

Letter to the Editor

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Stability of lactate in venous blood gas and sodium fluoride-potassium oxalate plasma: a 6-year retrospective database analysis

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To the Editor,

An increase in circulating lactate reflects impaired tissue oxygenation that may occur in many critical pathological processes, such as acute pulmonary insufficiency, severe trauma, cardiogenic, hemorrhagic, or septic shock [1]. Hence, lactate is of great importance for intensive care units and emergency rooms, and many studies have pointed out its monitoring in the blood as a useful tool in the risk assessment of patient mortality [2]. With the intent of reducing morbi-mortality, the Third International Consensus Definitions for Sepsis and Septic Shock include lactate in their guidelines, emphasizing the need for repeated measurements in cases of initial hyperlactatemia [3]. Furthermore, lactate kinetics-guided therapies have shown their convenience in improving the clinical

outcomes of patients with sepsis-associated hyperlactatemia [4]. From a laboratory point of view, lactate measurements are known to be influenced by many pre-analytical factors, the best known of which are tube additives, time and temperature of transport or storage, and hemolysis [5]. In blood specimens, lactate concentration increases over time, because of the continuing glycolysis, requiring stabilizing antiglycolytic agents like sodium fluoride, usually associated with an anticoagulant, like potassium oxalate or K_3EDTA . However, lactate from critically ill patients is mainly measured using heparinized blood gases syringes that do not contain antiglycolytic stabilizer, and therefore in which lactate concentration may increase over time. Tubes with additives are alternatives to counteract this drawback. Lactate levels and stability have been studied in different types of tubes or in blood gases, but rarely compared in both, and most of the time in groups of limited sizes and/or using assay protocols that do not reflect the laboratory routine [6, 7]. Therefore, based on a retrospective database analysis, we aimed to 1) compare lactate concentrations measured in venous blood gas (VBG) to those assayed in sodium fluoride/potassium oxalate plasma (NaF/KOx) and 2) determine the limit turnaround time (LTAT) of lactate in these two matrixes.

In our laboratories, VBG samples are mainly drawn for the measurement of gases/electrolytes associated with a lactate (50%), gases/electrolytes without lactate (46%), or lactate without gases/electrolytes (4%). VBG lactate ($n=86,844$), and NaF/KOx plasma lactate ($n=22,858$) results, assayed over a 6.5-year period (from October 2014 to May 2021), were extracted from our laboratory information system (GLIMS® software, MIPS-CliniSys, Chertsey-Surrey, UK). These two tests were proposed on the same medical prescription sheet; hence, we paired the concomitant VBG and NaF/KOx plasma results. Turn-around time (TAT) was calculated as the time between blood sampling and technical validation. Exclusion

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criteria were 1) VBG and NaF/KOx plasma with a transport time ≤ 1 min (considered as the minimum transport time along the pneumatic tube), 2) VBG with a TAT > 60 min and NaF/KOx plasma with a TAT > 120 min, 3) lactate results out of linearity ranges (blood gas: 0–30 mmol/L; plasma: 0.02–13.32 mmol/L), and/or 4) NaF/KOx plasma with hemolysis (≥ 30 g/dL hemoglobin), icterus (≥ 40 μ mol/L total bilirubin), and/or lipemia (≥ 10 lipemia index). Venous blood was collected on heparinized safePICO® 1.5 mL blood gas syringes (references 956-622 or 956-616; Radiometer Medical ApS, Copenhagen, Denmark), and on BD Vacutainer® NaF/KOx (2.5/2 mg/mL) 4.0 mL tubes (reference 368921; Becton-Dickinson, Franklin Lakes, NJ, US). As recommended, VBG syringes were kept at room temperature from sample collection to analysis since plastic syringes are known to be more permeable to gases at lower temperatures, and since ice increases the risk of hemolysis [8, 9]. Over the study period, VBG lactate was measured using amperometry on ABL800Flex® blood gas analyzers (Radiometer), and NaF/KOx plasma lactate was measured using an enzymatic method (lactate oxidase; Abbott reagent kit: 9D89-20) on Architect C16000/C8000 or Alinity analyzers (Abbott, Chicago, IL, US). Statistics and plots were computed in R (version 4.0.5, R Foundation, Vienna, Austria) using the following comparison tests: weighted Deming regression and Passing-Bablok ('mcr' R-package), and Bland-Altman plots ('blandr' R-package), showing the mean bias and its lower and upper limits of agreement (LLoA and ULoA) calculated as bias ± 1.96 * standard deviation. The distribution of

differences between VBG and NaF/KOx plasma lactate was not normally distributed, displaying asymmetry and skewness. We therefore added the median, 2.5th and 97.5th quantile-based regression curves on the Bland-Altman plots. The LTATs were determined using a quantile-based regression of the lactate-to-TAT relationships, considering the within-subject biological variation from Ricós (CVi $\pm 27.2\%$) and the desirable analytical CV (CVa ± 0.5 * CVi, i.e. $\pm 13.6\%$) as allowable limits. The quantile-based regression curves were determined using the quantile additive generalized model 'qgam' R-package [10], programmed with cubic regression spline smooths, and at least 10 base dimensions to allow sufficient degrees of freedom.

A total of 2,308 paired VBG and NaF/KOx plasma lactate results were selected. The weighted Deming regression and Bland-Altman plot are displayed in Figure 1A, B. Mean lactate concentration was 20% lower in NaF/KOx plasma than in VBG (1.53 ± 1.34 vs. 1.83 ± 1.21 mmol/L), with a mean bias of -0.30 mmol/L (LLoA -1.10 , ULoA $+0.50$). The Passing-Bablok-based intercept of VBG lactate (y) was $+0.33$ mmol/L (95%CI from $+0.31$ to $+0.35$) with a slope 0.96 (95%CI from 0.94 to 0.98), as compared to NaF/KOx plasma (x). The lactate-to-TAT relationships are shown in Figure 2A, B. VBG lactate increased over time, up to the limit CVa reached at 38 min (95%CI 33–44 min), but remained within the limit CVi up to 60 min. Despite a slight decrease, plasma lactate remained within the limit CVa with a median bias at 120 min of -5.5% (min -14.3% , max $+3.3\%$).

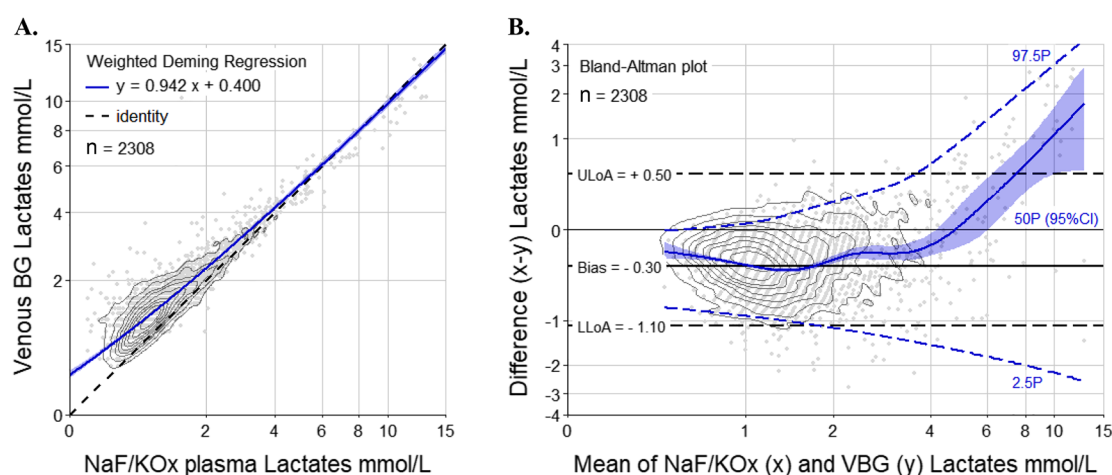


Figure 1: Weighted Deming regression (A) and Bland-Altman plot (B) of the comparison between VBG and NaF/KOx plasma lactate concentrations.

The concentric gray contour lines represent the 10-by-10 percentiles of the nonparametric kernel density estimation. The blue smoothed curves (B) represent the median (50P, with its 95% confidence interval), the 2.5th (2.5P), and the 97.5th (97.5P) quantile-based biases. BG, blood gas; NaF/KOx, sodium fluoride-potassium oxalate; ULoA and LLoA, upper and lower limit of agreement.

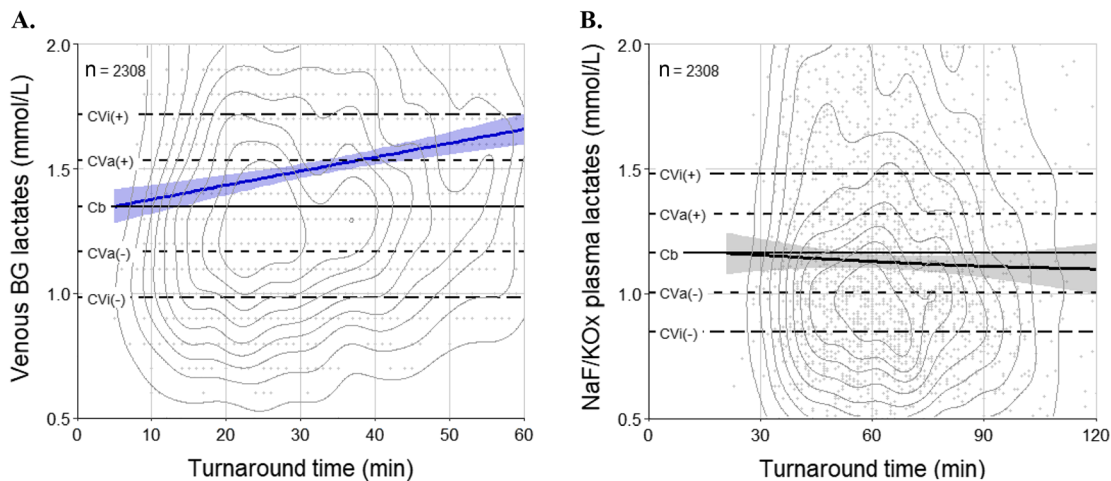


Figure 2: Relationship between lactate concentrations and turnaround times for VBG (A) and NaF/KOx plasma (B).

The solid horizontal black lines represent the lactate concentrations at baseline (Cb). The concentric gray contour lines represent the 10-by-10 percentiles of the nonparametric kernel density estimation. The short-dashed and long-dashed horizontal black lines represent the allowable analytical variation (CVa $\pm 13.6\%$) and the allowable intra-individual variation (CVi $\pm 27.2\%$) from Ricós et al. respectively. The blue and gray smoothed curves and areas represent the median quantile-based regressions with their 95% confidence intervals. BG, blood gas; CV, coefficient of variation; NaF/KOx, sodium fluoride-potassium oxalate.

Few studies have compared blood gas vs. NaF/KOx lactate. In 2011, Leino et al. observed lower lactate values using an ABL825 analyzer compared to a Roche ModularP800 core analyzer (mean difference of -0.21 mmol/L), especially at high concentrations [11]. Similarly, we observed lower VBG lactate at high concentrations (>4 mmol/L, Figure 1B), but contrary to this study, our mean lactate was higher in VBG than in NaF/KOx ($+0.30$ mmol/L). One could argue that the lactate in the Leino et al. study was assessed on 30 samples only, assayed first on heparin blood gas syringes (without specification about the arterial or venous origin), from which the remaining blood was then transferred into secondary tubes and centrifuged for lactate measurement in the supernatant heparin plasma, a matrix which is not comparable to NaF/KOx plasma. Finally, Leino et al. concluded to a good correlation (slope 0.96; intercept -0.08 mmol/L), and a negligible variability considering the allowable clinical limit for lactate of $\pm 12\%$ (Finnish recommendations). We cannot claim that our mean bias of $+20\%$ of VBG lactate is negligible, but this difference remains within the Ricós-based intra-individual variation, keeping in mind that the intra-patient biological variation in patients with hyperlactatemia >4 mmol/L is about half that of normal patients [12]. Regarding stability, lactate has been shown to be stable for 24 h in NaF/KOx and NaF/K₃EDTA plasma from tubes centrifuged within 15 min after venepuncture, and kept at room temperature [6, 7]. However, the

stability is shortened to 6 h if the NaF/K₃EDTA tubes are not centrifuged immediately [6]. To our knowledge, no study has investigated lactate stability in NaF/KOx tubes kept up to 2 h before centrifugation. Like us, Zavorsky et al. showed that blood gas lactate remains stable up to 45 min at room temperature, with a mean increase of 0.008 mmol/L/min [7].

To conclude, lactate concentrations are higher in VBG than in NaF/KOx plasma, at least for concentrations <4 mmol/L, but the difference remains within the intra-individual variation. As expected, NaF/KOx plasma lactate remains stable and within the analytical variation for at least 2 h. VBG lactate can be considered as stable for up to 45 min from an analytical standpoint, and for up to 1 h considering the intra-individual variation.

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