Blood return at the end of renal replacement therapy provided clues on fluid responsiveness in critically ill patients with shock

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Abstract

Objectives

To observe if blood return, also defined as the blood infusion test (BIT) could predict fluid responsiveness in critically ill patients with shock and continuous renal replacement therapy.

Methods

Before BIT, the passive leg raise test (PLRT) was performed to record the changes of cardiac output (ΔCO) by thermodilution and ΔCO >=10% was defined as fluid responders. Meanwhile, the changes in velocity time integral (ΔVTI) were recorded by echocardiography and ΔVTI>=15% was defined as fluid responders. Then the changes in COs and VTIs were recorded during BIT about several minutes after PLRT. The receiver-operating characteristic curves of ΔCO and ΔVTI were compared between PLRT and BIT.

Results

Forty-three patients were enrolled in our study. 25 patients (58.1%) were recognized as responders during PLRT while 22 of these patients (51.2%) had increased COs during BIT. And according to the receiver-operating characteristic curves, the optimal cutoff value of ΔCO was 8.5% and ΔVTI was 19% during BITs with the area under curve were 0.947 (95% CI 0.87-1.0) and 0.952 (95% CI 0.893-1), respectively.

Conclusions

BIT in continuous renal replacement therapy could identify fluid responsiveness in critically ill patients with shock.

(Trial registration: ChiCTR-DDD-17010534). Registered on 30/01/2017 (retrospective registration).

Background

Patients with renal injury and shock happened almost every day in the intensive care unit. According to Hoste et al, hypotension happened in 47.6 per 100 intensive care unit adult patients who had a high risk of acute kidney injury with 53.8% (1). Shock/hypotension is attributed to kinds of reasons, one of which is hypovolemia. Dynamic tests, like the passive leg raise test (PLRT) and infusion of small volumes of fluid (2), have been widely used to observe the changes in cardiac output (CO) to identify fluid responsiveness. These tests could induce short-term changes in cardiac preload which are dependent on the heart-lung interaction. Kinds of techniques could obtain the hemodynamic evaluations during the tests above, including echocardiography (3) and thermodilution (4) which are used broadly in intensive care units.

Although renal replacement therapies (RRTs) have powerful effects on fluid management, they cannot have the patient with the 'optimal volume' during the course of treatment every time. When it has to be terminated due to kinds of reasons, the patient is probable of being with insufficient volume or overload. The future direction of fluid management would have a setting specific aim if we could tell the insufficient volume at the end of RRTs. We have already found that the blood pump-out test (BPT) at the initial procedure of RRTs could serve as a complementary maneuver to predict fluid responsiveness (5). Blood return has a similar effect on fluid expansion due to about 200ml of blood going back to the body. We hypothesized that the procedure of venous blood return, also known as the blood infusion test (BIT) could also be another supplemental method to predict fluid responsiveness. Our goal of this study was to observe if the changes of COs and velocity time integrals (VTIs) during BIT could identify fluid responders from all critically ill patients with shock.

Methods

This is a single-center, prospective, observational study in a medical care unit of Guangdong Provincial People's Hospital (ChiCTR-DDD-17010534). It was approved by the hospital's Ethical Committee (No. GDREC2016313H) and informed consent was obtained from all included participants or their immediate family members.

Patients

Patients who met the following criteria were included: 1) ≥ 18 years old, 2) with acute circulatory failure, 3) undergoing RRT, 4) transpulmonary thermodilution device (Pulse Contour Cardiac Output 2 (PiCCO2) device, Pulsion Medical Systems, Munich, Germany) already in place. Exclusion criteria were pregnancy and end-stage malignant tumors.

Acute circulatory failure was defined as 1) systolic pressure < 90mmHg or > 40mmHg decreased from normal reference values, or 2) blood pressure maintained with vasopressors, or 3) urine < 0.5ml/kg/h for more than two hours, heart rate > 100 bpm, skin tinea, or lactate > 2mmol/L.(6)

Study protocol

All enrolled patients would go through a two-step protocol. The first one was the PLRT which was described in a previous study (7). The second one was a BIT several minutes after PLRT, the process of blood return from the blood filter and pipelines to the body at the end of RRT. The BITs were initiated with a flow rate of 100ml/minute for blood return (lasting about 2 minutes). All fluids were stopped during both tests and vasopressors were maintained at a constant speed if no dramatic decrease in mean arterial pressure occurred.

The maximal COs were recorded by PiCCO2 and the maximal left ventricular outflow tract (LOVT) VTIs were recorded by ultrasound. Parameters mentioned above were acquired just before and 2 minutes after PLRTs or BITs. And the changes between these two-time points were calculated as ΔCO [= ($CO_{\text{after PLRT/BIT}}$

$-CO_{\text{before PLRT/BIT}})/ CO_{\text{before PLRT/BIT}}]$ and $\Delta VTI [= (VTI_{\text{after PLRT/BIT}} - VTI_{\text{before PLRT/BIT}})/ VTI_{\text{before PLRT/BIT}})$. And the interval between PLRT and BIT was about 2 minutes which was long enough to have the COs or VTIs go back to baselines. Patients who had more than or equal to 10% of ΔCO (8) and 15% (9) of ΔVTI were taken as the responders in PLRTs, which was considered 'the golden standard' to recognize fluid responsiveness. Otherwise, the rest of them were non-responders. Then ΔCOs and ΔVTIs in BITs were compared with that in PLRTs.

Statistical analysis

A target sample size of 40 patients was based on a 92.5% sensitivity observed in the previous experiment and the intention to obtain the statistical significance of $\alpha = 0.05$, allowing for an error of $\delta = 0.08$. The normality of data was tested by the Kolmogorov-Smirnov normality test. Continuous variables were expressed as mean ± standard deviation. Comparisons before and during PLRTs/BITs were assessed with the Wilcoxon test. Comparisons of variables were assessed by a two-tailed Student's t-test or a Mann-Whitney U test, as appropriate. A receiver-operating characteristic curve was constructed to test the ability of BITs induced changes in CO to predict fluid responsiveness. The standard of fluid responsiveness in this study was defined as a > = 10% increase in pulse contour analysis-derived COs and > = 15% in VTI during PLRTs. Sensitivities, specificities, and area under curve were expressed as mean and 95% confidence interval (CI). The diagnostic cutoff value was determined by the best Youden index value. SPSS19.0 software was used to analyze the data. $P \leq 0.05$ was considered statically significant.

Results

There were 43 patients included in our study (Table 1). Only mean arterial pressure increased after BITs compared to baselines ($p = 0.002$). Other hemodynamic variables, including heart rate, central venous pressure, stroke volume, and inferior vena cava collapse index had no significant change, no matter during PLRTs or BITs (Table 2).

Table 1
Patient characteristics

	Total (n = 43)
Gender (male/female)	20/23
Age (years old)	79 ± 12
APACHE II scores	26 ± 6
SOFA scores	13 ± 4
Vasopressors	19
No Vasopressor	3
Norepinephrine < 0.2ug/mg/h	13
Norepinephrine0.2-0.4ug/mg/h	3
Norepinephrine > 0.4ug/mg/h	2
Norepinephrine + Dopamine	3
Sodium nitroprusside	
Serum creatinine (umol/L)	226 ± 106

Table 2
Hemodynamic variables during PLRTs and BITs

	Heart Rates (HR) (beats/minute)	Mean Artery Pressure (MAP) (mmHg)	Central Venous Pressure (CVP) (mmHg)	Stroke volume (SV) (ml) from PiCCO2	Inferior vena cava-collapse index (IVC-CI) from Ultrasound
Baseline	88 ± 20	82 ± 11	9 ± 5	65 ± 26	0.13 ± 0.08
After PLRTs	90 ± 22	86 ± 20	11 ± 5	70 ± 27	0.13 ± 0.11
After BITs	88 ± 21	92 ± 13*	11 ± 6	71 ± 26	0.11 ± 0.06
* P-value < 0.05 compared to Baseline					

Compared to before PLRTs in all patients, COs increased significantly after PLRTs (5.5 ± 1.9 VS 6.0 ± 2.2 L/min, $p < 0.005$). Meanwhile, VTIs had the same changes before and after PLRTs (33.4 ± 19.4 vs. 37.8 ± 18.7cm/s, $p = 0.049$).

Both COs (6.00 ± 2.0 vs. 5.5 ± 1.9 L/min, $p < 0.005$) and VTIs (38.8 ± 18.1 vs. 33.4 ± 19.4 cm/s, $p < 0.005$) ascended after BITs compared to before BITs. According to our observation, COs could return to the same baseline after PLRTs and before BITs. Because the volume from both lower extremities was the only

factor that could have an influence on COs when the vasoactive agents and cardiac contractile function were kept at the same level.

We took ΔCO ≥ 10% and ΔVTI ≥ 15% during PLRTs as golden standards for fluid responsiveness. And there were 25 patients (58.1%) identified by ΔCO and 19 patients (44.2%) identified by ΔVTI who were fluid responders during PLRTs. Based on the golden standard, the optimal cutoff value of ΔCO was 8.5% during BITs with a sensitivity of 92% and a specificity of 100%. The area under curve was 0.947 (95% CI 0.87-1.0) (Fig. 1A). Similarly, the optimal cutoff value of ΔVTI was 19% during BITs with a sensitivity of 84% and a specificity of 95.8%. The area under curve was 0.952 (95% CI 0.893-1) (Fig. 1B).

Discussions

According to our study, patients had increased COs and VTIs both after PLRTs and BITs compared with those before these two tests, which indicated that the changes of COs and VTIs during BITs could identify fluid responsiveness in circulatory shock patients with RRT.

The evaluation of fluid responsiveness happens all the time in intensive care units which play a vital role in fluid management. Fluid bolus, which could be treated as preload challenge, was classically used to test if it could induce hemodynamic improvement. But it was possible to be overloaded if no attempt was made to evaluate fluid responsiveness with volume expansion. So static parameters like central venous pressure and dynamic markers like pulse pressure variation and stroke volume variation were used based on heart-lung interaction(10). And PLRT, taken as a reversible preload challenge, could be repeated frequently without any fluid dripping into the body(11) and was accurate even in patients spontaneously complicated with cardiac arrhythmias, and low respiratory system compliance(12). Additionally, an increase in CO after the mini-fluid challenge could also define fluid responsiveness (13). In our opinion, PLRT was proved to be the most useful and convenient maneuver reported to be reliable consistent with studies, and reversible in preload challenges (2). Therefore, we adopted the changes of preload during PLRTs, expressed by CO and velocity-time integral, as the ‘golden standard’ in our study to test if BIT could have the same power to identify the fluid responders from all patients with shock and RRTs. The reliability of CO measurements by pulmonary thermodilution in RRT was challenged because it was found that the thermodilution curve forms were modified resulting in inaccurate calculation of related hemodynamic parameters.(14) But we noticed that the thermal indicator was injected through a dialysis catheter in this study which was not a normal way stipulated by factory settings. Additionally, Dr. Dufour and his colleagues confirmed that hemodynamic measurements derived from transpulmonary thermodilution were not affected by RRTs.(15) So we could take the changes of CO derived from PiCCO2 as the golden standard to recognize fluid responders.

Transthoracic echocardiography was performed excellently in estimating cardiac out based on LVOT-VTI compared with pulmonary artery catheter (16, 17). Additionally, LVOT-VTI combined with PLRT could screen volume responsiveness from end-stage renal disease patients after hemodialysis with the mean VTI increasing from 30.31cm to 34.91cm and the mean ΔVTI between 12.64% and 16.84% (18). And

LVOT-VTI is reliable and repeatable in distinguishing fluid responders from all shock patients. As reported in the study of Lill Bergenzaun and his colleagues (19), LVOT-VTI was the best repeatable echocardiographic parameter in the evaluation of left ventricular systolic function.

Little similar studies were found according to our findings except the one published by our team last year which focused on volume changes during BPT at the early stage of continued blood purification(5). From our collected data, general hemodynamic parameters (heart rate, mean arterial pressure, and central venous pressure) had no significant difference before and after PLRTs or BITs. Just as reported in Andreas Umgelter's study, the above hemodynamic parameters had no change after infusion of 200ml of 20% albumin. Furthermore, no difference was detected between responders and non-responders(20). Additionally, even stroke volume from PiCCO and inferior vena cava-collapse index from echo examination had little change before and after PLRTs or BITs from this study due to various interfering factors in the calculation of stroke volume from PiCCO, like zero setting of arterial pressure, and VTI-CI from echocardiography, like respiratory rate. However, COs and LVOT VTIs increased significantly both in PLRTs and BITs. There were nearly 60% of patients companied by remarkable increased COs with relatively high COs during PLRTs. That was to say, the cause of shock in this population remained partly due to insufficient volume indicating that more fluids should be given to these patients. Such facts implied that, firstly, if the patient had received sufficient fluid management; secondly, the following goals of fluid treatment should be made on account of the results after BIT.

Our study was limited by the following facts. Firstly, it should be a 'round-trip' trial if we're intended to demonstrate BITs do have an impact on fluid responsiveness, which means there should be a BPT just after BIT. However, it couldn't be carried out in practical daily work due to standards of medical ethics. Secondly, we took PLRT as 'the golden standard' in our study instead of fluid-challenge with a certain number of crystalloids. But such a volume as 500ml was not necessary and might be a heavy burden to the patient that could worsen the unstable hemodynamics.

Conclusions

BITs could serve as a prediction test at the end of RRT which might indicate the directions of treatment in the following therapeutic schedule.

Abbreviations

RRT, renal replacement therapy

BIT, blood infusion test

PLRT, passive leg raise test

VTI, velocity time integral

BPT, blood pump-out test

PiCCO, Pulse Contour Cardiac Output

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by Ethical Committee of Guangdong Provincial People's Hospital (No. GDREC2016313H). Informed consent was taken from all individual participants. This clinical trial has been registered at Chictr.org.cn as ChiCTR-DDD-17010534.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors have no other conflicts of interest to declare.

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Authors' contributions

Daozheng Huang: Conceptualization, Supervision.

Jie Ma: Formal analysis, Writing - original draft.

Shouhong Wang: Investigation.

Tiehe Qin: Resources.

Feier Song: Writing - review & editing.

Tieying Hou: Project administration.

Huan Ma: Data curation.

All authors read and approved the final manuscript.

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The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting, and editing of the paper and its final contents.

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Figures

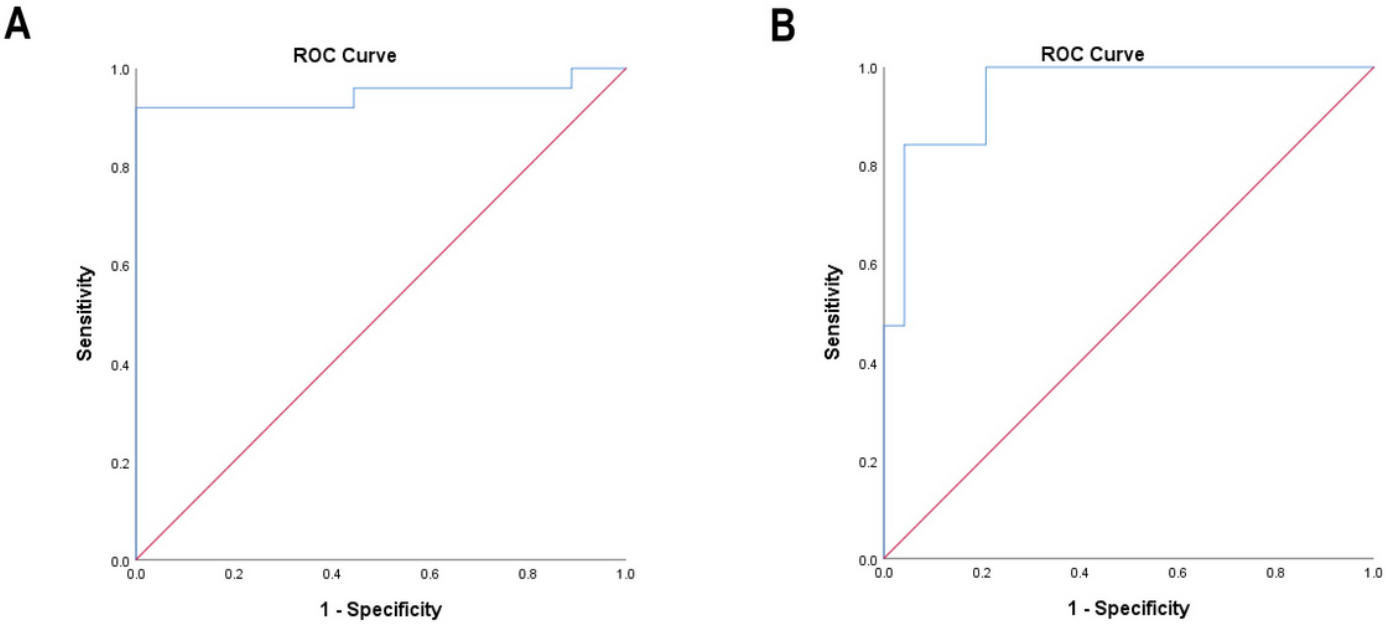

Figure 1

Prediction of fluid responsiveness.

The receiver-operating characteristic curves of the changes in cardiac output (ΔCO) (A) and the changes in velocity time integral (ΔVTI) (B)