

Point-of-care Detection of Lactate in Cerebrospinal Fluid

Caspar Stephani (✉ CStephani@med.uni-goettingen.de)

University Medical Center Göttingen: Universitätsmedizin Göttingen <https://orcid.org/0000-0002-2989-8251>

Alexis H.K. Choi

University Medical Center Göttingen: Universitätsmedizin Göttingen

Onnen Mörer

University Medical Center Göttingen: Universitätsmedizin Göttingen

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Abstract

Purpose: Measurements of cerebrospinal fluid (CSF)-lactate can aid in detecting infections of the central nervous system and surrounding structures. Neurosurgical patients with temporary lumbar or ventricular CSF-drainage harbor an increased risk for developing infections of the central nervous system which require immediate therapeutic responses. Since blood-gas-analyzers enable rapid blood-lactate-measurements we were interested to find out if CSF-lactate may be reliably measured by this point-of-care technique. Methods: Neurosurgical patients on our intensive care unit (ICU) with either lumbar or external ventricular drainage due to a variety of reasons were included in this prospective observational study. Standard of care included measurements of leucocyte counts, total protein and lactate measurements in CSF by the neurochemical laboratory of our University Medical Center twice a week. With respect to this study we additionally performed nearly daily measurements of cerebrospinal-fluid by blood gas analyzers to determine the reliability of CSF-lactate measured by blood-gas-analyzers as compared to the standard measurements with a certified device. Results: 62 patients were included in this study. 514 CSF measurements were performed with blood-gas-analyzers. 180 of these could be compared to the in-house standard CSF-lactate measurements. Both techniques correlated highly significant (Pearson correlation index 0.94) even though lacking full concordance in a Bland-Altman-plotting. Of particular importance, regular measurements enabled immediate detection of central infection in 3 patients who had developed meningitis during the course of their treatment.

Conclusion: CSF-lactate was reliably measured by blood-gas-analyzers and detected developing meningitis timely. In addition to and triggering established CSF-diagnostics, CSF-lactate measurements by blood-gas-analyzers may improve surveillance of central nervous infections in patients with CSF-drainage.

This study was retrospectively registered on April 20th 2020 in the German trial register. The trial registration number is: DRKS00021466.

Take Home Message

Cerebrospinal-fluid (CSF)-lactate levels in patients with a temporary external ventricular or lumbar CSF-drainage can be measured sufficiently accurate by a common blood-gas-analyzer. Such a complementary diagnostic option may facilitate postsurgical surveillance and detection of possible infectious complications in this group of patients.

Introduction

Lactate is the end-product of anaerobic glycolysis and elevated blood-values of lactate thus indicate anaerobic cell metabolism. The tight endothelial barrier between blood and cerebrospinal fluid (CSF) largely restricts transfer of blood-lactate into CSF [1]. Accordingly, the primary source of CSF-lactate is endocranial and -spinal. While reference values of CSF-lactate are <2 mmol/l a CSF-lactate ≥ 4.2 mmol/l

is regarded as a strong indicator of a non-viral meningitis [2] with a diagnostic sensitivity and specificity of up to 93-99% and 88-94%, respectively [3, 4]. This has been demonstrated for patients after neurosurgical interventions as well [1, 5, 6] even though there are contradictive results [7, 8]. Within the group of neurosurgical patients those with a temporary external-drainage of the CSF are under particular risk for developing an infection of the CSF and the central nervous system. Therefore, regular CSF-analysis is mandatory in this patient group. Unfortunately, CSF-analysis often requires specialized laboratory facilities the availability of which often is discontinuous. Therefore, a previous study explored the ability of conventional blood-gas-analyzers to measure CSF-lactate in patients after a single lumbar puncture and demonstrated a good correlation between values measured by a blood gas-analyze and those measured with an established device in a neurochemical laboratory even though error probability increased with increasing lactate-values [9]. Here, we investigated if a conventional blood-gas-analyzer is able to reliably measure CSF-lactate in neurosurgical ICU-patients in need for regular CSF-monitoring due to a temporary external CSF-drainage.

Methods

This study was approved by the ethics committee of the University of Göttingen, and conforms to the Declaration of Helsinki. All patients or their legal guardians gave their informed consent to participation in the study.

Study design: This study was designed as longitudinal observational study. Any patient ≥ 18 years of age with a temporary lumbar or ventricular drainage based on an acute neurosurgical indication and being treated on the anesthesiological and surgical intensive care unit of the University Medical Center Göttingen was eligible for inclusion. Inclusion and data collection took place between July 2019 and October 2020. There were no specific exclusion criteria defined for this study. The study-related diagnostic measure consisted of nearly daily additional analyses of CSF taken out of the ventricular or lumbar drainage. 400-500 μl of CSF were carefully obtained with an uncoated 2ml plastic syringe under aseptic conditions at the patient-nearest outlet of the drainage. This sample was immediately (i.e. within approximately 2 minutes) analyzed by a blood gas analyzer (GEM Premier 5000®, Instrumentation Laboratory, Bedford, U.S.A.). In the majority of cases the analysis was performed twice i.e. repeated with another blood-gas-analyzer of the same specification for control purposes immediately after the first analysis. Additionally, and as part of the routine patient care an arterial blood sample was analyzed using a blood-gas-analyzer mostly within one hour of analyzing CSF. Independent from that and according to the internal standard operating procedure for CSF-analysis in patients with continuous external CSF drainage a probe of CSF was sent to the neurochemical laboratory of the hospital twice a week. Therefore, for these days we were able to compare CSF analyzed by the internal reference device for CFS-diagnostics (respon®910, Diasys, Holzheim, Germany) with that from the blood-gas-analyzer. If CSF-lactate as determined by blood-gas-analyzer and on days without regularly planned CSF-measurement by the standard method deviated significantly from the reference range or previous measurements, additional CSF was collected and send for confirmation of the results into our reference laboratory. However, pathological CSF-results as determined by blood-gas-analyzer were immediately put into clinical

context and treatment was modified if indicated based on all available data. CSF-Glucose-measurements by blood-gas-analyzers likewise were used for this study but were not compared to a certified standard method. Lactate- and glucose-measurements by the given blood-gas-analyzers are based on an amperometric technique in which an enzymatic reaction of oxygen with metabolites of lactate and glucose, respectively, drives the oxidation of a platinum electrode inducing a current which thus is proportional to the metabolite-concentration. The equation $I = (S * \text{metabolite}) + IZ$ with I being the measured current, S standing for the sensitivity and IZ for the reference current, data both of which can be derived from preanalytic settings, therefore allows calculation of the metabolite-concentration (information derived from the manufacturers product manual).

Statistical analysis: To determine correlations of measured values we calculated Pearson's correlation index and compared CSF-lactate as determined by blood-gas-analysis to CSF-lactate as measured by the internal standard-method. Additionally, CSF-lactate and blood-lactate as well as CSF-glucose and blood-glucose each measured by blood-gas-analyzers were compared in this manner. With respect to determining the accuracy of the methods we applied the method of Bland-Altman [10]. For data processing and statistical analysis we used Excel2013® (Microsoft) as well as SPSS26® (IBM).

Results

We included 62 patients (23 female, mean age 59.5 ± 12.3 years of age) with either lumbar or extraventricular drainage in our study (main diagnoses are given in table 1). There were 514 complete pairs of CSF-lactate and blood-lactate measurements. In 292 cases CSF-lactate was measured twice demonstrating high reliability of single CSF-lactate-values as measured by blood-gas-analyzers (Pearson-index 0.98) Two pairs of CSF-lactate measurements were eliminated from further analysis due to significant discordance between both lactate and other values indicating a technical or procedural problem. As expected the correlation between CSF-lactate and blood-lactate was very weak (Pearson-index: 0.14), but still statistically significant on a two-sided test-level ($p=0.001$) (Fig. 1). There were 512 complete pairs of CSF-glucose and blood-glucose measurements. In 289 cases two CSF-glucose measurements were available demonstrating high reliability of single CSF-glucose-values as measured by blood-gas-analyzers (Pearson-index 0.98) The Pearson-correlation-index regarding blood- and CSF-glucose was 0.4 being significant on a two-sided level ($p<0.001$). Descriptive statistics for CSF- and blood-glucose and -lactate can be found in table 2. A total of 180 sample-pairs consisting of a lactate measurement by a blood-gas-analyzer were paralleled by measurements by the reference method of our neurochemical laboratory and were included in the final analysis of feasibility. One pair of measurements had been excluded prior to further analysis due to delayed measurement by the reference method. Mean lactate values were 4.13 ± 1.77 mmol/l and 4.19 ± 1.86 mmol/l for reference method and blood-gas-analyzer, respectively and thus nearly identical without significant difference ($p=0.18$). Regarding our main analysis i.e. comparison between CSF-lactate measured either by the blood-gas-analyzer or the reference method we calculated a Pearson-correlation-index of 0.94 (highly significant correlation on a two-sided significance-testing ($p<0.001$)) (Fig. 2). In order to determine accuracy or equality of both methods we prepared a Bland-Altman-plot (Fig. 3). Aside of a single outlier, both methods showed a high

level of concordance for the full range of measurements with only few differences outside the reference range of 1.96*standard-deviation. In all 3 of the 62 patients with continuous external CSF-drainage who have had regular CSF-analysis by blood-gas-analyzer and who had developed a meningitis as diagnosed based on subsequent leucocyte counts in CSF, this measurement accelerated diagnosis and therapeutic intervention based on the higher frequency and availability of testing as compared to our standard procedure.

Discussion

Agreement between lactate measurements by blood-gas-analyzer and routine-CSF-measurement was high as indicated by the Pearson-correlation index of 0.94. Formally, the resulting Bland-Altman diagram does indicate that the methods compared are not fully interchangeable. However, even though no complete agreement between both methods was found with single values minimally outside the predefined boundaries of agreement (Fig. 3) unlike previously published results our values interestingly demonstrate high agreement for the full range of lactate values i.e. the correlation did not decrease with increasing lactate values. Hence, this method appears robust as indicator of CSF-alterations for the clinically relevant range of CSF-lactate values. Reasons for differences between measurements may include different times between taking CSF and its analysis which was negligible (around 2 minutes) in case of measurements by blood-gas-analyzers but could take several hours due to internal transport- and processing-times within the hospital. Due to its instability at room temperature prompt measurement of lactate (within 60 minutes after sampling) generally is preferable. In fact, processing time related decay may affect CSF-lactate values and indeed, the mean of CSF-lactate measurements by the standard analyzer including the aforementioned delay was lower (4.13 mmol/l) as compared to the results obtained by the blood-gas-analyzers (4.19 mmol/l) even though this difference was not significant. In order to address this source of possible bias lactate should have been measured simultaneously by blood-gas-analyzer and the reference method which this study did not account for. But obviously, immediacy is a systematic advantage of point-of-care-testing. Moreover, the usefulness of timely and frequent lactate-measurements as offered by blood-gas-analyzers becomes particularly apparent in light of those three patients who have had received a drainage for non-infectious maladies of the central nervous system and who later developed a catheter-associated meningitis. Rapid bed-side lactate-testing detected increases in lactate prior to our reference method which led to more immediate and accelerated anti-infective treatment as compared to the standard procedure.

Importantly, CSF lactate is an unspecific metabolite and may be elevated in a range of diseases including bacterial and fungal meningitis as well as Meningeosis neoplastica [11, 12]. The predominant source of CSF-lactate even in bacterial meningitis is the host organism, i.e. neuronal and immune cells, as studies differentiating D-lactate (prokaryotic) and L-lactate (eukaryotic) in CSF have shown [13] and which is supported by the positive correlation between leucocyte count and lactate levels in patients with meningitis [14]. Still, a cut-off for CSF-lactate of >3.5 – 4.2 mmol/l has demonstrated a high reliability in predicting a non-viral meningitis as confirmed by a recent study [3]. On the other hand, CSF-lactate values alone turned out to be of relatively low predictive value with respect to the development of a postsurgical

meningitis in neurosurgical patients [7, 8]. This has been confirmed by a recent study of neurosurgical pediatric patients and retrospective analysis of 215 CSF-samples. Authors stated especially that the “added value of LCSF for diagnosing CSF infections in children with a history of neurosurgical procedures is unclear and may be influenced by the extent of blood in the CSF” [15]. Indeed, a general limitation of CSF-lactate as a predictor of CSF-infection is possible contamination of CSF by blood-derived lactate. Almost half of our patients had suffered from subarachnoid hemorrhage often introducing a high amount of blood into CSF. While only mild effects of blood-contamination on CSF-concentrations of amino-acids and a group of vitamins were found [16] blood contamination influences CSF protein diagnostics [17]. Still, in a more experimental setting the addition of different amounts of blood to otherwise normal CSF of 33 adults did not influence the lactate level significantly, but led to higher glucose measurements [18]. In general, single CSF-lactate-measurements in post-neurosurgical patients with external CSF-drainage especially in case of major blood-contamination may be less reliable in predicting CSF-infection as compared to otherwise non-contaminated CSF. Nonetheless, by providing a longitudinal view regular postsurgical measurements of CSF-lactate may help to readily detect inflammatory events in the CSF. Additionally, point-of-care blood-gas-analyzers are able to simultaneously deliver glucose measurements in CSF. As measurements of blood-glucose by blood-gas-analyzers is part of the routine for nearly any ICU-patient a pair of CSF- and blood-glucose is easily generated. This is important since CSF-glucose on its own has a rather poor while a low ratio of CSF-to-blood-glucose of <0.4 has a well-established predictive value for detecting a non-viral meningitis [19]. Importantly however and in contrast to the CSF-lactate-measurements we did not control for the accuracy of the blood-gas-analyzer derived CSF-glucose-measurements by comparing them to results generated by an established CSF-glucose-analyzer. Hence, these values so far remain not validated. Still, a recent study demonstrated that point-of-care-glucometers can reliably measure CSF-glucose and help to detect meningitis with a sensitivity of 94% and a specificity of 91% when using a cut-off for the CSF/blood glucose ratio of 0.46 [20]. As outlined before the major advantage of the lactate measurements by a blood-gas-analyzer is the immediate availability of results. Additionally though, broad availability of blood-gas-analyzers would facilitate diagnostic capabilities in resource limited situations as has been previously suggested and is currently under investigation for point-of-care CSF-glucometry [21, 22].

Conclusion

CSF-Lactate-measurements by a blood-gas-analyzer may accelerate detection of potential CSF-inflammation in patients with temporary external CSF-drainage.

Declarations

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Conflicts of interest/Competing interests: There are no study-specific conflicts of interest for any of the authors.

Availability of data and material: The row-data of the study can be provided upon request.

Code availability: Not applicable.

Authors' contributions: All authors contributed to the study conception and design. Material preparation and data collection were performed by Jemima Choi and Caspar Stephani. Data analysis was performed by Caspar Stephani. The first draft of the manuscript was written by Caspar Stephani and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: This study was approved by the ethics committee of the University of Göttingen, and conforms to the Declaration of Helsinki.

Consent to participate: All patients or their legal guardians gave their informed consent to participation in the study.

Consent for publication: Not applicable.

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Tables

Table 1 Frequency of main diagnoses of patients with external drainage of cerebrospinal fluid included in this study. Other diagnoses were: hydrocephalus, subdural bleeding, epidural bleeding, abscess, CSF-fistula, cerebral infarction

Main diagnosis	N (female)	age
All diagnoses	62 (23)	59.5 ± 12.3
Subarachnoid hemorrhage	30 (15)	56.6 ± 12.6
Intracranial bleeding	15 (5)	63.8 ± 15.5
Traumatic brain injury	8 (0)	66.9 ± 11.5
Others	9 (3)	54.3 ± 16.1

Table 2 Descriptive statistics of glucose and lactate measurements in cerebrospinal fluid (CSF) and blood by blood-gas-analyzers

		CSF	Blood
Glucose (mmol/l) N=512	Mean (standard-deviation)	3.7 (±1.6)	8 (±2.2)
	Median (min.-max.)	3.8 (0.2 – 10.5)	7.7 (2.1 – 19.9)
Lactate (mmol/l) N=514	Mean (standard-deviation)	4.1 (±1.8)	1.1 (±0.6)
	Median (min.-max.)	3.7 (1.3 – 11.5)	0.9 (0.4 – 5.6)

Figures

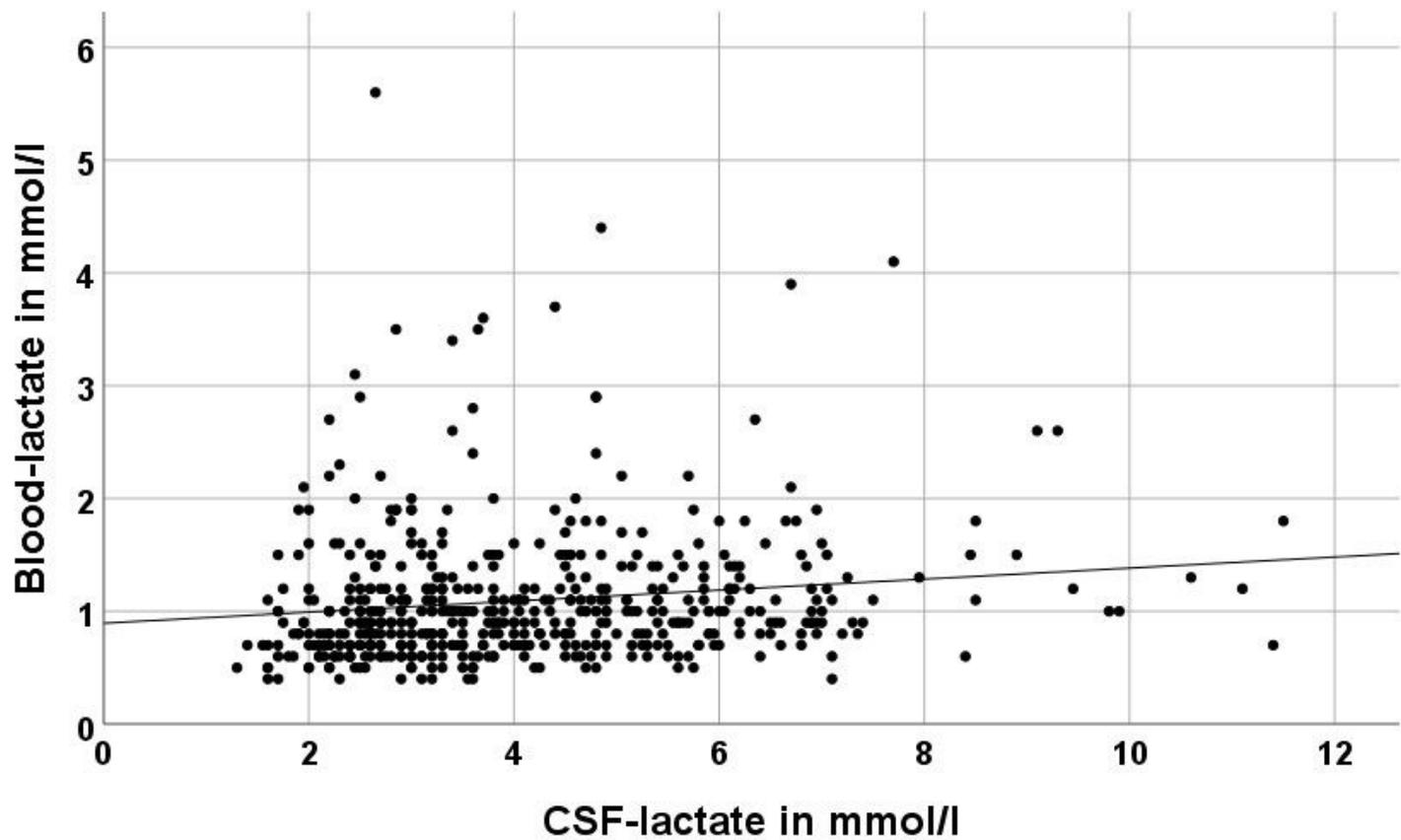


Figure 1

Pearson correlation plot demonstrating the correlation between measurements of lactate in CSF and serum in mmol/l

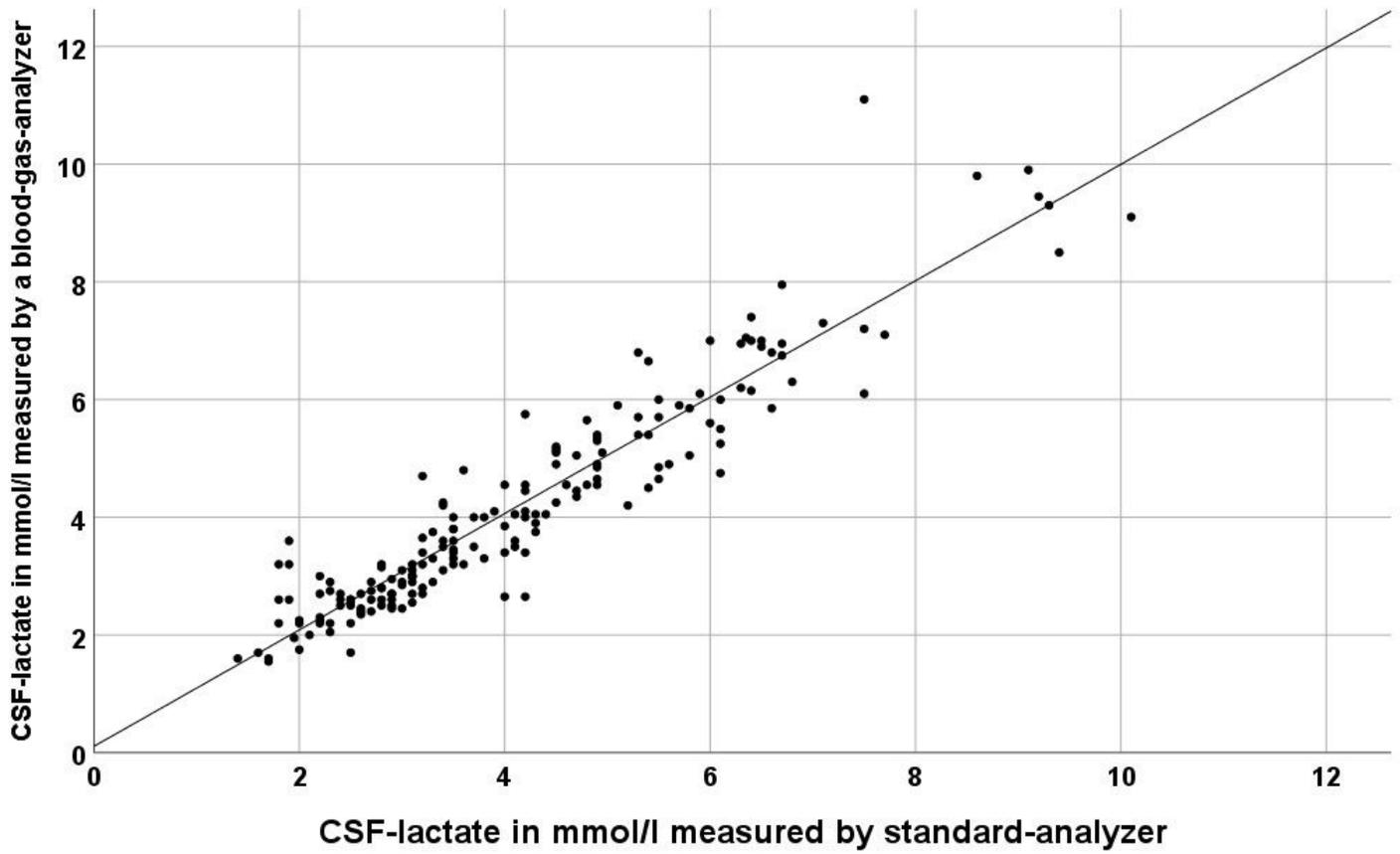


Figure 2

Pearson correlation plot demonstrating the correlation between measurements by the standard-method and by the blood gas-analyzer in mmol/l

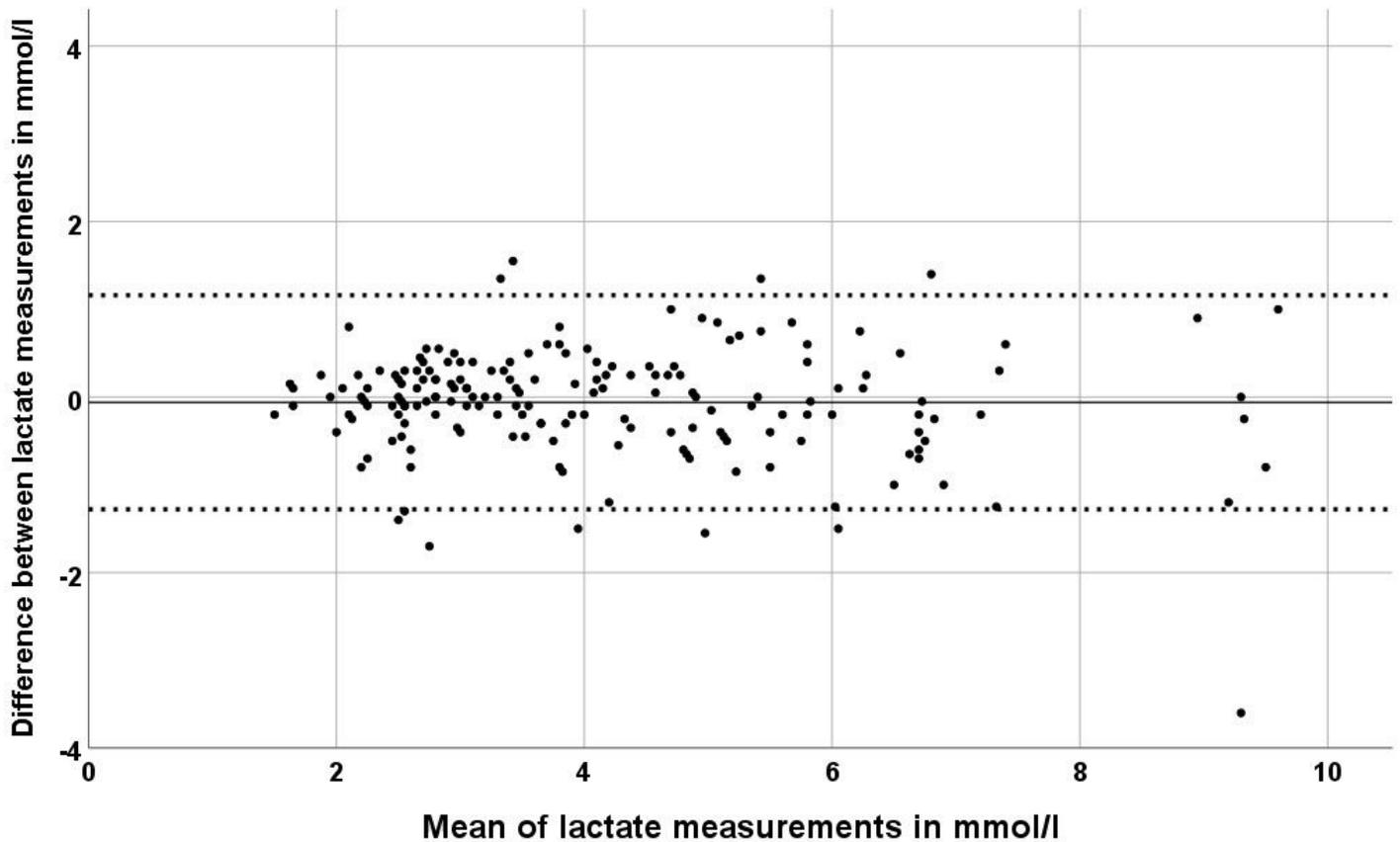


Figure 3

Bland-Altman-Plot depicting the comparison between CSF-lactate measurements with the standard-method and those with the blood gas-analyzer by relating the difference between each pair of values to their mean. The dotted lines indicate the range of 1.96 times the standard deviation from the mean of the differences. Aside of 10 marginal there is only one clear outlier (in the lower right part of the diagram) not within the reference interval of the diagram

Supplementary Files

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