CORRELATION BETWEEN INDICATORS OF HYPOVOLEMIA AND RESPONSE TO INFUSION THERAPY IN FLUID RESUSCITATION OF PATIENTS WITH SEPTIC SHOCK

KORELACJA POMIĘDZY WSKAŹNIKAMI HIPOWOLEMII I REAKCJĄ NA TERAPIĘ INFUZYJNĄ W UZUPEŁNIANIU PŁYNÓW U PACJENTÓW ZE WSTRZĄSEM SEPTYCZNYM

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Summary

Background. Infusion therapy is the primary stage of resuscitation in patients with septic shock. But excess fluids may cause adverse outcomes, so which indicators should doctors monitor to predict whether the infusion volume is sufficient?

Material and methods. The prospective clinical study included 68 consecutive intensive care unit (ICU) adult patients with septic shock, who had an active surgical infection. Results from the PLR test and reaction to infusion therapy revealed a slight positive correlation (R=0.239, P=0.018), initial ScvO2 and reaction to infusion therapy revealed a moderate negative correlation (R=-0.305, P=0.009).

Conclusions. In intra-abdominal septic shock patients, the PLR test is not a reliable predictor of response to infusion, but low initial ScvO2 levels can be used for the prediction of response to infusion. Administering a fluid challenge with dynamic indicators (such as CO) is the most accurate method for clinicians to determine the need for further infusion therapy.

Keywords: septic shock, fluid therapy, intra-abdominal infections, cardiac output, intra-abdominal hypertension
Introduction

Infusion therapy is a key component of septic shock treatment [1]. Timely infusion therapy is crucial for cardiac output (CO) improvement, restoration of oxygen delivery, and prevention of multiple organ dysfunction syndrome (MODS) in septic shock [1]. Therefore, infusion therapy is recommended as a first-line intervention for the resuscitation of patients with this pathology [2]. Timely fluid resuscitation is associated with a reduction in in-hospital mortality [3], while a delay in resuscitation is associated with the release of inflammatory mediators, mitochondrial dysfunction, and a poorer prognosis [4].

The large volumes of transfused fluid often required in the treatment of septic shock can lead to hypervolemia, which is no less dangerous than hypovolemia [5]. Also, the recommendations of the Surviving Sepsis Campaign 2016 [6] indicate that after the initial infusion of crystalline solutions at a dose of 30 mL/kg, further liquid demand should be determined individually based on dynamic indicators, but which indicators should be given priority are not specified. Data from existing literature favors dynamic indicators e.g. CO and cardiac index (CI) over static indicators (ScvO₂, CVP, lactate level) [7].

According to modern concepts, the pace of infusion therapy must be corrected depending on the body's response to the fluid introduction; if the CO increases in response to infusion, the transfusion of fluid should be continued. If CO does not increase, the pace of infusion should be decreased along with the use of vasopressors and cardiotonics. It is considered that a passive leg raising test (PLR test), which induces 150-300 mL of blood to flow back from the venous circulation of the lower body to the chest (self-volume challenge), is useful for assessing the body's response to a fluid transfusion.

Central venous blood saturation (ScvO₂) is one of the parameters for determining the global adequacy of oxygen transport and oxygen demand, and the most common reason for decreased ScvO₂ in patients with septic shock is global organ perfusion disorder due to decreased CO caused by hypovolemia.

The objective of this study was to determine the correlation between different indicators of hypovolemia and the reaction to infusion therapy in fluid resuscitation of patients with septic shock. Since the “fluid challenge” presents a risk of developing hypervolemia, we aim to explore which parameters can most accurately predict response to fluid challenge thereby reducing the risk of hypervolemia in patients with septic shock.

Material and methods

A prospective clinical study was carried out in the Department of Anesthesiology and Intensive Care of Kyiv City Clinical Hospital No. 4, Ukraine. Permission to conduct the research was received from the Ethics Committee of Kyiv City Clinical Hospital No. 4.

The study involved patients over 18 years old, who were hospitalized in ICU, had an active surgical infection (intestinal obstruction, hollow organ perforation, infected pancreatitis, abscess of the parenchymatous organs, peritonitis of other origins), and were in a state of septic shock following surgical intervention. Septic shock was defined according to the criteria of The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [8], as sepsis (an increase of SOFA score of 2 or more points) with plasma lactate level above 2 mmol/L and the need for vasopressors to maintain mean arterial pressure (MAP) at a level ≥ 65 mmHg.

The study did not include patients whose condition was considered non-curable (terminal stage of cancer, total mesenteric thrombosis), or those who at the time of screening had already received a significant amount of infusion therapy (>1,000 ml) within the last 3 hours.

After screening of patients, but before the beginning of infusion, basic parameters of hemodynamics, plasma lactate level and parameters of general and biochemical blood tests were measured according to local standards of treatment of patients of Kyiv City Clinical Hospital No. 4. Hemodynamic parameters such as CO, CI, stroke volume (SV) and stroke volume index (SVI) were monitored using an esophageal Doppler transducer and associated monitor (CardioQ ODM+, Model No. 9051-6935, Deltex Medical, UK) and pulse-wave velocity analysis (bedside monitor with continuous CO measurement by esCCO™ method, model: BSM-3562, Nihon Kohden, Japan). The lactate content was determined using a photometric express system (Accutrend Plus, Roche, Germany). Non-invasive blood pressure, pulse oximetry, heart rate, ECG, ScvO₂, central venous pressure (CVP), and vasopressor demand were also monitored.

The PLR test was performed before infusion by raising the lower limbs to a 45° angle while the patient's trunk was lowered, as previously reported by Monnet et al. [9]. If the CO increased by ≥ 10% after lifting the lower limbs, the PLR test was considered positive.

An isotonic crystalloid solution with a volume of 500 mL was used for resuscitation. The internal jugular vein was catherized in all patients and the solution was injected through the central venous catheter (certofix duo 720, B. Braun, Germany), catheter diameter G16, injection speed 27-33 mL/min. We recorded the CO before and
after infusion. If CO increased by ≥ 10% following infusion, the reaction to the infusion was considered positive. Vasopressor doses and mechanical ventilation (MV) parameters did not change during the study.

Statistical processing was performed in SPSSStatistics 25.0.0 software (IBM Corporation, 2018). Kolmogorov-Smirnov and Shapiro-Wilk criteria were used to check the distribution normality. Depending on the type of data distribution, methods of parametric (Student’s criterion) and non-parametric (chi-square criterion, Mann-Whitney U-test) statistics were used. Correlation was calculated using Pearson correlation coefficient. In the results, the data with parametric distributions are presented as arithmetic mean (M) ± standard deviation (SD). When submitting graphical information, the standard error (SE) is displayed. For some indicators -95% and + 95% confidence intervals (CI) are specified. Non-parametric internal data are presented as median (lower quartile; upper quartile). The rule of arithmetic rounding was used to present all results of statistical processing with an accuracy of corresponding experimental indicators. The difference was considered statistically significant when the probability of a false refutation of the null hypothesis was less than 5% (P<0.05).

Results

The characteristics of 68 patients, included in the study, are presented in Table 1.

Table 1. Patient characteristics (n=68)

| Age (years) | Arithmetic mean (M) ± standard deviation (SD) | 66.64 ± 16.73 |
| Sex | Male | 28 (41.2%) |
| | Female | 40 (58.8%) |
| Weight (kg) | Median (lower quartile; upper quartile) | 67 (60; 80) |
| Height (cm) | Arithmetic mean (M) ± standard deviation (SD) | 167.52 ± 8.88 |
| BMI (kg/m²) | Median (lower quartile; upper quartile) | 24.17 (22.20; 27.08) |
| BSA (m²) | Median (lower quartile; upper quartile) | 1.78 (1.64; 1.92) |
| APACHE II score, points | Arithmetic mean (M) ± standard deviation (SD) | 15.71 ± 1.80 |
| Initial SOFA score, points | Arithmetic mean (M) ± standard deviation (SD) | 8.33 ± 3.45 |
| Initial lactate level, mmol/L | Median (lower quartile; upper quartile) | 4.1 (3.15; 6.35) |
| Initial MAP, mmHg. | Arithmetic mean (M) ± standard deviation (SD) (95% CI) | 66.29 ± 8.81 (63.73-68.85) |
| Noradrenaline administration rate (µg/kg/min) | Median (lower quartile; upper quartile) | 0.16 (0.04; 0.39) |

Table 2 shows the distribution of patients according to the location of surgical infection.

Table 2. Patient distribution by source of surgical infection

| Source of surgical infection | Number of patients | Percentage |
| --- | --- | --- |
| Intestinal obstruction | 27 | 39.7% |
| Hollow organ perforation | 22 | 32.4% |
| Infected pancreatitis | 7 | 10.3% |
| Partial mesenteric thrombosis | 5 | 7.4% |
| Abscess of the parenchymatous organs | 3 | 4.4% |
| Peritonitis of other origins | 4 | 5.9% |
| Total | 68 | 100% |

The results of PLR testing are presented in Table 3, sensitivity (ability to detect positive reaction to infusion) = 53.8% with 100% correctness; specificity (ability to detect negative reaction to infusion) = 100% with a correctness of 9%; test accuracy = 55.9%.
Table 3. Organization of data to evaluate PLR test informativeness

| PLR-test | Infusion response according to CO | Total |
|----------|----------------------------------|-------|
|          | Positive                         | Negative |       |
| Positive | 35                               | 0       | 35 (51.5%) |
| Negative | 30                               | 3       | 33 (48.5%) |
| Total    | 65 (95.6%)                       | 3 (4.4%) | 68 (100%) |

Notes: In the septic shock patients with abdominal infection, 51.5% were true positive PLR-test results, 0% were false positive PLR-test results, 44.1% were false negative PLR-test results, and 4.4% were true negative PLR-test results. Test sensitivity = 53.8%, test specificity = 100%.

Almost half of the patients had negative PLR test results, however, taking into account other clinical and laboratory parameters, including ScvO₂, the decision was made to perform a test with 500 mL isotonic crystalloid solution infusion (fluid challenge). Then, the correlation relations of the two methods and the reaction to fluid infusion were determined.

The relationship of ScvO₂ and the response to infusion are presented in Table 4, sensitivity (ability to detect positive reaction to infusion) = 70.8% with 100% correctness; specificity (ability to detect negative reaction to infusion) = 100% with a correctness of 13.6%; test accuracy = 67.6%.

Table 4. Evaluation of ScvO₂ as a predictor of response to infusion (fluid challenge)

| ScvO₂ | Infusion response according to CO | Total |
|-------|----------------------------------|-------|
|       | Positive                         | Negative |       |
| ScvO₂ < 70% | 46                               | 0       | 46 (67.6%) |
| ScvO₂ ≥ 70% | 19                               | 3       | 22 (32.4%) |
| Total  | 65 (95.6%)                       | 3 (4.4%) | 68 (100%) |

Notes: The predictive results of initial ScvO₂ levels for infusion response in septic shock patients with abdominal infection, 67.6% were true positives, 0% were false positives, 27.9% were false negatives, and 4.4% were true negatives. Sensitivity = 70.8%, specificity = 100%.

At the stage of fluid resuscitation of patients with septic shock, PLR-test and reaction to infusion therapy revealed a slight positive correlation (R=0.239, P=0.018) (Figure 1), initial ScvO₂ and reaction to infusion therapy revealed a moderate negative correlation (R=-0.305, P=0.009) (Figure 2). The Chaddock scale was used to estimate the strength of the correlation relation.
Among the patient group studied, 39.7% were diagnosed with intestinal obstruction, 32.4% were diagnosed with perforation of luminal organs, and 10.3% were diagnosed with infected pancreatitis. We divided the patients with these three diagnoses into three subgroups and found that there was a strong positive correlation between PRL-test and infusion response in the intestinal obstruction subgroup (R=0.67, P=0.012). However, there was no such correlation found in patients with luminal organ perforation or infected pancreatitis (P=0.192 and 0.426 respectively).

**Discussion**

In the course of conducting this research, contradictory data that conflicts with existing researches was obtained [10-15]. In particular, the passive leg raising test (PLR-test) showed low sensitivity to positive infusion, and most patients with a negative PLR-test had a positive infusion response anyway. Among the possible causes may be the abdominal genesis of sepsis in patients of the research, because current literature data shows the ineffectiveness of the PLR test in patients with intra-abdominal hypertension (IAH) [16,17], and abdominal surgery is a risk factor for the development of intra-abdominal hypertension and abdominal compartment syndrome [18].

Nasogastric drainage tubes were inserted into all patients during their surgical procedure. In principle, they help to maintain a relatively normal intra-abdominal pressure (IAP) level, however the intra-abdominal pressure was not measured routinely in patients in the study, which is a limitation of our study. The influence of IAP on hemodynamics is complex. The direct effect of IAP on the extrathoracic veins leads to an increase in venous return pressure, but a significant increase of right atrial pressure causes venous return and CO to decrease. When the IAP increases from 0 to 30 mmHg, SV and CO decrease. The increase of IAP increases the left ventricular (LV) afterload by increasing the resistance of the extrathoracic arteries, and is accompanied by an increase in right atrial pressure and right ventricular afterload, which may cause a decrease in CO. In this study, we were more concerned about the effect of IAP on dynamic parameters. In fact, in the study of A. Beurton et al. [19], the PLR test decreases IAP in patients with IAH as well as in patients without it. IAH decreases the amplitude of the PLR-induced increase in CO in fluid responders. It is responsible for some of the false negatives which occurred when testing the PLR test as a predictor of fluid responsiveness.

Also, a strong predictor of the response to infusion therapy was low initial ScvO₂, despite the existing published data on the low diagnostic value of this indicator. The working hypothesis of the research group is

![Figure 2. Correlation of initial ScvO₂ and reaction to infusion therapy](image-url)
that the most accurate method of determining fluid requirement is a direct measurement of the response to the test dose of fluid (fluid challenge), followed by the accuracy of the PRL-test, but the final results are somewhat different. The incidence of IAH in patients with severe acute pancreatitis is high (60-80% depending on the population considered) [20]. The septic shock caused by the perforation of hollow organs is associated with IAH occurring in 62% [21]. Due to the increase of intestinal contents [22], intestinal obstruction is also a risk factor for IAH. But most studies of intra-abdominal pressure in patients with intestinal obstruction were carried out before operational intervention. In fact, the problem of obstruction was solved during operation, so the postoperative intra-abdominal pressure was significantly reduced [23]. This may explain why there is a weak positive correlation between PRL-test and infusion response in these patients with a strong positive correlation found in the intestinal obstruction subgroup, but no similar correlation found in the hollow organ perforation subgroup and infected pancreatitis subgroup.

Doctors sometimes ignore IAH when there is a decompression system and a "soft abdomen". When deciding to provide infusion therapy to patients with abdominal septic shock, different parameters need to be monitored, and it is important to compare benefits and risks individually. For patients with the risk of IAH, IAP should be measured before PRL-testing. Routine measurement of IAP is necessary for septic shock patients who have undergone abdominal surgery.

Conclusions

1. The results show that the PLR test is not a reliable predictor of the response to infusion in patients with intra-abdominal septic shock.
2. A low initial ScvO\textsubscript{2} is an indication for assessing the response to infusion in patients with septic shock.
3. The direct measurement of the response to the infusion (fluid challenge) is the most accurate method of determining the need for further infusion therapy.
4. The data confirm that almost all patients have initial hypovolemia and a positive reaction to the infusion. After the initial infusion, an assessment using dynamic indicators is necessary to determine the further need for infusion therapy.

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