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Viewpoint

Accuracy of pipeline blood glucose monitoring in patients with severe liver injury undergoing artificial liver support system treatment

Hua-Fen Zhang[a,b], Zhong-Yang Xie[a,c], Xiao-Xi Ouyang[a,c], Xiao-Wei Xu[a,b], Xiao-Yan Wang[a,b], Jian-Rong Huang[a,b], Lan-Juan Li[a,c,*]

[a] State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China
[b] Department of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China
[c] Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, China

Severe deterioration of liver function in patients can be characterized by coagulation disorders, jaundice, hepatic encephalopathy, ascites, and other symptoms. Severe liver injury can develop as acute liver failure, subacute liver failure, acute-on-chronic liver failure, or further worsening of end-stage liver disease [1]. Liver transplant is the standard therapy for patients with severe liver injury; however, it is hampered by a shortage of organ donors, complications caused by post-transplant immune rejection, and high cost [2]. Artificial liver support system (ALSS), based on the principle of temporarily replacing liver function, have been proposed as new therapeutic options to treat severe liver injury. In the past few decades, various types of ALSSs have been developed and applied to the treatment of severe liver injury [3]. These include plasma exchange (PE), the molecular adsorbent recirculating system (MARS), and the double plasma molecular adsorption system (DPMAS) [4]. Li's artificial liver system (Li-ALSS), is a kind of ALSS that organically coupled by plasma exchange, plasma adsorption, and hemofiltration [5]. DPMAS is a part of Li-ALSS that combines two hemoperfusion columns to efficiently remove toxins from the plasma [6].

Severe liver injury impairs the ability of the liver to maintain glucose homeostasis [7]. Many studies have shown that in patients with severe liver injury, either hyper- or hypoglycemia can affect prognosis, and are both associated with increased mortality [8–10]. Therefore, blood glucose monitoring is necessary during ALSS treatment of patients with severe liver injury. In our experience, blood glucose monitoring during ALSS therapy is currently mainly performed with a portable blood glucose meter to detect capillary blood glucose (CBG). The CBG method requires pricking the finger to extract capillary blood, which could cause pain and bleeding, particularly in patients with severe liver injury and resultant coagulopathy. Another method is to detect the blood glucose using whole blood collected from the arterial at the end of the purification pipeline outside the human body during ALSS treatment [11]. Whether the *in vitro* blood glucose (IBG) level in ALSS pipelines represents actual blood glucose level is unclear.

In this study, we compared the values of IBG from Li-ALSS with CBG (as a reference) in patients with severe liver injury. We also monitored blood glucose values over the course of Li-ALSS treatment. Our goal was to establish a new method of monitoring blood glucose in patients undergoing Li-ALSS treatment for severe liver injury, and to reduce the pain of the blood glucose monitoring.

Table 1
Clinical characteristics of patients receiving ALSS treatment ($n = 117$).

Characteristics	Data
Age (yr)	51 ± 13
Sex (male)	86 (74%)
Diabetes	13 (11%)
Hypertension	20 (17%)
Cirrhosis	36 (31%)
Alcohol intake	32 (27%)
Smoking	21 (18%)
Etiology of liver injury	
HBV-ACLF	65 (56%)
Drug-induced liver injury	23 (20%)
Acute HEV hepatitis	11 (9%)
Autoimmune liver disease	11 (9%)
Liver cancer	2 (2%)
Postoperation of cholangiolithiasis	1 (1%)
Alcoholic cirrhosis	1 (1%)
Undetermined	3 (3%)
Laboratory data	
ALT (U/L)	298 (115–723)
AST (U/L)	204 (96–442)
TBil (μmol/L)	308 (223–397)
Cr (μmol/L)	60 (52–70)
INR	1.47 (1.23–1.71)

Data are expressed as mean ± SD or median (IQR) or number (percentage). HBV-ACLF: hepatitis B virus related acute-on-chronic liver failure; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBil: total bilirubin; Cr: creatine. INR: international normalised ratio.

* Corresponding author.
E-mail address: ljli@zju.edu.cn (L.-J. Li).

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Table 2
Comparison of CBG and IBG measurements in different groups.

Groups	N (pairs)	CBG (mmol/L)	IBG (mmol/L)	*P* value	*r*	Parameters of Bland-Altman plots			
						Differences ($M \pm 1.96SE$)	LoA	95% CI	LoS
Total	862	9.9 ± 3.2	10.2 ± 3.0	**<0.0001**	0.966	4.2 ± 0.6	−12.07 to 20.44	−13.01 to 21.39	±15%
Pre-ALSS	309	9.2 ± 3.1	9.5 ± 3.0	**<0.0001**	0.965	3.5 ± 1.0	−14.80 to 21.72	−16.59 to 23.51	±15%
Inter-ALSS	279	9.9 ± 3.1	10.3 ± 2.9	**<0.0001**	0.971	4.7 ± 0.9	−11.23 to 19.09	−11.23 to 20.57	±15%
Post -ALSS	274	10.5 ± 3.3	10.9 ± 3.0	**<0.0001**	0.962	4.5 ± 0.9	−11.02 to 20.07	−12.63 to 21.68	±15%
HG (CBG > 11.0 mmol/L)	230	14.1 ± 2.7	14.2 ± 2.6	0.426	0.915	0.5 ± 1.0	−14.32 to 15.37	−16.01 to 17.06	±15%
NG (CBG = 5.6–11.0 mmol/L)	615	8.4 ± 1.4	8.9 ± 1.5	**<0.0001**	0.893	5.4 ± 0.6	−10.60 to 21.31	−11.70 to 22.41	±15%
LG (CBG < 5.6 mmol/L)	17	5.2 ± 0.3	5.8 ± 0.4	**<0.0001**	0.619	0.6 ± 0.2	0 to 1.27	−0.30 to 1.57	±0.83 mmol/L

Data are expressed as mean ± SD, the data in LG group are shown in mmol/L, and the rest are shown in percent. Paired-samples *t*-test is used to calculate the *P* value, *r* represents Pearson correlation coefficient. CBG: capillary blood glucose; IBG: *in vitro* blood glucose; HG: high glucose group; NG: normal glucose group; LG: low glucose group. LoA: the actual limits of agreement. LoS: the acceptable limits of agreement.

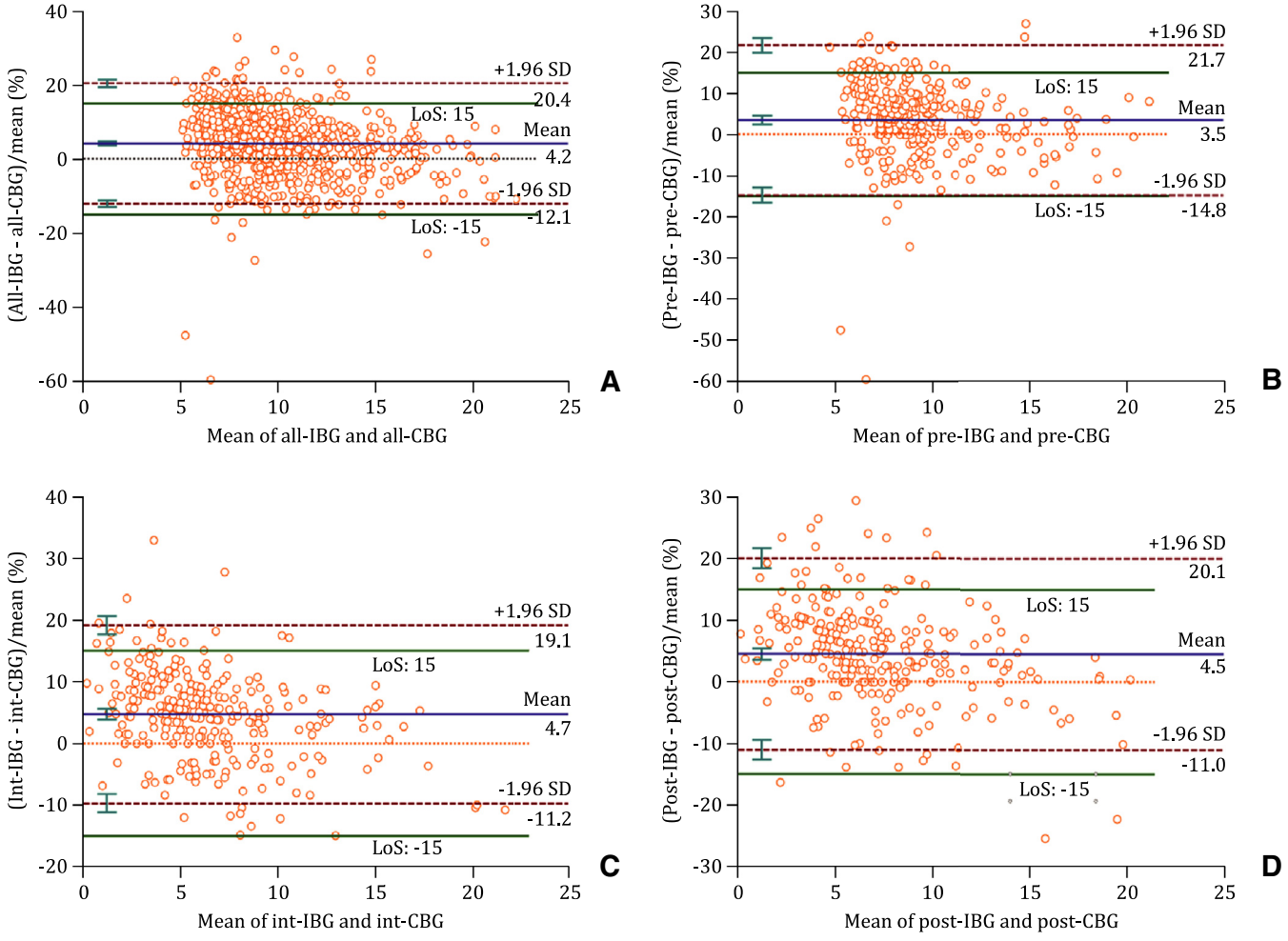

Fig. 1. Bland-Altman scatter graphs of samples taken from different points in the ALSS process. **A:** Consistency analyses of all samples of IBG and CBG; **B:** pre-ALSS; **C:** inter-ALSS; **D:** post-ALSS. Blue line: mean difference; green line: the acceptable limits of agreement (LoS); red dotted line: 95% the actual limits of agreement (LoA), ±1.96SD.

We analyzed 862 paired sets of blood samples from 117 patients. An Accu-Chek Performa meter (Roche, Basel, Swiss) was used to measure the glucose concentration in the plasma of each blood sample. Each blood glucose assay was divided into three time points: prior to ALSS treatment (pre-ALSS), during ALSS treatment (inter-ALSS), and after ALSS treatment (post-ALSS). Pre-ALSS was defined as the time point when the blood circuit tube was first filled with the patient's blood. Inter-ALSS refers to the time point 1.5 h after the start of perfusion. Post-ALSS was defined as the time point after perfusion had been completed but before the blood was returned to the patient's body.

The mean age of the patients who underwent this test was 51±13 years and 86 subjects (74%) were men (Table 1). Hepatitis B virus related acute-on-chronic liver failure (HBV-ACLF) was the

most common type of severe liver injury, accounting for 56% of the cases. The second most common type was drug-induced liver injury, making up 20% of the cases. All patients had elevated levels of ALT, AST, TBil, and INR, indicating severe liver injury.

A total of 862 pairs of blood glucose measurements were obtained. Glucose measurements are shown in Table 2. Paired *t*-test results showed a significant difference ($P < 0.0001$) between IBG group and CBG group in total. Measurements of IBG were higher (10.2 ± 3.0 mmol/L) than those of CBG (9.9 ± 3.2 mmol/L). Then the linear regression analysis was conducted to fit the data and showed the equation as following: IBG = 1.017 × CBG − 0.526, the regression coefficient was 1.017, and 95% CI was 0.998 and 1.035, respectively. There was a strong correlation between the IBG and CBG measurements ($r = 0.966$). We divided CBG readings into three groups according to their glucose concentrations. The low glucose (LG) group ($n = 17$ pairs) was defined as samples with CBG readings less than 5.6 mmol/L, the normal glucose (NG) group ($n = 615$ pairs) were those with readings between 5.6 and 11.0 mmol/L, and the high glucose (HG) group ($n = 230$ pairs) were those with CBG greater than 11.0 mmol/L. A paired *t*-test was performed on each group, and the differences between IBG and CBG were tested. The parameters of these *t* tests are listed in Table 2. The differences between IBG and CBG readings were statistically significant in all groups except the HG group ($P = 0.426$).

We conducted Bland-Altman analyses to determine the consistency between the two methods of blood glucose measurements (Table 2). According to the ISO 15197:2013 criteria [12], 95% of measurements are required to fall within an error range of ±15% to be considered clinically consistent. Based on this preset clinical consistency interval, we chose to use the percentage of difference between IBG and CBG as the Y axis and the average of IBG and CBG as the X axis on a Bland-Altman scatter plot, as shown in Fig. 1A. The lower limit across all samples was −12.07% (95% CI: −13.01% to −11.12%), the upper limit was 20.44% (95% CI: 19.50% to 21.39%), and the mean percentage of difference was 4.2% (95% CI: 3.6% to 4.7%). While the lower limit is within the acceptable minimum of −15%, the upper limit exceeds the acceptable maximum limit of 15%. The difference between IBG and CBG measurements thus exceeds the acceptable clinical range and therefore IBG cannot entirely replace CBG for blood glucose monitoring. We also conducted Bland-Altman analyses of the three measuring time points (Fig. 1B–D) and three blood glucose concentration groups (Fig. 2).

In analyses of the effects of measuring time points, the actual limits of agreement (LoA) of the three time points were all beyond the acceptable limits of agreement (LoS) as described above. Of the three sampling time points, the pre-ALSS group showed the highest range of deviation between IBG and CBG. According to ISO 15197:2013 criteria, when the serum glucose concerntration ≥5.55 mmol/L (100 mg/dL), the minimum accuracy error must be less than ±15%, while the serum glucose concerntration <5.55 mmol/L (100 mg/dL), the minimum accuracy error must be less than ±0.83 mmol/L (15 mg/dL) [12]. Therefore, in blood glucose concentration groupings, the NG and HG groups were compared to a LoS of −15% to 15%, while the LG group was compared to an LoS of −0.83 to 0.83 mmol/L. While the lower limit of agreement in the LG group fell within the LoS, the upper limit of agreement was beyond the LoS, which means that IBG gives higher values than CBG in this group. The difference between the two measurements in this group varied from 0 to 1.27 mmol/L. In the NG group, the data were evenly distributed within the consistency range, but positive deviations were still present and the LoA still exceeded the LoS. In the HG group, however, the mean of deviation was nearly zero (0.5%); the LoA of this group almost coincided with the LoS.

We found that there was a positive deviation between IBG and CBG. Generally, IBG gave higher measurements than CBG. The progression of Li-ALSS had little effect on the deviation, but the

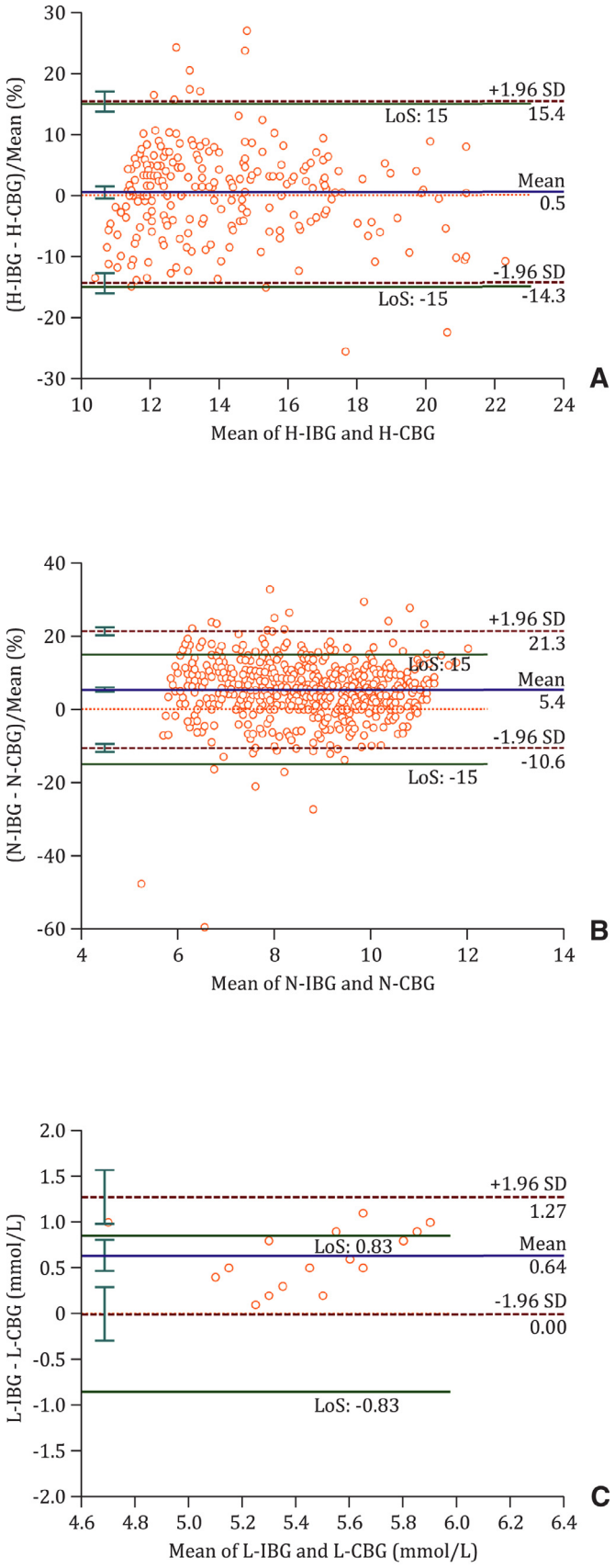

Fig. 2. Bland-Altman scatter graphs of different levels of blood glucose are displayed. LG: low blood glucose group; NG: normal blood glucose group; HG: high blood glucose group. Blue line: mean difference; green line: the acceptable limits of agreement (LoS); red dotted line: 95% the actual limits of agreement (LoA), ±1.96SD.

deviation gradually decreased as the patient's blood glucose level increased.

In conclusion, this study compared different methods of measuring blood glucose in patients undergoing Li-ALSS treatment for severe liver injury. We found that glucose measurements of *in vitro* blood were higher than those of capillary blood. We also found that the Li-ALSS process had little effect on the difference between IBG and CBG, and that hyperglycemia could limit the difference between IBG and CBG. Based on our results, IBG does not have the potential to completely replace CBG for monitoring blood glucose levels in severe liver injury patients undergoing Li-ALSS treatment.

Contributors

ZHF, OXX and LLJ conceived and designed the study. ZHF and OXX collected the data. XZY and HJR analyzed and interpreted the data. XXW and WXY drafted the manuscript. All authors contributed to the analysis and preparation of the manuscript and approved the final version. ZHF and XZY contributed equally to this article. LLJ is the guarantor.

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Ethical approval

This study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (2018-986).

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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