, et al. Time lag of glucose from intravascular to interstitial compartment in humans. Diabetes. 2013;62:4083–7.
30. Scuffi C, Lucarelli F, Valgimigli F. Minimizing the impact of time lag variability on accuracy evaluation of continuous glucose monitoring systems. J Diabetes Sci Technol. 2012;6:1383–91.

31. Rebrin K, Sheppard NF, Steil GM. Use of subcutaneous interstitial fluid glucose to estimate blood glucose: revisiting delay and sensor offset. J Diabetes Sci Technol. 2010;4:1087–98.
32. Boyne MS, Silver DM, Kaplan J, Saudek CD. Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. Diabetes. 2003;52:2790–4.
33. Cengiz E, Tamborlane WV. A tale of two compartments: interstitial versus blood glucose monitoring. Diabetes Technol Ther. 2009;11:S-11–6.
34. Lorencio C, Leal Y, Bonet A, Bondia J, Palerm CC, Tache A, et al. Real-time continuous glucose monitoring in an intensive care unit: better accuracy in patients with septic shock. Diabetes Technol Ther. 2012;14:568–75.
35. Holzinger U, Warszawska J, Kitzberger R, Herkner H, Metnitz PGH, Madl C. Impact of shock requiring norepinephrine on the accuracy and reliability of subcutaneous continuous glucose monitoring. Intensive Care Med. 2009;35:1383–9.
36. Siegelaar SE, Barwari T, Hermanides J, van der Voort PHJ, Hoekstra JBL, DeVries JH. Microcirculation and its relation to continuous subcutaneous glucose sensor accuracy in cardiac surgery patients in the intensive care unit. J Thorac Cardiovasc Surg. 2013;146:1283–9.
37. Igarashi M, Yamatani K, Fukase N, Daimon M, Ohnuma H, Takahashi H, et al. Sepsis inhibits insulin-stimulated glucose transport in isolated rat adipocytes. Diabetes Res Clin Pract. 1992;15:213–8.
38. Jansson PA, Fowelin J, Smith U, Lonnroth P. Characterization by microdialysis of intracellular glucose level in subcutaneous tissue in humans. Am J Physiol Endocrinol Metab. 1988;255:E218–20.
39. Rebrin K, Steil GM. Can interstitial glucose assessment replace blood glucose measurements? Diabetes Technol Ther. 2000;2:461–72.
40. Brunner R, Adelsmayr G, Herkner H, Madl C, Holzinger U. Glycemic variability and glucose complexity in critically ill patients: a retrospective analysis of continuous glucose monitoring data. Crit Care. 2012;16:R175.
41. Martin Bland J, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;327:307–10.
42. Engelhardt L, Wollersheim T, Pachulla J, Mörgeli R, Balzer F, Mai K, Weber-Carstens S. Accuracy of a subcutaneous continuous glucose management system in critically ill patients. Intensive Care Med Exp. 2015;3(Suppl 1):A291.

# Additional file 1

## Supplementary Method

### CGM Device

The interstitial CGM device includes a disposable sensor, a reusable processor line and a touchscreen monitor. According to manufacturer´s information, the sensors of the interstitial CGM device consist of four independently working electrodes, which are embedded in two cannulas. This multisensory system provides enhanced signal stability and accuracy in critically ill patients. The electrodes are coated by glucose oxidase. In the enzymatic reaction, electrons are released and create an electrical gradient, which is proportional to the interstitial glucose concentration. Based on the electrical signal, measured by the parallel working electrodes, the CGM algorithm calculates one "valid" glucose value, which is displayed on a bed sided monitor. In case of "poor sensor signal" the data display is temporary terminated. Reasons include a major bias between calibration glucose value and expected sensor glucose, sensor dislocation or a weak electrical signal. Calibrations may stabilize the signal. The monitor displays "sensor failure" if the alert "poor sensor signal" remains for four hours. Visual and audible alarms are generated in case of excursions of the trend line above or below the target range. The advanced Sentrino® CGM technology avoids drug interferences of about 100 frequently used drugs, including acetaminophen, in critically ill patients.

# Supplementary Tables

**Table S1. The local insulin protocol.**

| Procedure | Glucose level |
|---|---|
| Start intravenous insulin therapy | Moderate hyperglycemia > 149mg/dl |
| Give intravenous bolus of insulin | Severe hyperglycemia >179mg/dl |
| Stop intravenous insulin therapy | 80mg/dl |
| Give intravenous bolus of glucose/dextrose | Moderate hypoglycemia <71mg/dl |
| Reduce nutrition | Moderate (>150mg/dl) or severe hyperglycemia (>180mg/dl) despite intravenous insulin infusion of max. 6-8IU/h |
| **Perform arterial blood gas analysis to control blood glucose every two to four hours and 30minutes after changes in insulin infusion.** | |

**Table S2. Detection of dysglycemic events.** n=532, 19 patients

| Reference blood glucose [mg/dl] | CGM glucose readings [mg/dl] | | | | | |
|---|---|---|---|---|---|---|
| | Glucose Range | Severe Hypoglycemia ≤40mg/dl | Moderate Hypoglycemia 41-70mg/dl | Euglycemia 71-149mg/dl | Moderate Hyperglycemia 150-179mg/dl | Severe Hyperglycemia ≥180mg/dl |
| | ≤ 40mg/dl | 0 | 0 | 1 | 0 | 0 |
| | 41-70mg/dl | 0 | 0 | 1 | 0 | 1 |
| | 71-149mg/dl | 1 | 12 | 311 | 38 | 12 |
| | 150-179mg/dl | 0 | 2 | 24 | 48 | 22 |
| | ≥180mg/dl | 0 | 1 | 7 | 15 | 36 |

Out of 188 displayed dysglycemic events, 104 (55.5%) were incorrect, including one hyperglycemia during actual hypoglycemia. The device missed 3/3 (100%) hypoglycemic events, and failed to simultaneously display 71/155 (45.8%) hyperglycemic events. The Chi-Square Test showed a significant difference in distribution between the detected dysglycemic events by reference method and CGM readings.

**Chi-Square Tests**

| | Value | df | Asymp. Sig. (2-sided) |
|---|---|---|---|
| Pearson Chi-Square | 273.827 | 16 | .000 |
| Likelihood Ratio | 244.912 | 16 | .000 |
| Linear-by-Linear Association | 197.132 | 1 | .000 |
| N of Valid Cases | 532 | | |

**Table S3a. Confounding factors on MARD.** n=532 values, 19 patients

| | Number of readings | MARD | p value (t test) |
|---|---|---|---|
| SIRS | 453 | 15.7% (95% CI 13.7-17.8) | p=.137 |
| No SIRS | 79 | 12.5% (95% CI 9.3-15.7) | |
| Vasopressors | 191 | 18% (95% CI 14-22) | p=.001* |
| No Vasopressors | 431 | 13.7% (95% CI 12.1-15.3) | |
| Diabetes mellitus | 112 | 15.8% (95% CI 12.8-18.7) | p=.888 |
| No diabetes mellitus | 420 | 15.1% (95% CI 13-17.2) | |

*Results are expressed as mean with 95% confidence interval (CI).*

*Abbreviations: Mean absolute relative difference (MARD), Systemic inflammatory response syndrome (SIRS)*

**Table S3b. Spearman´s correlation of paO2, temperature, lactate, pH-value, hemoglobin, potassium and SOFA-Score and MARD.** n=532 values, 19 patients.

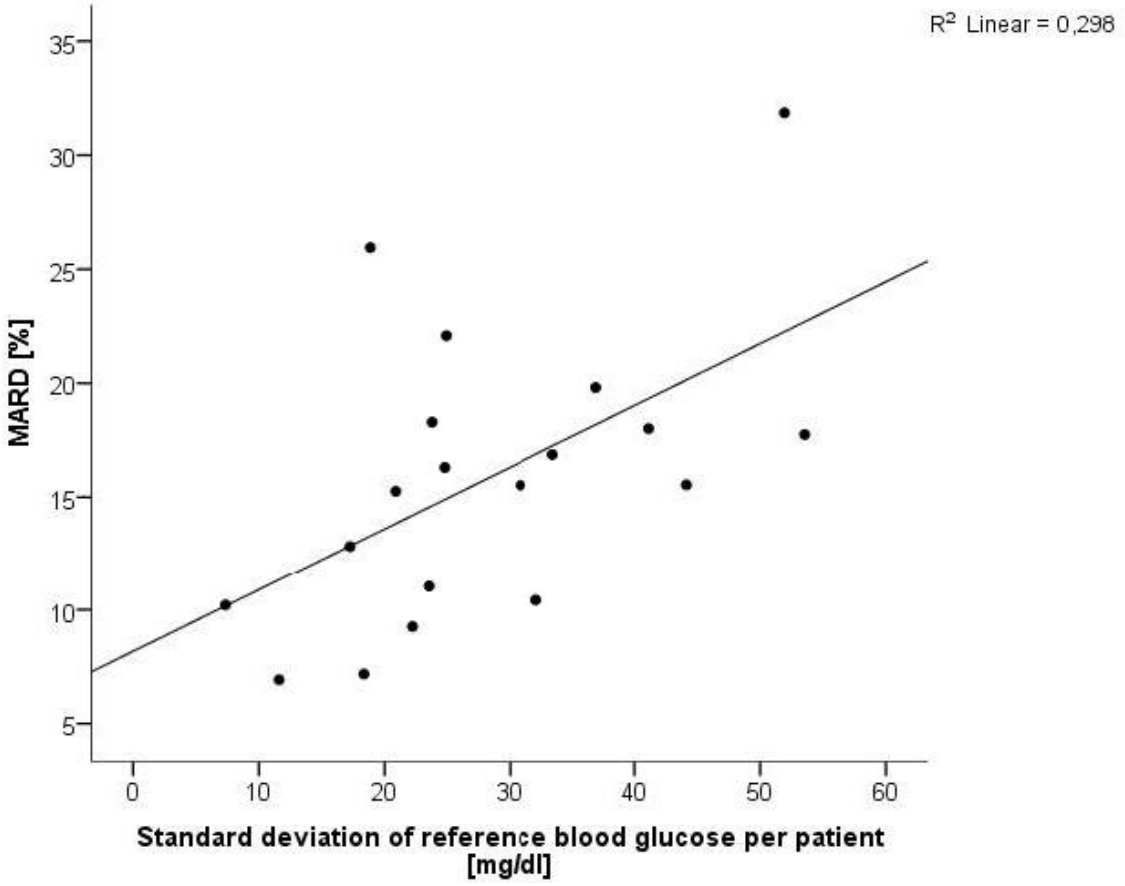
| | **MARD** | **paO2** | **temperature** | **lactate** | **pH-value** | **Hemoglobin** | **Potassium** | **SOFA Score** |
|---|---|---|---|---|---|---|---|---|
| **MARD Spearman-Rho k** | 1 | -.089 | -.049 | .064 | -.051 | .081 | -.023 | .088* |
| **p-value** | | .054 | .266 | .139 | .245 | .063 | .589 | .043 |

*Venous blood gas analyzes were excluded from the correlation of paO2 and MARD*

*Abbreviations: Mean absolute relative difference (MARD), Sequential Organ Failure Assessment (SOFA) Score*

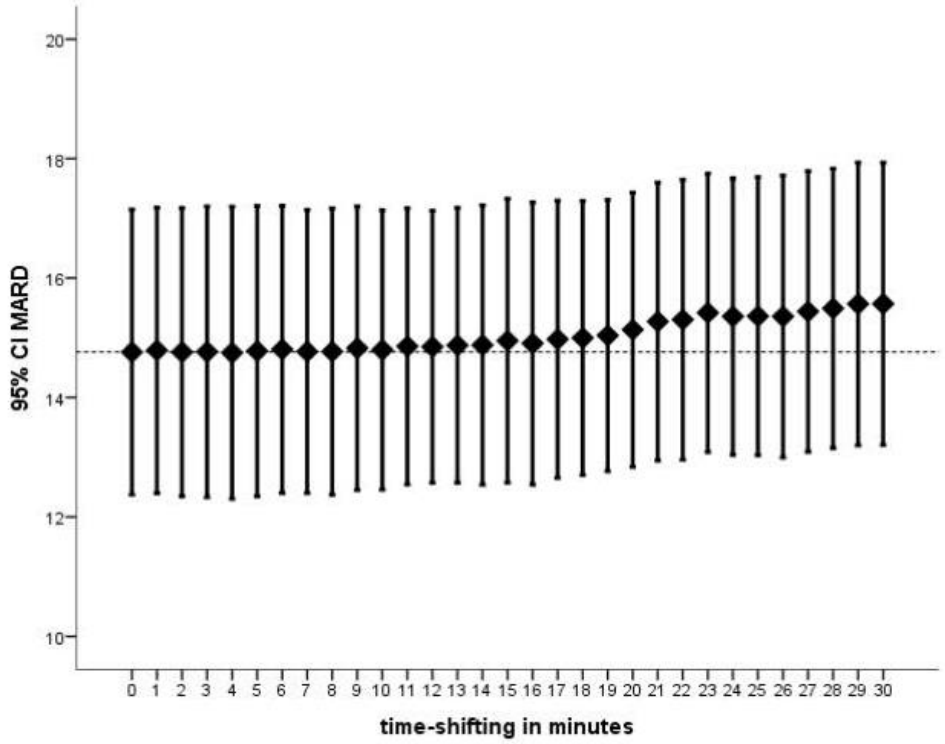
## Supplementary Figures

**Fig. S1. Correlation of blood glucose variability per patient and MARD per patient**




Glycemic variability measured in standard deviation of blood glucose. n=19, k=.593, p=.001, $r^2$=0.298.

**Fig. S2. MARD after time-shifting the reference a fixed amount (1 up to 30 minutes)**




n=19 patients, 305 reference glucose values, 9455 CGM values. There was no significant improvement or deterioration of MARD after time shifting the reference glucose a fixed amount of 1 up to 30 minutes. Even after 30 minutes, MARD was not significantly different (p=.107) compared to time point 0.

## Fig. S3. Nurse questionnaire

**Nurse acceptance of MedtronicSentrino® CGM in the daily ICU setting - Questionnaire for the nursing staff**

Date: _____ ☐ Early shift ☐ Late shift ☐ Night shift

**Do not use the device for therapeutic decisions. Perform changes in insulin therapy only after controlling blood glucose levels with the blood gas analyzer.**

| **Medtronic Sentrino® CGM** |
|---|
| **Is the use of MedtronicSentrino® CGM in this shift beneficial?**<br><br>☐ yes ☐ no if yes, name advantages? ..... |
| **Is the use of MedtronicSentrino® CGM in this shift disadvantageous?**<br><br>☐ yes ☐ no if yes, name disadvantages? ..... |
| **In case of accidental sensor removal, what was the reason?**<br><br>☐ Sensor removed by the patient<br>☐ Nursing care (bedding, washing)<br>☐ Mobilization<br>☐ surgery, CT, MRI<br>☐ Others: ..... |
| **Would you recommend to use Medtronic Sentrino® CGM in the ICU in the future?** ☐ yes ☐ no |

**Mörgeli R***, Wollersheim T*, Engelhardt LJ, Grunow JJ, Lachmann G, Carbon NM, Koch S, Spies C, Weber-Carstens S. Critical illness myopathy precedes hyperglycaemia and high glucose variability. J Crit Care. 2021 Jan 29;63:32–9.
* Shared first-authorship

https://doi.org/10.1016/j.jcrc.2021.01.012

## Curriculum vitae

Due to data protection reasons, my curriculum vitae will not be published in the electronic version of my of my work.

# Publication List

04/2021 Heinrich M, Müller A, Cvijan A, **Mörgeli R**, Kruppa J, Winterer G, Slooter AJC, Spies CD, BioCog Consortium. Preoperative Comparison of Three Anticholinergic Drug Scales in Older Adult Patients and Development of Postoperative Delirium: A Prospective Observational Study. Drugs Aging. 2021 Apr;38(4):347–54. JIF: 2.824

03/2021 Schmieding ML, **Mörgeli R**, Schmieding MAL, Feufel MA, Balzer F. Benchmarking Triage Capability of Symptom Checkers Against That of Medical Laypersons: Survey Study. J Med Internet Res. 2021 Mar 10;23(3):e24475. JIF: 5.034

01/2021 **Mörgeli R***, Wollersheim T*, Engelhardt LJ, Grunow JJ, Lachmann G, Carbon NM, Koch S, Spies C, Weber-Carstens S. Critical illness myopathy precedes hyperglycaemia and high glucose variability. J Crit Care. 2021 Jan 29;63:32–9. JIF: 2.685

10/2020 Rosenthal M, Grunow JJ, Spies CD, **Mörgeli R**, Paul N, Deffland M, Luetz A, Mueller A, Piper SK, Neuner B, Nothacker M, Weiss B. Critical care guidelines on pain, agitation and delirium management: Which one to use? A systematic literature search and quality appraisal with AGREE II. J Crit Care. 2020 Oct;59:124–9. JIF: 2.685

10/2020 Lammers F, Zacharias N, Borchers F, **Mörgeli R**, Spies CD, Winterer G. Functional Connectivity of the Supplementary Motor Network Is Associated with Fried's Modified Frailty Score in Older Adults. J Gerontol A Biol Sci Med Sci. 2020 Nov 13;75(12):2239–48. JIF: 5.236

07/2020 Heinrich M, Müller A, Lammers-Lietz F, Borchers F, **Mörgeli R**, Kruppa J, Zacharias N, Winterer G, Slooter AJC, Spies CD. Radiological, Chemical and Pharmacological Cholinergic System Parameters and Neurocognitive Disorders in Older Pre-Surgical Adults. J Gerontol A Biol Sci Med Sci. 2020 Jul 25; JIF: 5.236

04/2020 Weiss B, Grunow JJ, Rosenthal M, Hilfrich D, **Mörgeli R**, Neuner B, Borchers F, Kraft A, Krampe H, Denke C, Spies CD. Guideline-conform translation and cultural adaptation of the Addenbrooke's Cognitive Examination III into German. Ger Med Sci. 2020;18:Doc04. JIF: NA

02/2020 Lachmann G*, **Mörgeli R***, Kuenz S, Piper SK, Spies C, Kurpanik M, Weber-Carstens S, Wollersheim T, BIOCOG Consortium. Perioperatively Acquired Weakness. Anesth Analg. 2020 Feb;130(2):341–51. JIF: 4.305

12/2019 Luetz A, Grunow JJ, **Mörgeli R**, Rosenthal M, Weber-Carstens S, Weiss B, Spies C. Innovative ICU Solutions to Prevent and Reduce Delirium and Post-Intensive Care Unit Syndrome. Semin Respir Crit Care Med. 2019 Oct;40(5):673–86. JIF: 2.028

11/2019 Birkelbach O*, **Mörgeli R***, Spies C, Olbert M, Weiss B, Brauner M, Neuner B, Francis RCE, Treskatsch S, Balzer F. Routine frailty assessment predicts

postoperative complications in elderly patients across surgical disciplines - a retrospective observational study. BMC Anesthesiol. 2019 Nov 7;19(1):204. JIF: 1.695

09/2019 Olbert M, Eckert S, **Mörgeli R**, Kruppa J, Spies CD. Validation of 3-minute diagnostic interview for CAM-defined Delirium to detect postoperative delirium in the recovery room: A prospective diagnostic study. Eur J Anaesthesiol. 2019 Sep;36(9):683–7. JIF: 4.500

05/2019 Knaak C, Wollersheim T, **Mörgeli R**, Spies C, Vorderwülbecke G, Windmann V, Kuenz S, Kurpanik M, Lachmann G. Risk Factors of Intraoperative Dysglycemia in Elderly Surgical Patients. Int J Med Sci. 2019;16(5):665–74. JIF: 2.523

02/2019 Fürstenau D, Spies C, Gersch M, Vogel A, **Mörgeli R**, Poncette A-S, Müller-Werdan U, Balzer F. Sharing Frailty-related information in perioperative care: an analysis from a temporal perspective. BMC Health Serv Res. 2019 Feb 7;19(1):105. JIF: 1.987

11/2018 Olbert M, Eckert S, **Mörgeli R**, Marcantonio E, Spies C. [3D-CAM Guideline-Conform Translation for German-Speaking Countries]. Anasthesiol Intensivmed Notfallmed Schmerzther. 2018 Nov;53(11–12):793–6. JIF: 0.265

09/2018 Lachmann G, Weiss B, **Mörgeli R**, Wolf A, Spies C. The Evolution of Intensive Care Medicine: From Recumbency to Fully Functioning in Every Day Life. In: The Evolution of Intensive Care Medicine. 2018. (Nova Acta Leopoldina; vol. 421). JIF: NA

08/2018 Spies C, **Mörgeli R**, Wolf A, Müller A, Birkelbach O. Aged Patients with a Frailty Syndrome. In: Fellahi J-L, Leone M, editors. Anesthesia in High-Risk Patients [Internet]. Cham: Springer International Publishing; 2018 [cited 2018 Sep 28]. p. 285–301. Available from: https://doi.org/10.1007/978-3-319-60804-4_19. JIF: NA

08/2018 Koch S, Rupp L, Prager C, **Mörgeli R**, Kramer S, Wernecke KD, Fahlenkamp A, Spies C. Incidence of epileptiform discharges in children during induction of anaesthesia using Propofol versus Sevoflurane. Clin Neurophysiol. 2018 Aug;129(8):1642–8. JIF: 3.675

04/2018 Scholtz K, Spies CD, **Mörgeli R**, Eckardt R, von Dossow V, Braun S, Sehouli J, Bahra M, Stief CG, Wernecke K-D, Schmidt M, PERATECS Group. Risk factors for 30-day complications after cancer surgery in geriatric patients: a secondary analysis. Acta Anaesthesiol Scand. 2018 Jan 22; JIF: 2.228

12/2017 Spies C, **Mörgeli R**, Birkelbach O, Olbert M. Patienten mit Frailty: Anästhesiologie in der Verantwortung. Anästhesiol Intensivmed Notfallmed Schmerzther. 2017 Nov;52(11/12):756–7. JIF: 0.262

12/2017 Birkelbach O*, **Mörgeli R***, Balzer F, Olbert M, Treskatsch S, Kiefmann R, Müller-Werdan U, Reisshauer A, Schwedtke C, Neuner B, Spies C. [Why and How Should I Assess Frailty? A Guide for the Preoperative Anesthesia Clinic].

Anasthesiol Intensivmed Notfallmed Schmerzther. 2017 Nov;52(11–12):765–76. JIF: 0.262

12/2017 **Mörgeli R***, Wollersheim T*, Spies C, Balzer F, Koch S, Treskatsch S. [How to Reduce the Rate of Postoperative Complications in Frail Patients?]. Anasthesiol Intensivmed Notfallmed Schmerzther. 2017 Nov;52(11–12):785–97. JIF: 0.262

08/2017 **Mörgeli R**, Scholtz K, Kurth J, Treskatsch S, Neuner B, Koch S, Kaufner L, Spies C. Perioperative Management of Elderly Patients with Gastrointestinal Malignancies: The Contribution of Anesthesia. Visc Med. 2017 Aug;33(4):267–74. JIF: NA

10/2017 Koch S, Stegherr AM, **Mörgeli R**, Kramer S, Toubekis E, Lichtner G, von Dincklage F, Spies C. Electroencephalogram dynamics in children during different levels of anaesthetic depth. Clin Neurophysiol. 2017 Aug 9;128(10):2014–21. JIF: 3.614

03/2017 Spies C, Koch S, Wolf A, **Mörgeli R**, Weiss B. The Role of Intravenous Agents in Delirium. In: Total Intravenous Anesthesia and Target Controlled Infusions [Internet]. Springer, Cham; 2017 [cited 2018 Jan 17]. p. 725–48. Available from: https://link.springer.com/chapter/10.1007/978-3-319-47609-4_40. JIF: NA

02/2017 Wolf A, **Mörgeli R**, Müller A, Weiss B, Spies C. [Delirium, analgesia, and sedation in intensive care medicine : Development of a protocol-based management approach]. Med Klin Intensivmed Notfmed. 2017 Feb;112(1):65–74. [Erratum in Med Klin Intensivmed Notfmed. 2017 Mar;112(2):155. doi: 10.1007/s00063-017-0267-z.]. JIF: 0.791

12/2016 Wollersheim T, Engelhardt LJ, Pachulla J, **Moergeli R**, Koch S, Spies C, Hiesmayr M, Weber-Carstens S Accuracy, reliability, feasibility and nurse acceptance of a subcutaneous continuous glucose management system in critically ill patients: a prospective clinical trial. Ann Intensive Care 2016 Jul 21; 6:70. JIF: 3.656

08/2016 Müller A, Lachmann G, Wolf A, **Mörgeli R**, Weiss B, Spies C. Peri- and postoperative cognitive and consecutive functional problems of elderly patients. Curr Opin Crit Care. 2016 Aug;22(4):406–11. JIF: 3.063

09/2014 Koch S, Wollersheim T, Bierbrauer J, Haas K, **Mörgeli R**, Deja M, Spies CD, Spuler S, Krebs M, Weber-Carstens S. Long-term recovery In critical illness myopathy is complete, contrary to polyneuropathy. Muscle Nerve. 2014 Sep;50(3):431–6. JIF: 2.283

## Acknowledgements

My deepest gratitude goes to the patients involved in our investigations, as well as their families. Thank you for your trust, and for giving us the opportunity to learn and improve care for future patients.

I thank my advisor and mentor, Prof. Dr. Steffen Weber-Carstens, for the years of guidance and support. You have contributed immensely to my development as a researcher and as a physician. Thank you for your patience, kindness, and motivation. I would also like to thank our research team, whose hard work and cooperation made the project possible. I especially thank Dr. Tobias Wollersheim for partaking in this journey, and for always being willing to share his knowledge and experience.

To Prof. Dr. Claudia Spies, thank you for your drive and vision. Thank you for investing so heavily in young physicians, providing us the opportunity to expand our horizons. You have created an efficient and productive team, and I am glad to learn from such capable colleagues.

I am grateful to my friends and family for backing this and my many other projects and undertakings. Thank you for your trust, your patience, and your loyalty.

My darling wife, Dr. Claudia Mörgeli, I cannot thank you enough for your loving support and encouragement. Thank you for all the long days and late nights of work that were only possible because you were there, allowing this dissertation to move forward. Nevertheless, I am also grateful to my little daughter Liv for the much-needed breaks from work, and for ensuring that I lead a balanced life, come what may.