Value of Cerebrospinal Fluid Lactate Levels in Diagnosing Shunt Infections in Pediatric Patients

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■ OBJECTIVE: **The diagnosis and timely treatment of shunt infections (SI) in children is of paramount importance. In some cases, the standard cerebrospinal fluid (CSF) variables will not be sufficient for an accurate diagnosis of SI. CSF lactate (LCSF) has been found to assist in differentiating bacterial from nonbacterial meningitis in non-neurosurgical patients. To the best of our knowledge, the use of lactate in diagnosing or confirming the presence of SI has not yet been discussed. The goal of the present study was to describe the role of LCSF levels in children with shunts and Ommaya reservoirs and to evaluate its role in the accurate diagnosis of shunt-related infection.**

■ METHODS: **We retrospectively collected data for a consecutive series of pediatric patients treated at a large tertiary pediatric neurosurgical department, for whom CSF samples from shunts had been collected during a 2-year period (2016–2017). The lactate levels were correlated with the presence of SI.**

■ RESULTS: **A total of 61 CSF samples were analyzed, with 6 SIs found. The LCSF levels and white blood cell count were both found to correlate with the presence of CSF infections. A cutoff value of ≥2.95 mmol/L reached a sensitivity of 83%, specificity of 83%, and positive predictive value of 50%. LCSF <2.95 mmol/L had a negative predictive value of 96%.**

■ CONCLUSIONS: **LCSF levels can be used as an additional chemical marker for the diagnosis and confirmation of SIs. An LCSF value of <2.95 mmol/L had a high negative predictive value.**

INTRODUCTION

Shunt infections (SIs) in children with hydrocephalus have been a major cause of morbidity and mortality worldwide. Up to 35% of children with a shunt will develop a SI.[1-3] The timely diagnosis, antibiotic treatment, and replacement of the shunt hardware are crucial to reducing the morbidity when an SI occurs.

The reference standard diagnosis of SI is based on a positive cerebrospinal fluid (CSF) culture. However, in an acute setting (before the final culture results are available), the clinical condition of the patient, CSF pleocytosis with a high percentage of polymorphonuclear cells, the presence of hypoglycorrhachia, and a positive gram stain are all suggestive of the presence of a bacterial infection and mandate antibiotic treatment. In certain situations, the clinical and standard CSF test results will not be enough to diagnose SI (e.g., in partially treated children), and nucleic acid detection by polymerase chain reaction (PCR) should be performed.

In recent years, it has been shown that the lactate levels in the CSF (LCSF) will correlate with the presence of spontaneous bacterial infections in both adults and children.[4] Some studies have suggested a role for LCSF as a marker of bacterial infection in adults after a neurosurgical procedure.[5-10] To the best of our

Key words
- Bacterial
- Lactate
- Meningitis
- Pleocytosis
- Shunt infection

Abbreviations and Acronyms
CSF: Cerebrospinal fluid
LCSF: Lactate in cerebrospinal fluid
PCR: Polymerase chain reaction
SI: Shunt infection
WBC: White blood cell

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knowledge, the role of LCSF in differentiating bacterial SI from other conditions has not yet been described in children.

The goal of the present study was to evaluate the role of LCSF in diagnosing SI or Ommaya reservoir infection in children.

METHODS

After institutional review board approval, we retrospectively collected data from all the children with a shunt or Ommaya tap who had undergone CSF analysis for various indications from November 2015 to December 2017. The inclusion criteria were as follows:

1. Age <20 years
2. Presented for neurosurgical care and required CSF analysis from a shunt or an Ommaya reservoir
3. Available LCSF levels
4. Information regarding clinical history and course during hospitalization available

Patients with missing data (missing LCSF or clinical course data during hospitalization) were excluded from the analysis (no patients with a suspected SI were excluded). We also excluded patients who had undergone a neurosurgical procedure or sustained a traumatic brain injury within 1 month of CSF sampling.

Diagnosis of Infection

Once a patient was suspected of having an infection because of their clinical condition and/or traditional CSF findings (excluding lactate levels), broad-spectrum antibiotics (vancomycin plus ceftriaxone) were administered until the presence of a bacterial infection had been verified. The definite diagnosis of a central nervous system infection (e.g., meningitis, ventriculitis) was determined by positive culture or positive PCR findings. In no case, did we continue antibiotics if all final values (culture and/or PCR results) were negative. In the present study, those patients with abdominal pseudocysts or shunt erosion were excluded, unless the CSF culture or PCR findings were positive.

In selected cases, nucleic acid detection by PCR was performed. PCR was not routinely performed. It was reserved for questionable cases in which the clinical condition had raised the suspicion of an infection but the culture results were negative; however, the patient had recently received antibiotics, which could have led to a distortion in the test results and partial treatment.

During the study period, none of the patients treated with this algorithm had experienced an infection relapse attributed to stopping the antibiotic regimen. Also, none of our treatment decisions were altered or determined from the LCSF levels. Thus, we considered patients who had not received a full course of treatment (based on the absence of positive culture or PCR results) to be "not infected."

The collected data included demographic data, CSF results (red blood cells, WBCs, percentage of polymorphonuclear cells, glucose, protein, LCSF, gram stain, culture, and PCR if performed). Specific technical details were recorded as follows:

1. Recent (<48 hours) treatment with antibiotics (thus, consideration of "partial treatment")
2. Indications for CSF sampling: categorized as suspected infection or other indications, such as mechanical evaluation of shunts, cytology analysis, or any other indication not related to the suspicion of an infection
3. Existence of residual tumor or leptomeningeal spread

Lactate Measurement Technique

All CSF samples were analyzed using the RAPIDPoint 500 System (Siemens Healthineers, Erlangen, Germany). This system has typically been used for blood gas analysis. Because we were unaware of this limitation during the study period, and the study was retrospective, an evaluation of this system's accuracy for LCSF measurement was performed. We analyzed an additional 19 CSF samples (none of which were infected), using both the RAPIDPoint 500 System and a standardized verified technique (Beckman coulter reagent, using the Advia 2400 System [Siemens Healthineers]). A full description of the measurement techniques has been provided in **Supplementary Appendix 1**.

Agreement between measurement techniques was observed using the interclass correlation coefficient for absolute agreement. The Spearman correlation coefficient was used to evaluate the correlation between both techniques, and the 1 sample t test was used to compare the difference between methods to 0.

We found excellent agreement (interclass correlation coefficient, 0.964; $P < 0.001$) and a high correlation ($r = 0.951$; $P < 0.001$) between the 2 methods. No significant difference was found between the 2 methods (mean difference, 0.81; $P = 0.159$). The scatter plot and Bland-Altman plot are presented in **Supplementary Figures 1** and **2**.

Statistical Analysis

The data were tabulated using an Excel spreadsheet (Microsoft, Redmond, Washington, USA). SPSS Statistics, version 22, software was used for all statistical analyses (IBM Corp., Armonk, New York, USA). The categorical variables are reported as numbers and percentages. Continuous variables were evaluated for normal distribution using a histogram and are reported as the median and interquartile range. The correlations between continuous variables were evaluated using Spearman's correlation coefficient. The lactate levels were compared between categorical variables using the Mann-Whitney U test or Kruskal-Wallis test. All statistical tests were 2 tailed, and P values < 0.05 were considered significant.

RESULTS

During a 26-month period, 142 spinal taps were performed (118 from shunt valves; 24 from Ommaya reservoirs). We excluded 27 patients who had undergone any neurosurgical surgery (excluding shunt surgery) within 1 month before the tap owing to the potential effect on the LCSF levels. An additional 54 duplicate taps from the same patients were also excluded, because only the first tap for each patient was included. Accordingly, 61 taps were included (54 from shunt valves and 7 from Ommaya reservoirs).

The average patient age was 69 ± 65 months (median, 54; interquartile range, 12–116). The indications for the taps were as follows:

1. Suspected infection, $n = 37$
2. Verification of shunt flow, measurement of CSF pressure or reduction, and cytology samples, $n = 24$

Seven patients had a concurrent tumor or vascular lesion, including pilocytic astrocytoma in 2, medulloblastoma in 2, ganglioglioma grade I, in 1, mature teratoma in 1, and cavernoma in 1. Five patients had received antibiotics within 48 hours before the spinal tap. Of the CSF samples, 6 were infected; all had been taken from shunt taps. The pathogens included *Staphylococcus epidermidis* in 3, *Haemophillus influenzae* in 1, *Pseudomonas aurginosa* in 1, and *Staphylococcus aureus* in 1.

We analyzed 2 data sets: 1 consisting of the entire cohort and 1 consisting only of patients who had undergone a tap for a suspected infection. For both data sets, the WBC and LCSF levels were significantly greater for the infected group compared with the noninfected group (Tables 1 and 2 and Figure 1).

Using the receiver operating characteristic analysis (area under the curve, 0.785), an LCSF cutoff value of 2.95 mmol/L yielded a sensitivity and specificity of 83%, a positive predictive value of 50%, and a negative predictive value of 96%. Thus, LCSF values <2.95 mmol/L excluded the presence of an infection in 96% of cases. However, values >2.95 mmol/L were associated with an infection in only 50% of cases. In addition, 2 patients had had initially reassuring CSF values (both had had normal glucose and WBC levels). However, both were found to have an infection (*S. epidermidis* in 1 and *S. aureus* in 1). Both had had low LCSF levels (1.2 and 1.4 mmol/L).

Table 1. Differentiation Between Variables Stratified by Actual Infection for Entire Group

Infection	Patients (*n*)	Median (IQR)	*P* Value
Age at tap (months)			0.75
Yes	6	63.8 (18.7–123.4)	
No	55	48.8 (12.4–121.5)	
WBCs in CSF (cells/μL)			0.007
Yes	6	155 (5.2–1867.5)	
No	52	1.5 (0–26.2)	
PMN cells in CSF (%)			0.03
Yes	6	73 (23.5–87)	
No	38	0 (0–65.5)	
RBCs in CSF (cells/μL)			0.468
Yes	6	341 (0–4291)	
No	51	0 (0–325)	
Glucose in CSF (mg/dL)			0.176
Yes	6	35.5 (16.2–68.5)	
No	55	60 (46–67)	
Protein in CSF (mg/dL)			0.268
Yes	6	106 (17.7–251)	
No	55	28 (10–123)	
Lactate in CSF (mmol/L)			0.011
Yes	6	4.8 (2.5–9.4)	
No	55	1.8 (1.4–2.5)	

IQR, interquartile range; WBCs, white blood cells; CSF, cerebrospinal fluid; PMN, polymorphonuclear; RBCs, red blood cells.

DISCUSSION

To the best of our knowledge, the present study is the first to evaluate the role of LCSF levels for differentiating infected and noninfected CSF samples from shunts or Ommaya reservoirs in pediatric neurosurgical patients. Our results suggest 2 important points. First, we found a clear correlation between the LCSF levels and the development of SIs. Second, LCSF levels <2.95 mmol/L seemed to indicate a noninfected shunt (negative predictive value, 96%). However, only 50% of cases with LCSF values >2.95 mmol/L were associated with an infection (positive predictive value, 50%).

SIs will develop in ≤35% of hydrocephalic children.[1-3,11] Most infections occur during the first 3 months after shunt surgery; however, late infections can also develop. Suspicion of a SI has been based on clinical symptoms and signs, including fever, headache, vomiting, nuchal rigidity, local signs of infection over a shunt, and abdominal pain. Many patients with a shunt will not present with clear symptoms of SI, either because of an overlap with other concurrent diseases (e.g., fever, headache, vomiting, abdominal pain) or because of the baseline neurological findings (e.g., an inability to complain of headaches, spasticity). Thus, differentiating between infected and noninfected CSF in a child with fever will not always be trivial, and a CSF sample will be required.

LCSF testing has been included in the evaluation of spontaneous meningitis to differentiate between bacterial and aseptic meningitis in children and adults.[4,12] Lactate is produced by certain bacteria. Lactate is also a product of anaerobic metabolism of the brain tissue caused by hypoperfusion and various cytokines.[6] It has been shown that LCSF has a greater sensitivity, specificity, positive predictive value, and negative predictive value compared with other conventional measures such as glucose, protein, and cell count and differentiation.[12,13] Other parameningeal infections can also increase the LCSF levels.[14,15] In addition, it has been demonstrated that treatment with antibiotics can alter the LCSF levels in spontaneous meningitis and that a low LCSF level in pretreated patients does not rule out the presence of bacterial meningitis.[4,15]

To date, we have found very limited data relating LCSF levels in CSF samples taken from shunts.[6] The indications for shunt (or Ommaya) tapping include evaluation of an infection, mechanical issues (to verify proximal or distal flow), and oncological indications (e.g., cytology analysis or intrathecal chemotherapy). In the present study, we have demonstrated that in this subpopulation, the LCSF levels correlated with the

Table 2. Differentiation Between Variables Stratified by Actual Infection for Patients with Suspected Infection

Infection	Patients (*n*)	Median (IQR)	*P* Value
Age at tap (months)			0.105
Yes	6	63.8 (18.7–123.4)	
No	31	14.2 (7.4–48.8)	
WBCs in CSF (cells/μL)			0.046*
Yes	6	155.5 (5.2–1867)	
No	30	7.5 (1–67.5)	
PMN cells in CSF (%)			0.376
Yes	6	73 (23.5–87)	
No	21	47 (2.5–79)	
RBCs in CSF (cells/μL)			0.881
Yes	6	341 (0–4291)	
No	29	20 (0–689)	
Glucose in CSF (mg/dL)			0.185
Yes	6	35.5 (16.2–68.5)	
No	31	55 (44–67)	
Protein in CSF (mg/dL)			0.506
Yes	6	106 (17.7–251)	
No	31	33 (15–155)	
Lactate in CSF (mmol/L)			0.028*
Yes	6	4.8 (2.5–9.4)	
No	31	1.9 (1.5–2.8)	

IQR, interquartile range; WBCs, white blood cells; CSF, cerebrospinal fluid; PMN, polymorphonuclear; RBCs, red blood cells.
*Statistically significant.

presence of infection, up to a cutoff of 2.95 mmol/L. However, the strongest correlation with the LCSF levels was for exclusion of an infection (<2.95 mmol/L). The positive predictive value for levels >3 mmol/L demonstrated only a 50% correlation.

In addition, LCSF levels have been shown to increase in several noninfectious clinical scenarios, such as stroke,[16,17] seizures,[14,18,19] head injury,[14] and hypoglycemic coma.[20] In addition, the effect of CSF contaminated by blood on the LCSF levels is uncertain. Begovac et al.[21] stated that adding a blood drop to a CSF sample would not alter the LCSF levels. Others have shown that LCSF will be increased after in vitro and in vivo subarachnoid hemorrhage.[17,22-24]

In adult neurosurgical patients, LCSF has been generally shown to correlate with the presence of bacterial CNS infection, with high sensitivity, specificity, and positive and negative predictive values.[5-10,25] Generally, most studies have focused on patients with suspected meningitis,[5-10] with CSF sampled from lumbar taps,[5-8] and LCSF was found to differentiate bacterial and nonbacterial conditions. LCSF values of ≥3.45–5.9 mmol/L correlated significantly with the presence of bacterial infection.[5-8,10]

Study Limitations

The present study was a retrospective analysis, and, as such, some clinical data could have been missed. However, we had no false-negative results of infection. All the patients had been followed up over time and no late-onset infection developed, which could have suggested a misdiagnosis at the time of CSF sampling.

The number of included cases was relatively small (61 patients within 26 months), and only 6 of the patients had developed an infection. However, to the best of our knowledge, the present study is the largest to date to focus on this entity and might serve as a baseline platform for future larger studies, potentially a collaborative multicenter study.

Although some patients had antibiotic-impregnated shunts and others did not, we are unaware of any effect of shunt hardware on the LCSF levels. In addition, the present study had not sought to correlate the LCSF levels with the type of hardware used. In addition, no baseline LCSF levels were available. Potentially, the LCSF levels could be altered (irrespective of any infection) by the presence of hydrocephalus or the presence of certain brain tumors in specific locations. Surgery, tissue ischemia, and the use of blood products can also alter LCSF levels. However, we did not include any patients who had undergone recent surgery (within <1 month) or had recently experienced a brain injury.

Because of the small number of infections, we could not evaluate the effect of bacteria type or antibiotic response on the LCSF levels. For the same reason, our receiver operating characteristic analysis for sensitivity and specificity was limited. It is possible that larger numbers would improve the area under the curve value. We also could not discuss the natural history of LCSF over time, because multiple samples were not evaluated.

CONCLUSIONS

LCSF levels correlated with the presence of SIs. In our study, its major role was in ruling out infection when the values were <2.95 mmol/L. The role of LCSF in children who have undergone a recent neurosurgical procedure should be evaluated further because neurosurgical procedures could also potentially alter LCSF levels in noninfected patients. Thus, the above interpretation of LCSF levels should be limited to patients without recent surgery. We recommend further study of LCSF levels in all children with a history of any neurosurgical disease and a better definition of its value for infected and other clinical conditions.

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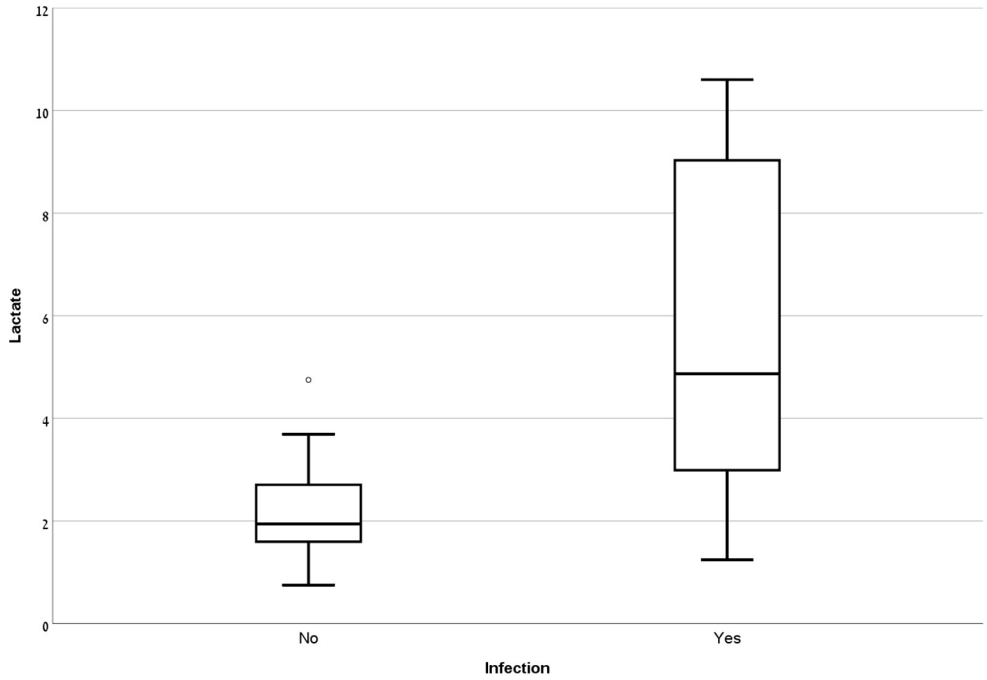

Figure 1. Box plot distribution of cerebrospinal fluid lactate according to the presence or absence a cerebrospinal fluid infection ($P = 0.011$).

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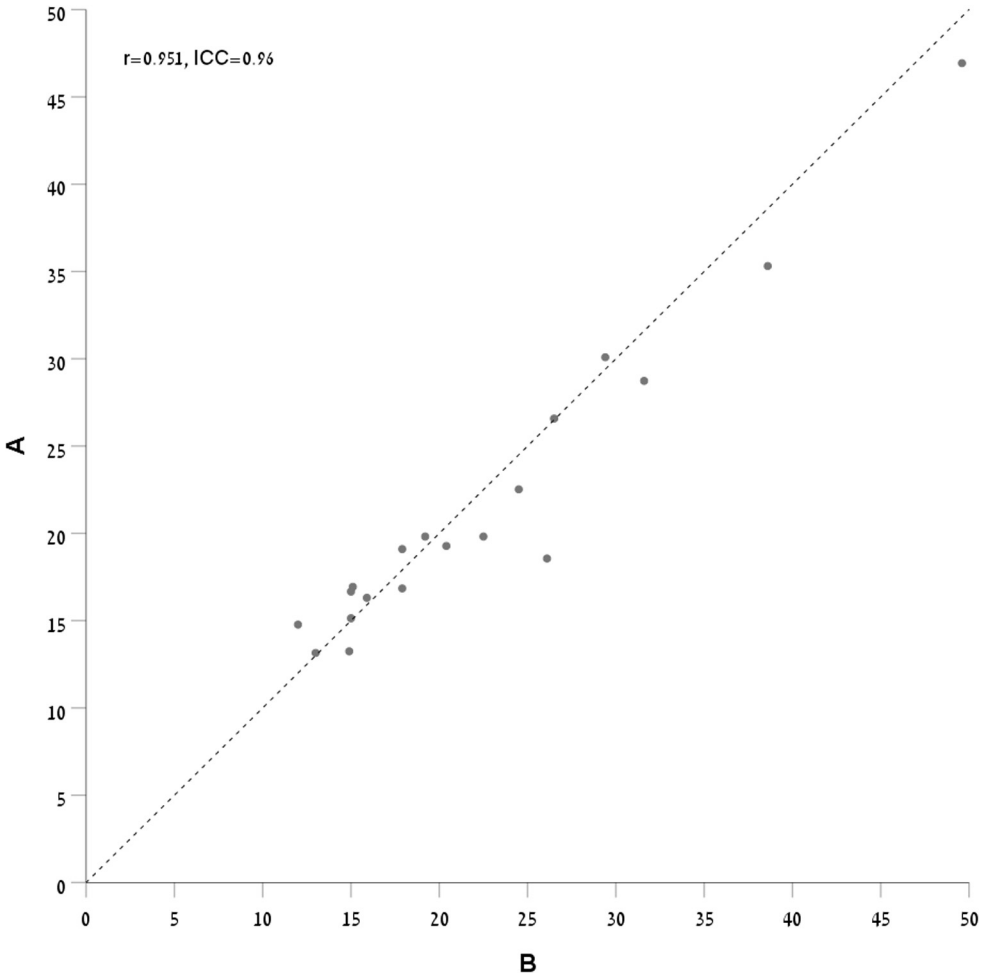
SUPPLEMENTARY APPENDIX 1: LACTATE MEASUREMENT TECHNIQUE

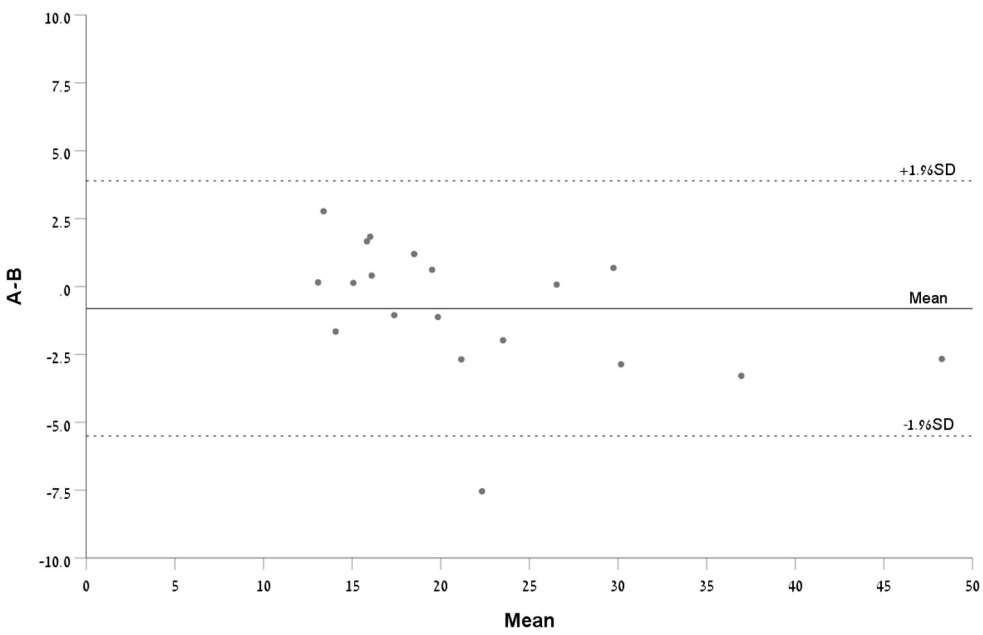
All cerebrospinal fluid (CSF) samples were analyzed using the RAPIDPoint 500 (Siemens Healthineers). This system is intended for use in point of care and laboratory systems for blood gas analysis, including lactate in whole blood. The lactate measurement using the RAPIDPoint 500 system (Siemens Healthineers) is performed by a sensor that incorporates amperometric technology. The amperometric RAPIDPoint 500 (Siemens Healthineers) lactate sensor interacts with the lactate sample to initialize the process that ends in electrochemical potential. This potential is directly proportional to the lactate concentration in the sample.

Thus, an evaluation of this system for CSF lactate measurement was performed by analyzing 19 CSF samples using the RAPIDPoint 500 (Siemens Healthineers) compared with a standardized verified technique (Beckman coulter reagent) using the Advia 2400 (Siemens Healthineers). L-lactate is oxidized to pyruvate and hydrogen peroxide by lactate oxidase. A colored product is produced by the reaction of peroxidase, hydrogen peroxide, 4-aminoantipyrine, and a hydrogen donor. The colored product is measured photometrically. The performance of this assay has <2.1% coefficient of variation. This performance was approved in the Advia 2400 (Siemens Healthineers) according to the conventional validation protocol.

Agreement between measurement techniques was observed using the interclass correlation coefficient for absolute agreement. Spearman's correlation coefficient was used to evaluate the correlation between the 2 techniques, and the 1-sample t test was used to compare the difference between the 2 methods to 0. Excellent agreement (interclass correlation coefficient, 0.964; $P < 0.001$) and high correlation ($r = 0.951$; $P < 0.001$) was found between the 2 methods. No statistically significant differences were found between the 2 methods (mean difference, 0.81; $P = 0.159$). A scatter plot and Bland-Altman plot are presented in **Supplementary Figures 1** and **2**, respectively.



Supplementary Figure 1. Scatter plot comparing the measurement of lactate using the 2 methods. *A* indicates that lactate was measured using the RAPIDPoint 500 system (Siemens Healthineers), and *B* indicates that lactate was measured using the Advia 2400 system (Siemens Healthineers). ICC, interclass correlation coefficient.



Supplementary Figure 2. Bland-Altman plot comparing the measurement of lactate using the 2 methods. *A* indicates that lactate was measured using the RAPIDPoint 500 system (Siemens Healthineers), and *B* indicates that lactate was measured using the Advia 2400 system (Siemens Healthineers). SD, standard deviation.