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Analytical and pre-analytical performance characteristics of a novel cartridge-type blood gas analyzer for point-of-care and laboratory testing

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ABSTRACT

Background: Point-of-care blood gas test results may benefit therapeutic decision making by their immediate impact on patient care. We evaluated the (pre-)analytical performance of a novel cartridge-type blood gas analyzer, the GEM Premier 5000 (Werfen), for the determination of pH, partial carbon dioxide pressure (pCO_2), partial oxygen pressure (pO_2), sodium (Na^+), potassium (K^+), chloride (Cl^-), ionized calcium ($_iCa^{2+}$), glucose, lactate, and total hemoglobin (tHb).

Methods: Total imprecision was estimated according to the CLSI EP5-A2 protocol. The estimated total error was calculated based on the mean of the range claimed by the manufacturer. Based on the CLSI EP9-A2 evaluation protocol, a method comparison with the Siemens RapidPoint 500 and Abbott i-STAT CG8 + was performed. Obtained data were compared against preset quality specifications. Interference of potential pre-analytical confounders on co-oximetry and electrolyte concentrations were studied.

Results: The analytical performance was acceptable for all parameters tested. Method comparison demonstrated good agreement to the RapidPoint 500 and i-STAT CG8 +, except for some parameters (RapidPoint 500: pCO_2, K^+, lactate and tHb; i-STAT CG8 +: pO_2, Na^+, $_iCa^{2+}$ and tHb) for which significant differences between analyzers were recorded. No interference of lipemia or methylene blue on CO-oximetry results was found. On the contrary, significant interference for benzalkonium and hemolysis on electrolyte measurements were found, for which the user is notified by an interferent specific flag.

Conclusion: Identification of sample errors from pre-analytical sources, such as interferences and automatic corrective actions, along with the analytical performance, ease of use and low maintenance time of the instrument, makes the evaluated instrument a suitable blood gas analyzer for both POCT and laboratory use.

1. Introduction

Point-of-care (POC) blood gas analyses could help in therapeutic monitoring and decision making of severely ill patients [1,2]. This is especially true when biochemical parameters are exceeding the clinical reference range, for which acute and effective treatment is essential. The last years, blood gas analyzers have become more sophisticated and are able to measure, along whole blood pH, partial carbon dioxide pressure (pCO_2) and partial O_2 pressure (pO_2), several electrolytes [sodium (Na^+), potassium (K^+), chloride (Cl^-), ionized calcium ($_iCa^{2+}$)], co-oximetry parameters [total hemoglobin (tHb), oxyhemoglobin (O_2Hb), carboxyhemoglobin (COHb), methemoglobin (metHb), deoxyhemoglobin (HHb)], glucose and metabolites (lactate, total bilirubin). The availability of rapid test results might promote earlier diagnosis and treatment decision making. Therefore, POC analyzers are attractive therapeutic instruments in acute patient care [3].

An important challenge in POC is maintaining consistent quality control across all testing sites with a wide range of operators. QC pro-

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; RCPA, Royal College of Pathologists of Australasia; eTE, estimated total error; ATE, allowable total error; CV, coefficient of variation; SD, standard deviation; SLS, sodium lauryl sulphate; pCO_2, partial carbon dioxide pressure; pO_2, partial oxygen pressure; Na^+, sodium; K^+, potassium; Cl^-, chloride; $_iCa^{2+}$, ionized calcium; tHb, total hemoglobin; ICU, Intensive Care Unit; POC, point-of-care; QC, Quality Control

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Table 1
Evaluation of total imprecision (CV%) on the GEM Premier 5000. Deviations from the preset criteria (Ricos and/or Lab) are indicated in bold.

Analyte	Total imprecision				Criteria			
	Level	Mean	SD	CV (%)	Ricos (%)	Lab (%)	i-STAT CG8 + (%)	Manufacturer (%)
pH	Low	7.133	0.007	0.10	0.1	0.2	0.1	0.3
	Medium	7.372	0.007	0.09	0.1	0.2	0.1	0.3
	High	7.581	0.003	0.04	0.1	0.2	0.1	0.3
pCO_2, mmHg	Low	14.0	0.000	0.0	2.4	7.6	3.3	17.9
	Medium	37.7	0.931	**2.5**	2.4	2.7	1.4	7.1
	High	90.0	2.041	2.3	2.4	7.6	1.5	4.0
pO_2, mmHg	Low	31.8	1.771	**5.7**	4.8	5.1	3.0	16.1
	Medium	87.0	2.643	**3.0**	4.8	1.7	2.5	5.7
	High	349.5	13.952	**4.0**	4.8	5.1	2.3	5.0
Na^+, mmol/L	Low	124.1	0.521	0.4	0.9	0.9	0.4	1.6
	Medium	139.6	0.824	0.6	0.9	1.0	1.2	1.4
	High	154.0	0.495	0.3	0.9	0.9	0.5	1.3
K^+, mmol/L	Low	2.4	0.000	0.0	6.8	1.9	0.0	10.4
	Medium	4.6	0.026	0.6	6.8	1.9	1.4	5.3
	High	7.7	0.062	**0.8**	6.8	1.9	0.6	3.5
Cl^-, mmol/L	Low	85.6	0.558	**0.7**	0.6	1.7	–	2.5
	Medium	108.5	0.575	0.5	0.6	1.7	–	2.5
	High	141.8	0.575	0.4	0.6	1.7	–	2.5
$_iCa^{2+}$, mmol/L	Low	0.64	0.005	0.8	0.9	2.1	0.9	7.8
	Medium	1.16	0.009	0.8	0.9	1.4	0.9	5.0
	High	1.59	0.018	**1.1**	0.9	2.1	0.9	5.0
Glucose, mg/dL	Low	43.1	1.465	**3.4**	2.3	12.0	0.4	6.5
	Medium	102.0	2.117	**2.1**	2.3	6.0	1.1	5.0
	High	383.5	5.617	1.5	2.3	12.0	2.5	5.0
Lactate, mg/dL	Low	7.1	0.309	**4.3**	13.6	3.3	–	25.0
	Medium	22.6	0.827	3.7	13.6	13.6	–	8.0
	High	66.5	0.685	1.0	13.6	11.1	–	7.5
tHb, g/dL	Low	7.7	0.133	**1.7**	1.4	1.4	1.7	4.5
	Medium	14.7	0.132	0.9	1.4	1.4	2.0	2.4
	High	21.0	0.165	0.8	1.4	1.4	1.0	2.4

Abbreviations: CV%: coefficient of variation; n, number of measurements; Lab (%): long-term laboratory RP500 imprecision results.

cesses not only require running appropriate controls at regular intervals, but also require thorough assessment of the analyzed results, taking corrective actions when necessary, and documenting the process in a systematic way. Prior to reporting patient results, each test result should also be verified to identify any obvious error or interference that may have occurred. However, this is not evident in a POC-setting. Measurement of blood gas parameters by means of POC methods is vulnerable to a number of pre-analytical errors. While common pre-analytical errors, such as missing or wrong patient ID labels and incorrect sampling, can affect blood gas tests in the same way as other laboratory tests, blood gas testing is more error-prone as some analytes are gaseous and more vulnerable to a set of errors and interferences [4,5].

In the present study, we evaluated the performance of the novel GEM® Premier™ 5000 for measurement in whole blood of pH, pCO_2, pO_2, Na^+, K^+, Cl^-, $_iCa^{2+}$, glucose, lactate and tHb, and compared the obtained results with the results of two other blood gas analyzers available in our lab. In addition to this analytical performance evaluation, we put special attention to interfering substances that potentially could influence co-oximetry and electrolyte results.

2. Materials and methods

2.1. Patient samples

Whole blood samples were randomly selected from those routinely collected from patients at the Intensive Care Unit (ICU) of the Ghent University Hospital and were prospectively included in the study. Leftover samples were used in anonymous way, thereby waiving informed consent according to the local ethical guidelines. The patient samples were anaerobically drawn from arterial or venous lines following the CLSI C46-A2 guidelines [6] and collected into Siemens Rapidlyte syringes, *i.e.* 3 mL syringe anti-coagulated with 70 IU lyophilized electrolyte-balanced heparin (Siemens Healthcare, Sudbury, UK). The samples were manually transported to the POC blood gas analyzers. The analysis of the samples occurred on site, randomized on the different analyzers.

2.2. Werfen GEM Premier 5000

The GEM Premier 5000 (Werfen, Barcelona, Spain) is a novel critical care analyzer providing rapid analysis of whole blood samples in a POC or central laboratory setting. This cartridge-type blood gas analyzer comprises all components necessary for analysis in a single closed PAK, including electrochemical sensors, reagents, an optical cell for CO-oximetry measurements, sampling stylus and waste container. This instrument is claiming an intelligent quality management technology that replaces periodic analysis of external liquid controls with software, internal process control solutions and calibration validation solutions that continually assess the functionality of the instrument. In addition, the analyzer has been designed to automatically initiate and document corrective actions after malfunction in an analytical channel of analytical interference.

We evaluated the analytical performance of the Werfen GEM

Table 2
Analytical deviation and estimated total error results for the GEM Premier 5000 against the preset criteria. Deviations from the preset criteria (Ricos, Lab and/or manufacturer) are indicated in bold.

Analyte	Results				Criteria				
	Level	Measured mean	Middle of target interval[a]	Estimated TE (%)	ATE Ricos	ATE Lab	Manufacturer		
							Target interval	Within range?	ATE
pH	Low	7.14	7.13	0.3	–	0.6[b]	7.09–7.17	Yes	0.6
	Medium	7.37	7.37	0.2	–	0.5[b]	7.33–7.41	Yes	0.5
	High	7.58	7.57	0.2	–	0.5[b]	7.53–7.61	Yes	0.5
pCO_2, mmHg	Low	14.0	13	**7.7**	5.7	22.7[c]	10–16	Yes	35.7
	Medium	37.0	36	**6.9**	5.7	8.0[c]	31–41	Yes	14.3
	High	88.4	90	5.5	5.7	8.0[c]	81–99	Yes	5.7
pO_2, mmHg	Low	31.0	29	**16.1**	–	5.0[b]	19–39	Yes	29.0
	Medium	87.4	90	**7.9**	–	5.0[b]	80–100	Yes	10.2
	High	349.4	360	**9.5**	–	15.4[b]	328–392	Yes	2.4
Na^+, mmol/L	Low	124.2	124	0.9	4.6	1.2[c]	119–129	Yes	3.2
	Medium	139.8	141	**1.8**	4.6	1.0[c]	136–146	Yes	2.8
	High	154.2	156	**1.7**	4.6	0.9[c]	150–162	Yes	2.6
K^+, mmol/L	Low	2.4	2.4	0.0	16.0	–	2.1–2.7	Yes	20.8
	Medium	4.6	4.6	0.9	16.0	–	4.2–5.0	Yes	10.6
	High	7.6	7.6	1.9	16.0	–	7.1–8.1	Yes	6.5
Cl^-, mmol/L	Low	85.2	85	1.3	1.5	5.0[c]	80–90	Yes	4.7
	Medium	108.2	108	1.1	1.5	5.0[c]	103–113	Yes	3.7
	High	141.4	142	1.1	1.5	5.0[c]	137–147	Yes	2.8
$_iCa^{2+}$, mmol/L	Low	0.64	0.64	**1.7**	2.0	1.0[b]	0.56–0.72	Yes	1.6
	Medium	1.16	1.15	**1.9**	2.0	1.4[b]	1.06–1.24	Yes	0.9
	High	1.58	1.56	**3.0**	2.0	2.1[b]	1.46–1.66	Yes	0.6
Glucose, mg/dL	Low	44.6	49	**14.6**	5.5	10.0[b]	40–58	Yes	13.0
	Medium	104.6	106	4.8	5.5	18.0[b]	94–118	Yes	5.8
	High	377.2	382	**3.7**	5.5	36.0[b]	350–414	Yes	1.6
Lactate, mg/dL	Low	7.0	7	7.2	30.4	10.0[b]	5–10	Yes	50.0
	Medium	23.4	23	7.8	30.4	–	19–28	Yes	16.0
	High	66.6	67	2.3	30.4	33.4[b]	59–74	Yes	5.5
tHb, g/dL	Low	7.7	7.8	3.6	4.1	–	7.1–8.5	Yes	9.0
	Medium	14.8	15.0	2.8	4.1	–	14.2–15.8	Yes	4.8
	High	21.2	21.3	1.9	4.1	–	20.1–22.5	Yes	4.8

Abbreviations: CV%: coefficient of variation; n, number of measurements; TE: Total Error; ATE: Allowable Total Error. The lab criteria on ATE are the criteria used for internal validation of blood gas analysis results.

[a] Middle of the range provided by the manufacturer.

[b] RCPA criteria.

[c] CLIA criteria.

Premier 5000 (Werfen, Barcelona, Spain) in comparison with the Siemens RapidPoint 500 analyzer (RP500, Siemens Healthcare, Sudbury, UK) and the Abbott i-STAT handheld analyzer using the CG8 + cartridge (Abbott Point of Care, East Windsor, NJ). All analyzers were handled according to the manufacturer's instructions. Specific attention was given to the performance characteristics of the iQM2 system for the detection of interferences on blood gas results.

2.3. Evaluation protocol

2.3.1. Imprecision, analytical deviation and estimated total error

To determine the total imprecision of the GEM Premier 5000, aqueous QC material (Werfen GEM System Evaluator level 1, 2 and 3) was used. Each analyte was tested at three concentration levels (low, intermediate and high). A single lot of every level of control material was used throughout the study (lot nrs. 1515, 2516, 3518). QC materials were aspired manually into the instruments.

The total imprecision was determined according to the CLSI EP5-A3 evaluation protocol [7]. For each level, two aliquots of test material were analyzed within a single run per day, during 20 consecutive days. The standard deviation (SD) and coefficient of variation (CV) of the observed data were calculated following the CLSI EP5-A2 guideline. According to this protocol, precision is estimated separately for each level and analyte tested. The obtained precision estimates were compared to the Ricos desirable specifications [8], intra-laboratory long-term Siemens RapidPoint 500 auto-QC and Abbott CG8 + QC imprecision data (own, unpublished data) and the specifications provided by the manufacturer [9].

We investigated whether the result of the first measurement on the first 5 days was within the target interval as claimed by the manufacturer in the GEM System evaluator leaflet.

The analytical deviation, which could serve as a surrogate marker for bias, was constructed by calculating the difference between the mean result and the middle value of the target interval claimed by the manufacturer. The estimated total error was calculated from the total imprecision and the analytical deviation by use of the formula: estimated total error = $\left|\text{analytical deviation}\right| + 1.65 \times$ total imprecision. A comparison against the desirable specifications was made [8,10–11].

2.3.2. Method comparison

The results obtained with the GEM Premier 5000 were compared to the Abbott i-STAT handheld analyzer using the CG8 + cartridge (Abbott Point of Care, East Windsor, NJ) and the Siemens RapidPoint 500 analyzer (RP500, Siemens Healthcare, Sudbury, UK) according to the CLSI EP9-A2 guidelines [12]. For glucose and tHb, method

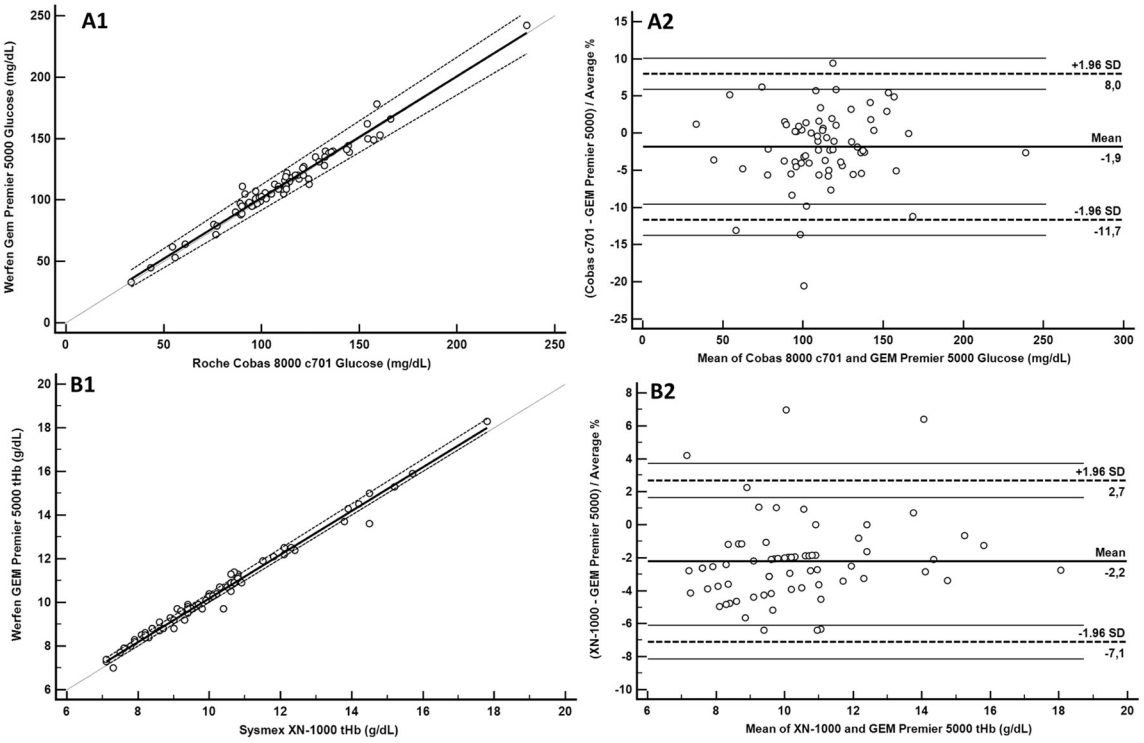

Fig. 1. Method comparison between GEM Premier 5000 between Roche Cobas 8000 and Roche Cobas 8000 for glucose (A) and between GEM Premier 5000 and Sysmex XN-1000 for tHb (B). Passing and Bablok regression analysis showing the identity line and 95% confidence interval for the regression line (1). Bland and Altman mean difference plots (2). The y-axis represents the relative difference (%) between results obtained with both analyzers and the x-axis represents the average of the test analyzers. The solid lines represent the mean difference and the limits of agreement (± 1.96 SD of the differences). The dashed lines represent the 95% confidence intervals around the upper and lower limit of agreement.

comparisons with the Roche Cobas 8000 c701 hexokinase/glucose-6-phosphate dehydrogenase method (Roche Diagnostics, Mannheim, Germany) and Sysmex XN-1000 SLS-method (Sysmex cooperation, Kobe, Japan) were performed, respectively. We aimed to include at least 40 patient samples per analyte, with analyte concentrations distributed over the analytical measurement range to the extent possible. The comparison was conducted over at least 5 operating days. Due to pre-analytical considerations, specimen testing was performed in singlet instead of duplicate. The order of analysis on the test and comparative instrument was random. Instruments were installed side-by-side so that the time interval between measurements was as short as possible (max 1–2 min). All measurements were conducted by one single operator and the samples were handled according to the available guidelines [6] to minimize bias due to pre-analytical errors. After being introduced into the first analyzer, possible air bubbles generated by the aspiration process in the remainder of the blood sample were removed immediately. Subsequently, the sample was reclosed with an airtight cap and thoroughly remixed by hand prior to analysis on the second analyzer.

2.3.3. Interference studies

Potential interferences were investigated on CO-oximetry and electrolyte concentrations by spiking whole-blood samples with serial dilutions of triglycerides, hemolysate, methylene blue and benzalkonium on the GEM Premier 5000 as well as on the RapidPoint 500.

Prior to spiking the sample with the possible interfering substance, a blank heparin anticoagulated whole-blood sample of a healthy volunteer was collected and mixed for 20 min. The oxygenated whole-blood sample was divided into different aliquots. Along with the measurement of the sample with the possible interferent, a blank heparin anticoagulated whole-blood sample without interferent was tested at the same time. For each aliquot, the spiked volume and final volume were kept constant (200 µL and 4 mL, respectively). Each concentration of the possible interfering substance was evaluated on both analyzers in triplicate. Significant differences in samples with and without the interferent were investigated by means of a Student *t*-test. Each spiked sample was compared against the blank sample.

Interference of lipemia was evaluated using Intralipid® (Baxter, Lessines, Belgium) to obtain 5 final lipemic whole blood samples with concentrations ranging from 0.2 to 2.0%. Interference of hemolysis was studied by freezing 5 lithium-heparin samples of a volunteer during different times to obtain different degrees of hemolysis. The degree of hemolysis was measured on the Roche Cobas 8000 c702 (Roche Diagnostics, Mannheim, Germany) using the Serum Index assay.

Interference of methylene blue (Merck, Darmstadt, Germany) was assessed using a 1000 mg/L solution in saline to obtain 4 final concentrations of methylene blue in whole blood samples of 10, 40, 80 and 100 mg/L. Potential interference of benzalkonium (Merck, Darmstadt, Germany) was investigated by diluting a 1 mg/mL stock solution of benzalkonium in saline to obtain 2 final concentrations of 5 and 10 mg/L.

2.4. Statistical analysis

Before statistical analysis, all data were subjected to an outlier detection and rejection procedure according to the CLSI EP9-A2 protocol [12]. Patient sample based method comparisons were evaluated by calculating Spearman rank correlation coefficients and the slope and

Table 3
Passing and Bablok regression analysis and Bland-Altman mean differences (%) of the GEM Premier 5000 compared to the Abbott i-STAT and Siemens RP500 analyzers. Significant differences are indicated in bold.

Analyte	GEM Premier 5000 *vs* Siemens RP500					GEM Premier 5000 *vs* Abbott i-STAT CG8 +				
	n	r_s	Slope (95%CI)	Intercept (95%CI)	Mean difference (95% CI)	n	r_s	Slope (95%CI)	Intercept (95%CI)	Mean difference (95% CI)
pH	260	0.953	1.000 (0.971–1.024)	− 0.001 (− 0.178–0.214)	− 0.01 (− 0.04–0.02)	43	0.971	1.000 (0.926–1.071)	0.002 (− 0.524–0.549)	− 0.02 (− 0.06–0.02)
pCO_2; mmHg	263	0.964	**0.909 (0.875–0.945)**	**7.000 (5.465–8.463)**	**− 7.2 (− 8.0 to − 6.5)**	43	0.964	0.916 (0.829–1.005)	3.578 (− 0.236–7.634)	0.2 (− 1.2–1.6)
pO_2; mmHg	261	0.990	1.082 (1.066–1.098)	− 0.272 (− 1.810–1.184)	**− 7.4 (− 8.1 to − 6.8)**	43	0.989	1.070 (1.012–1.122)	**4.140 (0.851–8.325)**	**− 11.9 (− 14.4 to − 9.5)**
Na^+; mmol/L	219	0.889	1.063 (1.000–1.127)	− 9.079 (− 17.916 to − 0.400)	0.3 (0.1–0.5)	43	0.918	1.000 (0.910–1.000)	− 2.000 (− 2.000–10.455)	**1.4 (1.2–1.7)**
K^+; mmol/L	221	0.981	1.111 (1.091–1.136)	**− 0.333 (− 4.341 to − 0.258)**	− 2.5 (−2.7 to − 2.2)	43	0.986	1.000 (1.000–1.071)	0.200 (− 0.093–0.200)	− 4.5 (− 5.0 to − 4.0)
Cl^-; mmol/L [a]	175	0.954	1.000 (1.000–1.000)	1.000 (1.000–1.000)	− 0.7 (− 0.9 to − 0.4)	–	–	–	–	–
$_iCa^{2+}$; mmol/L	220	0.931	1.000 (1.000–1.091)	0.030 (− 0.074–0.030)	**− 2.9 (− 3.2 to − 2.6)**	43	0.913	1.000 (0.800–1.063)	0.040 (− 0.028–0.268)	**− 4.4 (− 5.2 to − 3.6)**
Glucose; mg/dL	221	0.989	1.037 (1.019–1.055)	0.333 (− 1.450–2.096)	3.8 (3.3–4.4)	43	0.983	1.000 (0.962–1.048)	− 3.000 (− 8.429–1.231)	2.8 (2.0–3.6)
Lactate; mg/dL [a]	178	0.982	1.044 (1.020–1.071)	**− 2.235 (− 2.786 to − 1.735)**	7.1 (5.6–8.7)	–	–	–	–	–
tHb, g/dL	218	0.992	1.000 (1.000–1.000)	− 0.400 (− 0.400 to − 0.400)	**4.2 (3.8–4.6)**	43	0.946	1.020 (0.927–1.114)	0.733 (− 0.073–1.571)	**− 10.7 (− 13.0 to − 8.3)**

Abbreviations: CI: confidence interval; n: number of measurements; r_s = Spearman rank correlation coefficient.
[a] Parameters Cl^- and lactate are not included in the Abbott CG8 + cartridges

intercept using Passing and Bablok regression analysis. For each slope and intercept, two-sided 95% confidence intervals (CI) were calculated [13]. Secondly, using Bland-Altman difference plots, relative mean differences between the methods were visualized, along with limits of agreement which were defined as the mean difference ± 1.96 times the standard deviation of the differences [14]. The allowable total error was used to estimate whether the mean difference was clinically relevant. All statistical analyses were performed using Medcalc (Software version 15.6.1; Mariakerke, Belgium).

3. Results

3.1. Total imprecision and estimated total error

We evaluated the analytical performance of pH, blood gases (pCO_2, pO_2), electrolytes (iCa^{2+}, Na^+, K^+ and Cl^-), glucose, lactate, and tHb. The total imprecision (CV%) determined for the GEM Premier 5000 against the preset quality specifications is presented in Table 1. Overall, the results for total imprecision are acceptable, except for some parameters, for which the preset Ricos [pCO_2 (medium), pO_2 (low), Cl^- (low), Glucose (low), $_iCa^{2+}$ (high) and tHb (low)], internal lab [pO_2 (low and medium), lactate (low) and tHb (low)] or i-STAT CG8$^+$ [pCO_2 (medium and high), pO_2 (low, medium and high), K^+ (high), iCa^{2+} (high) and glucose (low and medium)] criteria are not reached. The total imprecision criteria as specified by the manufacturer were met.

The estimated total error results for the GEM Premier 5000 against the preset quality specification are presented in Table 2. For pCO_2 (low and medium), pO_2 (low, medium and high), glucose (low and high), Na^+ (medium and high) and $_iCa^{2+}$ (low, medium and high), the preset quality specifications are not met. For each parameter, the measured mean fell within the target range as claimed by the manufacturer (Table 2).

Bland and Altman mean difference between the Roche Cobas 8000 and the GEM Premier 5000 revealed a deviation of 1.9% for glucose (Fig. 1A).

3.2. Method comparison

The results of the Spearman rank correlation, Passing and Bablok regression analysis and Bland and Altman mean differences between the GEM Premier 5000, RP500 and i-STAT CG8 + are summarized in Table 3. Due to accidental analyzing errors (aspiration or calibration errors), our method comparison studies have different amounts of samples for the evaluation of the various analytes. As there were only a limited number of CG8 + cartridges available for analysis on the i-STAT, the number of samples included in the method comparison between the GEM Premier 5000 and i-STAT CG8 + is lower.

Spearman rank correlation analyses yielded generally high correlation coefficients ranging from 0.889 to 0.992 for both analyzers being correlated with the GEM Premier 5000 (Table 3). Especially for pCO_2, significant systematic (intercept ≠ 0) and proportional (slope ≠ 1) differences were observed between the GEM Premier 5000 and RP500 (Table 3). Also for K^+ and lactate, systematic differences were noted. Bland and Altman plots showed good agreement between the GEM Premier 5000 and RP500 (Fig. 2). For all analytes, the mean relative differences were within allowable error limits, with exception of pCO_2 [− 7.2% *vs.* 5.7% (Ricos)], pO_2 [− 7.4% *vs.* 5.0% (RCPA)], $_iCa^{2+}$ [− 2.9% *vs.* 2.0% (Ricos)] and tHb [4.2% *vs.* 4.1% (Ricos)]. With the exception of lactate, no apparent concentration dependency of the observed mean differences was observed (Fig. 2 I2). For glucose (*cf.* supra) and tHb, mean differences between the GEM Premier 5000 and hexokinase method on the Roche Cobas 8000 and sodium lauryl sulphate (SLS) method on the Sysmex XN-1000 were determined, respectively. These differences (glucose: 1.9%; tHb: − 2.2%) were within the preset Ricos total error criteria. Passing and Bablok regression analysis also

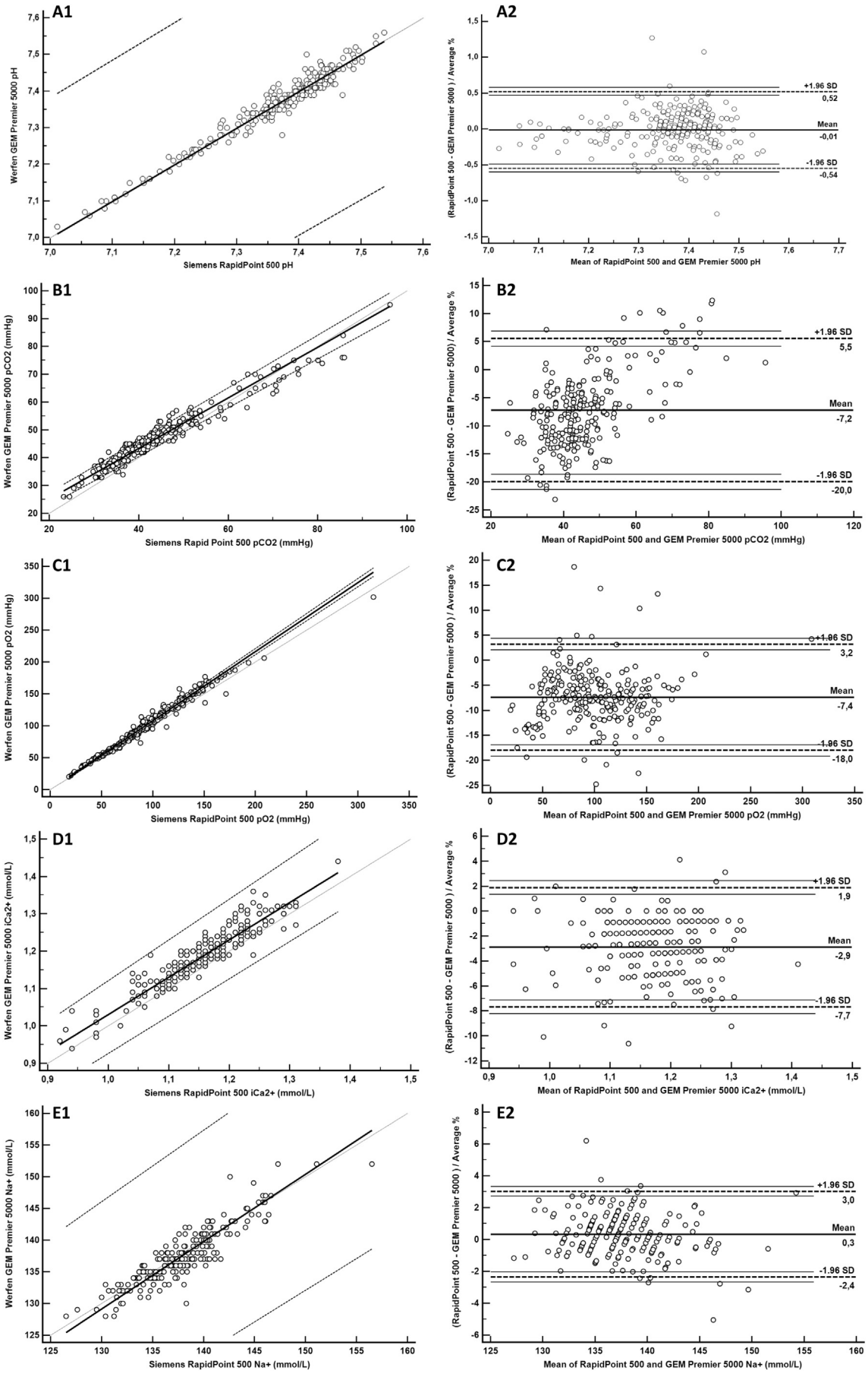

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Fig. 2. Method comparison between GEM Premier 5000 and RP500 for the different analytes tested. Passing and Bablok regression analysis showing the identity line and 95% confidence interval for the regression line (1). Bland and Altman mean difference plots comparing analytes (2). The y-axis represents the relative difference (%) between results obtained with both analyzers and the x-axis represents the average of the test analyzer and the RP500 values. The solid lines represent the mean difference and the limits of agreement (± 1.96 SD of the differences). The dashed lines represent the 95% confidence intervals around the upper and lower limit of agreement.

revealed no significant differences between the blood gas analyzer and the respective analyzers (Fig. 1).

The slope of the regression equations for the i-STAT CG8 + was never significantly different from 1 (Table 3). For one analyte (pO_2), the intercept was significantly different from 0. Bland and Altman plots showed good agreement between the GEM Premier 5000 and i-STAT (Fig. 3). For all analytes, the mean relative differences were within allowable error limits, except for pO_2 [− 11.9% *vs.* 5.0% (RCPA)], Na^+ [1.4% *vs.* 1.2% (CLIA)], $_iCa^{2+}$ [− 4.4% *vs.* 2.0% (Ricos)] and tHb [− 10.7% *vs.* 4.1% (Ricos)]. No concentration dependency was found in the difference plots (Fig. 3).

It should be noted that the layered data for some parameters in Figs. 2 and 3 reflect roundings of results by the analyzer. However, the IQM technology does not rely on these rounded values, but uses the precise raw measurement data.

3.3. Interference studies

No significant changes due to the presence of triglycerides (up to 1%) or methylene blue (up to 100 mg/L) were detected on co-oximetry results on both the RP500 and GEM Premier 5000. However, the user of the instrument is made aware of the possibility of a false result by generation of parameter specific flags ("*high turbidity*" or "*absorbance error*") in case of triglyceride concentrations of 1% or higher on the outprint next to the co-oximetry results on the GEM Premier 5000 (Table 4). For methylene blue, no flags were generated on both analyzers (Table 4).

On the contrary, significantly higher Na^+, K^+ and $_iCa^{2+}$ concentrations were measured in samples spiked with benzalkonium compared to blank samples. At a benzalkonium concentration of 10 mg/L, a specific flag was generated on the GEM Premier 5000 ("*On the last sample, interference was detected on sodium, potassium and calcium concentrations, probably due to benzalkonium*"), but not on the RP500. Significantly higher potassium concentrations were also obtained in samples with a high degree of hemolysis (hemolysis index > 88). In the hemolysed samples, no specific flags were generated on any instrument (Table 4).

4. Discussion

Use of POCT requires easy-to-use devices with preferably little maintenance tasks. Cartridge-type analyzers seem to fulfill these requirements as they consolidate all these requirements in one or more cartridges. In early studies evaluating the performance of blood gas analyzers, non-standardized protocols were often used and performance goals were lacking or arbitrarily chosen [15–22]. With the availability of cartridge-type blood gas analyzers, evaluation studies using more standardized protocols became available. Several studies have established the analytical performance of earlier generations of GEM instruments [22–26]. In the present study, a performance evaluation of the novel generation GEM Premier 5000 cartridge-type blood gas analyzer was performed using widely applied CLSI-protocols.

The imprecision of the GEM Premier 5000 was acceptable, with slightly higher variation coefficients for some parameters than the preset criteria (Table 1). These deviations from the preset criteria may at least partly be explained by the manual introduction of control material. Our results are in accordance with the imprecision results of two other studies on earlier generation GEM instruments [23–24,26]. Although these variations are higher than the preset criteria that are partly based on our current long-term internal quality control results, they are only of minor clinical importance.

We evaluated whether the measured mean fell within the target interval as claimed by the manufacturer and assessed whether the estimated total error was within the preset specifications. Large but clinically irrelevant deviations were observed both for pCO_2 and pO_2 on the low (estimated total error 7.7% and 16.1%, respectively) and medium (estimated total error 6.9% and 7.9%, respectively) levels (Table 2).

In addition to blood gas analyses, the measurement of glucose and lactate concentrations has gained importance on POC analyzers. Especially for glucose, a large analytical deviation (− 9.0%) and total error (14.6%) were observed for the low control level, which might affect clinical decision making. Given the current emphasis on strict blood glucose control at ICU, the performance of glucose determinations is an important issue. Therefore, we performed an additional method comparison with the hexokinase method on the Roche Cobas 8000 c701 used in our core laboratory, which showed acceptable results.

It should be noted that the real concentration of each analyte present in the Werfen GEM System Evaluator control material is not necessarily the middle value of the specified concentration range. According to the manufacturer, the measurement values should fall within the preset concentration range and an exact value of bias cannot be calculated by the user.

Other method comparison studies demonstrated differences between blood gas analyzers [23]. These differences become also apparent in external quality control schemes. In our study, important and often large differences between the GEM Premier 5000 and RP500 (pCO_2 and pO_2) and i-STAT CG8 + (pO_2 and tHb), exceeding the preset specifications, were found. These deviations may be attributed to the different sensor systems that react differently towards the same patient matrix.

To ensure an accurate and prompt response to blood gas analyses, control of pre-analytical variables is critical. It has been demonstrated that the prevalence of unsuitable specimens referred for blood gas analysis ranges between 1.2% and 3.7%, thereby representing a substantial hurdle to total quality management [27,28].

The iQM automated statistical QC assessment system on GEM instruments was introduced in 2003 by Westgard et al. [29]. iQM technology uses frequent measurements of internal process control solutions to monitor measurement variation and signal abnormal drifts, and applies pattern recognition algorithms to identify the type of error and consequently triggers appropriate corrective actions. The strength of the technology lies in the continuous monitoring of potential points of failure and automatic correction before a result is reported [30]. If an interfering substance is detected during measurement of a sample, an Intraspect® flag is generated and process control solutions will be analyzed after measurement to detect deviations from normality. If the results of these control solutions fall outside the predefined ranges, this indicates the presence of micro-clots, micro-bubbles, CO-oximetry absorbance errors or an interfering substance (*e.g.* benzalkonium or thiopental interference). This additional check takes approximately 75 s.

We demonstrated that the instrument is able to detect interference

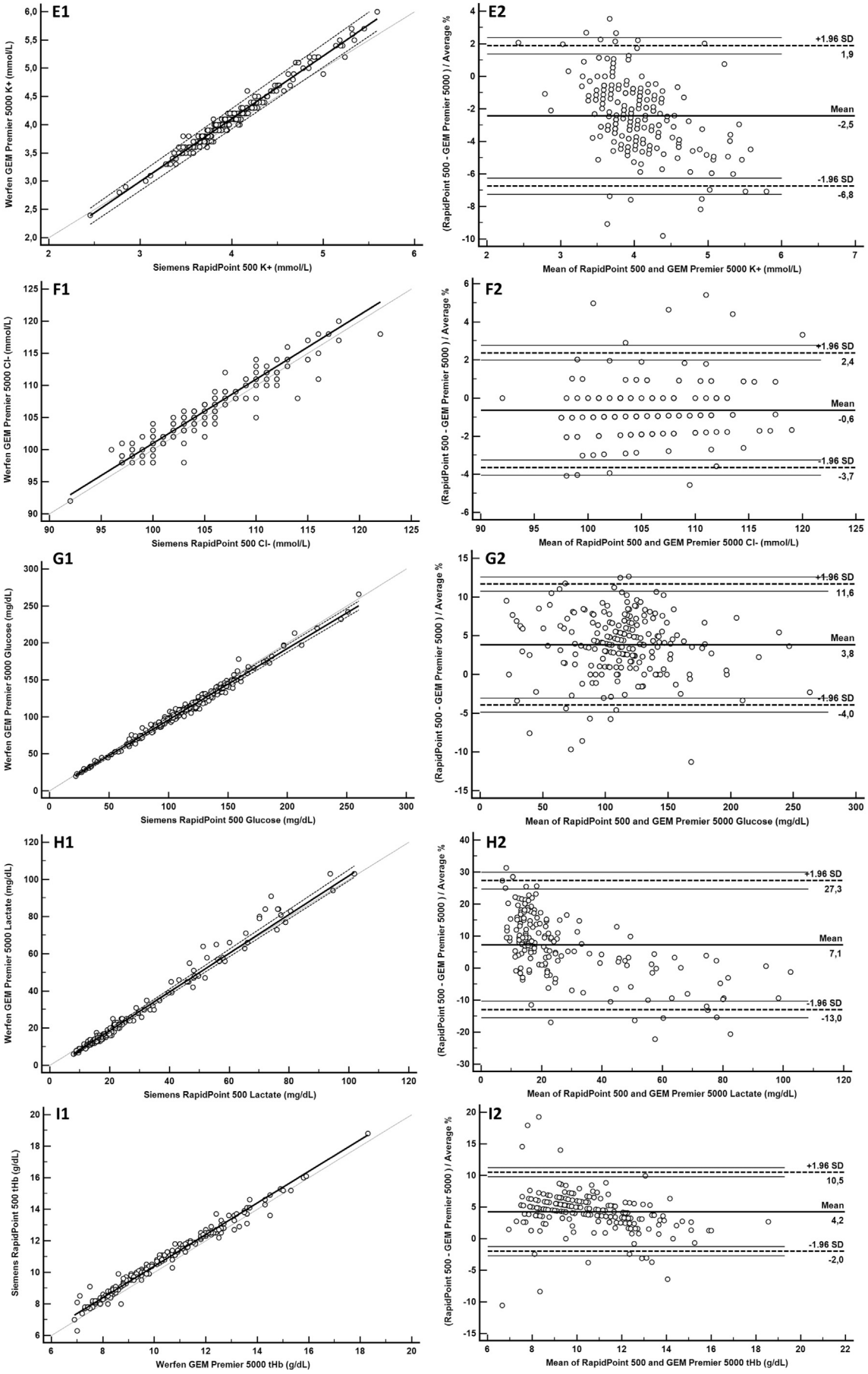

Fig. 2. (*continued*)

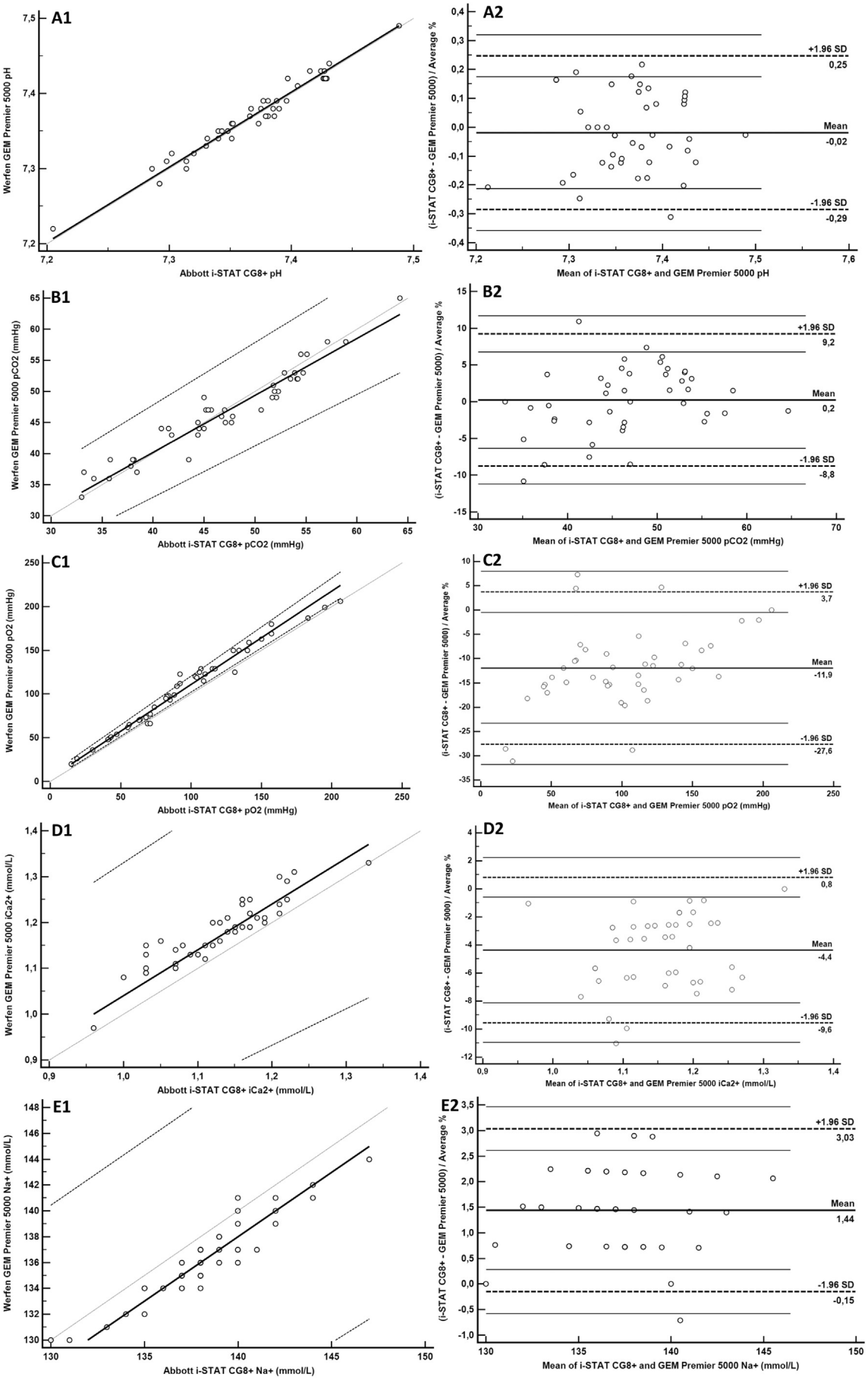

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Fig. 3. Method comparison between GEM Premier 5000 and i-STAT CG8 + for the different analytes tested. Passing and Bablok regression analysis showing the identity line and 95% confidence interval for the regression line (1). Bland and Altman mean difference plots (2). The y-axis represents the relative difference (%) between results obtained with both analyzers and the x-axis represents the average of the test analyzer and the i-STAT CG8 + values. The horizontal lines represent the mean difference and the limits of agreement (± 1.96 SD of the differences).

from benzalkonium, a large lipophilic compound frequently used as disinfectant in hospitals, on electrolyte measurements [31]. By generation of an appropriate flag, the user is informed that a result (either Na^+ or $_iCa^{2+}$) is invalid, although subsequent samples would not be affected. This is of interest as clinicians and nurses are often not aware of the influence of these substances on laboratory results. On the RP500 device, the user is not aware of this influence, since the interference is not mentioned on the print-out but is only available in the event log of the device. In addition, we investigated potential interference of lipemia and methylene blue, two compounds that strongly absorb in the same spectrophotometric region as hemoglobin derivatives. No interference of methylene blue, used as an antidote in nitrite-induced methemoglobinemia [32], was found. This is satisfying, as methylene blue is known to hinder the monitoring of methemoglobinemia treatment which relies on repeated MetHb measurement [33]. Likewise, no interference of lipemia was encountered, although a flag informing the user was generated.

In vitro hemolysis, *i.e.* breakdown of erythrocytes occurring during collection, management, transportation or storage of biological samples, is a substantial problem in laboratory diagnostics and is likely to introduce bias in blood gas analyses [34]. Manufacturers should develop instrumentation capable of identifying interfering substances in whole blood [35]. Interference of hemolysis on blood gas analysis was evaluated and revealed spuriously elevated K^+ concentrations. However, neither the GEM Premier 5000 nor other available blood gas analyzers are currently capable of generate flaggings informing users of the spuriously elevated concentrations.

Along with the acceptable analytical performance characteristics, technical features, fast measuring time and iQM2 technology (*i.e.* result available 45 s after aspiration if no interference is detected), the GEM

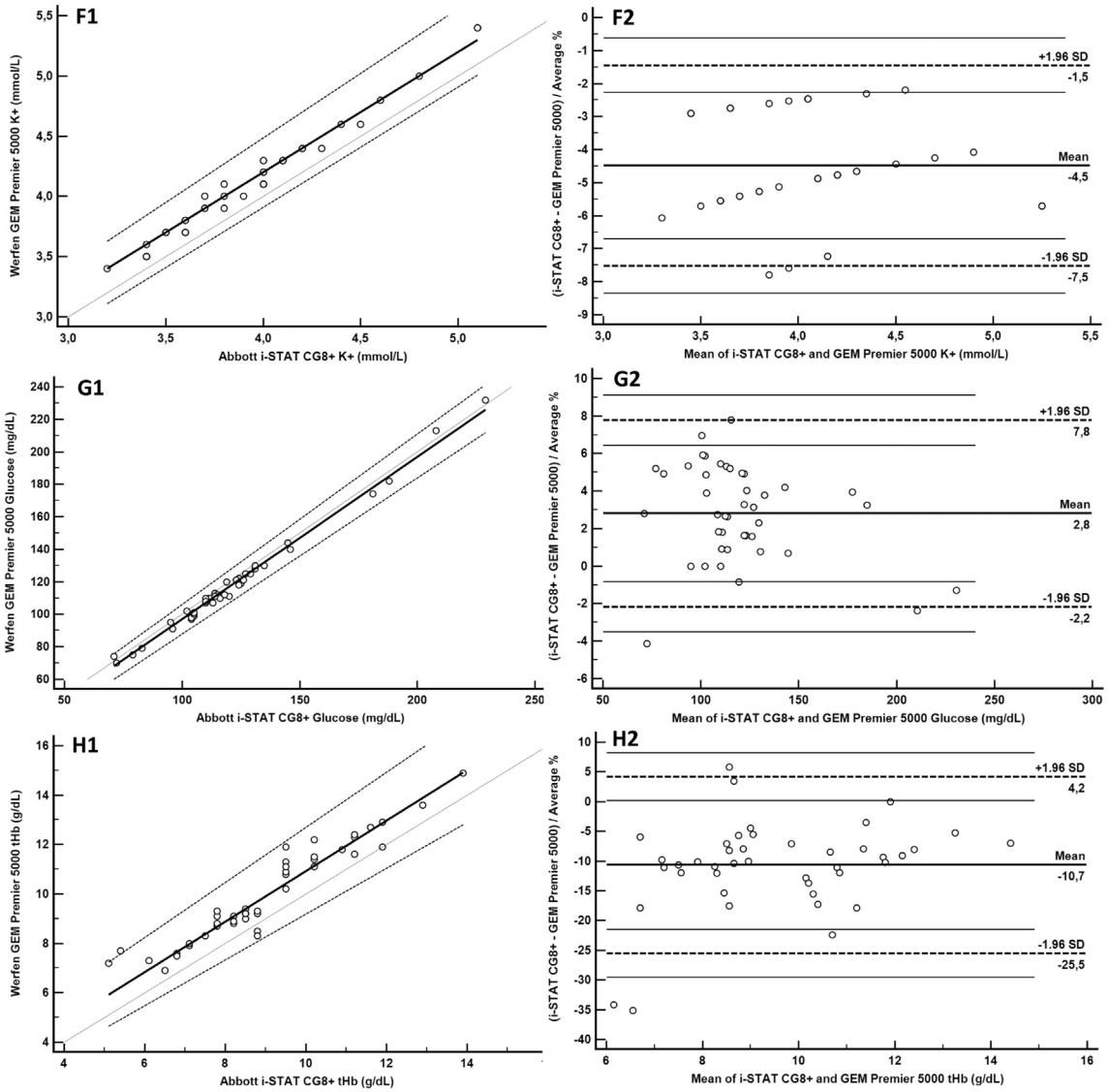

Fig. 3. (*continued*)

Table 4
Interference results. Summary of interferences tested on CO-oximetry and electrolyte concentrations. For each interference, we indicate whether or not the instrument generates an analyzer flag and whether the results are reported.

Interferent	Interference on	Interference?		Analyzer flag?		Results reported?[a]		Ref
		RP500	GEM 5000	RP500	GEM 5000	RP500	GEM 5000	
Lipemia	CO-oximetry of Hb-derivatives	No	No	No	Yes	Yes	Yes	[36,38]
Methylene blue	CO-oximetry of Hb-derivatives	No	No	No	No	Yes	Yes	[33,37]
Benzalkonium	Electrolytes (K^+, Na^+, $_iCa^{2+}$)	Yes	Yes	No	Yes	No	Yes	[31]
Hemolysis	Electrolytes (K^+)	Yes	Yes	No	No	Yes	Yes	[35]

[a] By analyzer

Premier 5000 was found an easy-to-use instrument (single disposable cartridge concept, storage at room temperature, cartridge auto-validation and 31-day cartridge stability) requiring hardly no maintenance. Future enhancements could consist of the integration of an automatic blood-sample mixing system that, along with the iQM2 technology, further diminishes the influence of the pre-analytical phase on blood gas results.

In summary, the analytical performance of this novel cartridge-type blood gas analyzer is in line with the results of other studies. The strength of this analyzer lies in the pre-analytical detection capabilities that function on every sample and provide an additional safeguard against reporting erroneous results due to interferences. These results, together with the favorable practicability of the instrument, demonstrate that this cartridge-type blood gas analyzer is suitable for both POC and laboratory use.

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