A Mini-fluid Challenge of 200 mL Predicts fluid Responsiveness Using Pulmonary Artery Catheter in Septic Shock Patients an Observational Study

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Abstract

Background: Mini-fluid challenge may predict fluid responsiveness and limit fluid overload. This study was designed to explore the minimal infusion volume in effectively predicting fluid responsiveness in septic shock patients.

Methods: ICU septic shock patients with indwelling pulmonary artery catheter received five sequential intravenous boluses of 100 mL 4% gelatin. Cardiac output was measured with thermodilution before fluid challenge (baseline) and three minutes after each bolus. Fluid responsiveness (FR) was defined as an increase in CO greater than 10% after 500 mL fluid infusion. The smallest volume which can perform an effective fluid challenge was analyzed.

Results: Forty-seven patients were included in this prospective study. After 500 mL volume expansion, thirty-six patients presented with FR (77%) and 11 patients were fluid nonresponders. A mini fluid of 100 mL colloid had a poor predictive value (AUC = 0.67, $p > 0.05$). The minimal volume required to predict FR in a mini fluid challenge was 200 mL. An increase in CO greater than 5.2% after 200 mL colloid infusion was able to predict FR with a sensitivity of 83.3% and specificity of 90.9%. The AUC under the ROC curve was 0.93 (95% CI: 0.84 – 1, $p < 0.05$).

Conclusion: In septic shock patients, a minimal volume of 200 mL 4% gelatin could reliably detect fluid responders and nonresponders.

Trial registration: ClinicalTrial.gov (NCT01941472). Registered on 13 September 2013.

Background

Fluid therapy is the cornerstone of septic resuscitation. According to the Early Goal Directed Therapy (EGDT) of sepsis bundle, an aggressive fluid resuscitation has been widely applied and known to improve survival in sepsis[1–4]. However, several retrospective studies have shown that 67% of patients with septic shock developed fluid overload on the first day of admission, with an average positive fluid balance of 4.2 L[5–8]. In recent decade, a restrictive fluid strategy has been applied to shock resuscitation for fewer complications and shorter hospital stays compared with a liberal fluid strategy[9–11]. Therefore, it is a reasonable step to assess the patient's response to fluid infusion to avoid excessive fluid administration[12, 13].

The Surviving Sepsis Campaign recommended dynamic cardiac measurements to guide fluid resuscitation in 2016. Mini-fluid challenge, passive leg raising (PLR) test and end-expiratory occlusion (EEO) test, all of these dynamic approaches allow the selection of fluid responders by inducible changes of hemodynamic parameters after changing the preload gaining popularity[14, 15]. Mini-fluid challenge and PLR test and EEO test share the same principle, which can prevent patient from unnecessary fluid. These tests require a precise and real-time hemodynamic assessment to be properly interpreted. However, mini-fluid challenge can be used when other tests are not available and are not limited by the patient's disease condition and position, such as intra-abdominal hypertension, amputation, and prone position during therapy. Thus, mini-fluid challenge has attracted more attention from both ICU physicians and anesthetists.

The mini fluid challenge was firstly described by Muller et al. in 2011. They found an infusion of 100 mL colloid over 1 minute and the assessment by cardiac output using velocity time integral (VTi) at the aortic outflow tract could predict fluid responsiveness (FR). Since then, a total of seven investigations have been published [16–21]. Although a mini-fluid challenge may help the decision-making process of fluid management, the investigation results differed from each other, especially in minimal volume and cut off value of hemodynamic parameters change. Wu et al.reported that a minimal volume of 50 mL could predict FR using TTE to calculate VTi[19]. Muller et al. used 100 mL to predict FR also with VTi by TTE. Guinot.'s and Wang.'s work showed similar results with SV measured by thoracic impedance cardiography (ICG) and cardiac output (CO) measured by pulse contour (PiCCO). Meanwhile, Smorenberg's study showed that a better predictive minimal volume was 200 mL by applying pulse contour cardiac output measurement (PulseCO^R, COIi) to calculate CO[16]. In addition to accessing the minimal volume by milliliter (mL), Aya.et al[22] demonstrated that a dose of 4 mL/Kg crystalloid could increase the transient stop-flow arm arterial-venous equilibrium pressure and detect FR. So here comes the question: what is the minimal infusion volume in effectively predicting fluid responsiveness. We noticed that when measuring CO, the method of thermodilution by pulmonary artery catheter (PAC), which is the gold standard of CO measurement, was not used in these studies. Furthermore, the majority participants of the studies were perioperative patients in a stable hemodynamic state. Another question that needs to be answered is: whether mini-volume can perform a real change in septic shock patients. Therefore, it is necessary to explore the minimal volume in fluid challenge by PAC and test its reliability in detecting responders (R) and nonresponders (NR).

In clinical practice, dynamic measurements are more recommended compared with static measurement. However, these measurements including CO monitor or echocardiograph require specific devices and skilled technicians. Therefore, a surrogate of CO which can be simply used and easily obtained to evaluate FR is needed. According to Fick equation, mixed venous oxygen saturation (SvO_2) is in the balance of

cardiac index (CI), oxygen saturation and oxygen consumption[23]. We hypothesized that SvO_2 can indirectly assess whether CO is sufficient enough to meet patient's enough. Based on the same hypothesis, the concept of finding parameters of oxygen metabolism to assess CO status seems to be reasonable and more convenient to apply to clinical settings. Central venous-to-arterial carbon dioxide partial pressure ($Pcv\text{-}aCO_2$) and central venous oxygen saturation ($ScvO_2$) are two parameters expected to be effective in clinical practice. In this study, we attempt to observe changes in physiological parameters and evaluate their predictive abilities in mini fluid challenge[24–26].

Methods

Study design

This was a single-center, prospective observational pilot study. The clinical trial was registered on ClinicalTrial.gov (NCT01941472). The study protocol was approved by the Ethical Committee of Peking Union Medical College Hospital (ZS1085). Written informed consent was obtained from all patients or their legal representatives.

Patients

This study was conducted from July 2019 to July 2020. Patients over age of 18 years and under 80 years who have been diagnosed with septic shock and required fluid resuscitation were included. Septic shock in this study was defined in accordance with international criteria[3]. The exclusion criteria included other types of shock diagnosed, such as cardiogenic shock with evidence of acute coronary syndrome, chronic cardiac dysfunction, known allergy to colloid fluids, pregnancy, and simultaneous participation in another biomedical study. All patients received CO monitoring by thermodilution of PAC during their ICU stays, and the contraindications of PAC monitoring CO were excluded.

Hemodynamic monitoring

The arterial blood pressure was monitored from an arterial line (Becton Dickinson infusion therapy systems Linc., Utah, USA) placed in a radial artery or dorsalis pedis artery. PAC with 6 canals was placed in the internal jugular vein, and CO was calculated by the continuous thermodilution technique equipped with this PAC (Swan-Ganz CCOmbo CCO/SvO_2, Vigilance II™ monitor, Edwards Lifesciences, Irvine, CA, USA). All the mentioned above catheters connected to pressure transducers and the IntelliVue Patient Monitor MP70 (Philips Medical System, Boeblingen, Germany).

Mini-FC

Fluid challenge was performed in patients with hypotension (SBP < 90 mmHg or MAP < 65 mmHg), or patients with evidences of tissue hypoperfusion (including but not limited to oliguria, skin mottling, altered mental status, cool peripheries, and hyperlactatemia, etc). This study consisted of six steps. The first set of measurements, including heart rate (HR), mean arterial pressure (MAP), pulmonary artery wedge pressure (PAWP), central venous pressure (CVP) and cardiac output (CO) as well as systemic vascular resistance (SVR) were recorded. CO values at each time-point were calculated from the average of three measured values. Baseline sets of blood gas were collected from arterial line (arterial blood gas), central venous in PAC canal (venous blood gas) and mixed venous canal in PAC canals (mixed venous blood gas) (S1). The first 100 ml of 4% gelatin [Gelofusine; B. Braun Medical (Suzhou) Company Limited, Suzhou, China] was manually infused with a syringe of 60 mL (50 mL twice) within 2 minutes using. The second set of measurements and blood gas were then recorded immediately within 8 minutes after FC (including 3 minutes to calculate the CO and 5 minutes to obtain blood gas) (S2). Then, we repeated the colloid injection (100 mL within 2 minutes), hemodynamic data collection and blood gas sets collection (within 8minutes) as described above every 10 minutes for 4 times (S3-S6). All the patients received a total volume of 500 mL during 40 minutes, and 6 sets of data were analyzed after then. A brief study design is described in the Fig. 1. Patients were well sedated and there were no alterations in therapy during min-FC. The decision to optimize circulation was at the discretion of the physicians. A CO increase of more than 10% at the end of 500 mL volume expansion was defined as FR.

Statistical analysis

Data were expressed as number, percentage, while continuous variables were expressed as the means ± standard deviation (SD) or median with interquartile ranges (IQR) within 25–75%, as appropriate. Before FC, patient characteristics between R and NR were compared using Student's T or Mann-Whitney U for continuous data and chi-square test for categorical data. A Student's paired t-test was used for within-group comparisons (between S1 and S2, S3, S4, S5, S6). The difference between R and NR was compared by Student's t-test. The receiver operator characteristic (ROC) curves generated for ΔCO_{100mL}, ΔCO_{200mL}, ΔCO_{300mL} and ΔCO_{400mL}, and the area under the ROC curve (AUROC) were calculated to assess predictive value. The Youden index was used to determine the optimal cutoff value of changes in cardiac output when the AUROC was greater than 0.5. Spearman's correlation coefficient r_s was used to quantify relations between continuous

variables. Statistical analyses was performed with SPSS 25.0 software (SPSS, Inc, Chicago, IL), MedCalc (statistical software version 15.6.1 for Windows) and GraphPad Prism 7. A value of $p < 0.05$ was considered to be statistically significant.

Results

During the study period, 142 patients with acute circulatory failure were admitted from July 2019 to July 2020 during the study period. 95 patients who met the exclusion criteria were excluded, leaving 54 patients with septic shock from different sites of infection were eligible to the study. In addition, 7 patients had not been completed the study because of different reasons. Thus, 47 patients were finally included and analyzed. The detailed information of patient flow diagram was recorded in the flow chart (Fig. 2). Baseline demographic and clinical characteristics of participants between R and NR are shown in the Table 1. Baseline hemodynamics and blood oxygen metabolism indices were described and compared in Supplemental Table 2. Except for CO and DAP, there was not significant differences between R and NR at baseline.

Table 1
Baseline demographic and characteristics of participants

Studied parameters	**Overall (n = 47)**	**R (n = 36)**	**NR (n = 11)**	***P***
Age (years)	58 ± 15	57 ± 16	59 ± 9	0.76
Weight (kg)	64 ± 12	63 ± 12	69 ± 13	0.17
Height (cm)	166 ± 7	166 ± 7	168 ± 8	0.24
BSA	1.8 ± 0.17	1.78 ± 0.17	1.87 ± 0.17	0.13
Sex (male/female)	27/20	18/18	9/2	0.16
Temperature (°C)	37.9 ± 0.8	37.8 ± 0.9	38 ± 0.8	0.34
APACHE II	24 ± 8	24 ± 8	23 ± 8	0.71
SOFA	12 ± 3	13 ± 3	12 ± 3	0.6
Vasopressor, n	47	36	11	0.2
Noradrenaline, n	47	36	11	0.2
Dose, mcg/min	36(18–70)	36(19–60)	70(18–96)	
Adrenaline, n	1	1		
Dose, mcg/min		2		
Infection sites				
Thoracic	23	16	6	
Pneumonia		1		
empyema				
Abdominal	15	4	2	
Cholangitis or cholecystitis Gastroenteritis	4	5	3	
Peritonitis	7	2		
	4			
Cavity Blood	4	4	0	
Others	5	4	1	

Abbreviations: BSA, Body Surface Area; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; R, Responders; NR, Nonresponders.

Table 2
Baseline clinical characteristics comparison between responders and non-responders

Studied parameters	Overall (n = 47)	R (n = 36)	NR (n = 11)	*P*
HR (bpm)	117 ± 25	118 ± 26	116 ± 22	0.97
SAP (mmHg)	115 ± 18	116 ± 19	111 ± 15	0.34
DAP (mmHg)	62 ± 8	63 ± 8	54 ± 4	< 0.05
MAP (mmHg)	78 ± 8	79 ± 8	75 ± 5	0.06
CVP (mmHg)	11 ± 5	10 ± 3	12 ± 5	0.29
PAWP (mmHg)	14 ± 4	14 ± 5	14 ± 4	0.86
CO (L/min)	6.6 ± 2.4	6.2 ± 2.4	8.0 ± 1.8	< 0.05
SV (mL)	58 ± 23·	55 ± 23	70 ± 17	0.06
SVR (dynes·s·cm^{-5})	976 ± 515	1051 ± 522	733 ± 426	0.2
HBG (g/dL)	9.4 ± 2.5	9.5 ± 2.6	9.5 ± 2.6	0.99
$ScvO_2$ (%)	71.7 ± 10.7	71.2 ± 10.7	72.5 ± 11.5	0.74
SvO_2 (%)	68.6 ± 9.2	68.2 ± 9	70.7 ± 10	0.45
Lac (mmol/L)	2.8 (1.4-4.0)	2.5 (1.5–3.2)	3 (1.4–4.2)	0.94

Abbreviations: HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; CVP, central venous pressure; PAWP, pulmonary artery wedge pressure; PAWP, pulmonary artery wedge pressure; CO, cardiac output; SV, stroke volume; SVR, systemic vascular resistance; HBG, hemoglobin; ScvO2, central venous oxygen saturation; SvO2, mixed venous oxygen saturation; Lac, lactate.

Hemodynamic parameters change with mini-fluid challenge

Of the 47 patients, 36 (77%) were FR to the FC. Hemodynamic variables with mini FC and their changes from the baseline are presented in the Table 3 and Table 4. The tendency of CO and ΔCO% after mini-fluid challenge in R and NR are shown in Fig. 3,4. After a volume expansion of 200 mL colloid, ΔCO% was significantly greater with R compared to NR ($p < 0.05$). HR decreased after fluid infusion in both R and NR, whereas SAP, DAP, MAP, CVP and PAWP all showed an upward trend in both R and NR, except for baseline of DAP, there was no difference between the R and NR groups.

Table 3
Hemodynamic variables before and after fluid challenge in R and NR.

Group	Infusion (mL)	CO (L/min)	SV (mL)	HR (bpm)	SAP (mmHg)	DAP (mmHg)	MAP (mmHg)	CVP (mmHg)	PAWP (mmHg)	SVR (dynes·s·cm^{-5})
Responders (n=36)	Baseline	6.2±2.4 [b]	55±23	118±26	116±19	63±8 [b]	79±8[b]	10±3	14±5	1051±522 [b]
	100	6.5±2.6 [a]	58±24 [a]	116±26[a]	122±21[a]	64±9	82±10 [a]	11±3 [a]	15±5 [a]	1026±505 [b]
	200	6.9±2.7 [a]	63±26 [a]	114±26 [a]	122±28	65±8 [a]	84±9 [a]	12±4 [a]	16±5 [a]	983±471[b]
	300	7.2±2.7 [a]	66±26 [a]	112±29 [a]	128±22 [a]	67±10 [a]	86±11 [a]	13±4 [a]	16±5 [a]	954±454 [b]
	400	7.4±2.8 [a]	67±26 [a]	113±26 [a]	130±23 [a]	67±9 [a]	87±11 [a]	13±4 [a]	17±5 [a]	930±425 [b]
	500	7.7±2.6 [a]	69±25 [a]	114±25 [a]	132±25 [a]	68±10 [a]	88±12 [a]	14±4 [a]	17±5 [a]	889±389
Nonresponders (n=11)	Baseline	8.0±1.8 [b]	70±17	116±22	111±15	54±4 [b]	75±5[b]	12±5	14±4	733±426 [b]
	100	8.1±2.0	74±23	114±22	116±20	61±6	78±7 [a]	13±5	15 ± 5	666±188 [b]
	200	7.8±2.1	72±21	114±21 [a]	119±21	61±6 [a]	79±8 [a]	13±5 [a]	16 ± 5 [a]	703±212 [b]
	300	8.0±1.8	73±20	114±22 [a]	122±22 [a]	62±8 [a]	80±9 [a]	14±5 [a]	17±4[a]	704±208 [b]
	400	8.0±2.0	72±21	114±22 [a]	121±25	63±8 [a]	82±10 [a]	15±5 [a]	18±4 [a]	702±220 [b]
	500	7.9±1.9	71±21	113±22 [a]	125±25 [a]	63±8 [a]	82±10 [a]	15±5 [a]	18±4 [a]	720±223

Abbreviations: CO, cardiac output; SV, stroke volume; HR, heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; CVP, central venous pressure; PAWP, pulmonary artery wedge pressure; PAWP, pulmonary artery wedge pressure; SVR, systemic vascular resistance. [a] $P<0.05$ between baseline and volune expansion from 100 mL to 500 mL in subgroup; [b] $P<0.05$ between responders and nonresponders.

Table 4
Changes in hemodynamics between R and NR

Group	Infusion (mL)	CO (L/min)	SV (mL)	HR (bpm)	SAP (mmHg)	DAP (mmHg)	MAP (mmHg)	CVP (mmHg)	PAWP (mmHg)	SVR (dynes·s·cm^{-5})
Responders (n = 36)	Baseline	6.2 ± 2.4 [b]	55 ± 23	118 ± 26	116 ± 19	63 ± 8 [b]	79 ± 8[b]	10 ± 3	14 ± 5	1051 ± 522 [b]
	100	6.5 ± 2.6 [a]	58 ± 24 [a]	116 ± 26[a]	122 ± 21[a]	64 ± 9	82 ± 10 [a]	11 ± 3 [a]	15 ± 5 [a]	1026 ± 505 [b]
	200	6.9 ± 2.7 [a]	63 ± 26 [a]	114 ± 26 [a]	122 ± 28	65 ± 8 [a]	84 ± 9 [a]	12 ± 4 [a]	16 ± 5 [a]	983 ± 471[b]
	300	7.2 ± 2.7 [a]	66 ± 26 [a]	112 ± 29 [a]	128 ± 22 [a]	67 ± 10 [a]	86 ± 11 [a]	13 ± 4 [a]	16 ± 5 [a]	954 ± 454 [b]
	400	7.4 ± 2.8 [a]	67 ± 26 [a]	113 ± 26 [a]	130 ± 23 [a]	67 ± 9 [a]	87 ± 11 [a]	13 ± 4 [a]	17 ± 5 [a]	930 ± 425 [b]
	500	7.7 ± 2.6 [a]	69 ± 25 [a]	114 ± 25 [a]	132 ± 25 [a]	68 ± 10 [a]	88 ± 12 [a]	14 ± 4 [a]	17 ± 5 [a]	889 ± 389
Nonresponders (n = 11)	Baseline	8.0 ± 1.8 [b]	70 ± 17	116 ± 22	111 ± 15	54 ± 4 [b]	75 ± 5[b]	12 ± 5	14 ± 4	733 ± 426 [b]
	100	8.1 ± 2.0	74 ± 23	114 ± 22	116 ± 20	61 ± 6	78 ± 7 [a]	13 ± 5	15 ± 5	666 ± 188 [b]
	200	7.8 ± 2.1	72 ± 21	114 ± 21 [a]	119 ± 21	61 ± 6 [a]	79 ± 8 [a]	13 ± 5 [a]	16 ± 5 [a]	703 ± 212 [b]
	300	8.0 ± 1.8	73 ± 20	114 ± 22 [a]	122 ± 22 [a]	62 ± 8 [a]	80 ± 9 [a]	14 ± 5 [a]	17 ± 4[a]	704 ± 208 [b]
	400	8.0 ± 2.0	72 ± 21	114 ± 22 [a]	121 ± 25	63 ± 8 [a]	82 ± 10 [a]	15 ± 5 [a]	18 ± 4 [a]	702 ± 220 [b]
	500	7.9 ± 1.9	71 ± 21	113 ± 22 [a]	125 ± 25 [a]	63 ± 8 [a]	82 ± 10 [a]	15 ± 5 [a]	18 ± 4 [a]	720 ± 223
Group		**ΔCO (%)**	**ΔSV (mL)**	**ΔHR (bpm)**	**ΔSAP (mmHg)**	**ΔDAP (mmHg)**	**ΔMAP (mmHg)**	**ΔCVP (mmHg)**	**ΔPAWP (mmHg)**	
Responders (n = 36)	100-Baseline	5.2 ± 5.8	3.1 ± 3.5	-1 ± 4	6 ± 10	1 ± 5	3 ± 6	1 ± 1	1 ± 2	
	200-Baseline	11.5 ± 7.1 [a b]	7.9 ± 6.8 [a b]	-3 ± 5	6 ± 19	2 ± 5 [a]	4 ± 7 [a]	2 ± 2 [a]	2 ± 2 [a]	
	300-Baseline	15.8 ± 7.3 [a b]	10.8 ± 6.6 [a b]	-4 ± 5 [a]	12 ± 16 [a]	3 ± 8 [a]	6 ± 10 [a]	3 ± 2 [a]	3 ± 2 [a]	
	400-Baseline	20.7 ± 9.8 [a b]	11.9 ± 5.9 [a b]	-3 ± 6 [a]	14 ± 16 [a]	4 ± 7 [a]	7 ± 10 [a]	3 ± 2 [a]	3 ± 3 [a]	

[a] $P<0.05$ between baseline and volume expansion from 100 mL to 500 mL in subgroup; [b] $P<0.05$ between responders and nonresponders.

Group	Infusion (mL)	CO (L/min)	SV (mL)	HR (bpm)	SAP (mmHg)	DAP (mmHg)	MAP (mmHg)	CVP (mmHg)	PAWP (mmHg)	SVR (dynes·s·cm^{-5})
	500-Baseline	23.2 ± 13.8[a b]	14.3 ± 6.7 [a b]	-3 ± 6 [a]	15 ± 17 [a]	4 ± 7 [a]	8 ± 10 [a]	3 ± 2 [a]	3 ± 3 [a]	
Nonresponders (n = 11)	100-Baseline	1.3 ± 7.6	3.5 ± 7.6	-2 ± 6	5 ± 10	3 ± 4	3 ± 4	1 ± 2	1 ± 1	
	200-Baseline	-3.2 ± 8.7 [b]	1.5 ± 7.4 [b]	-3 ± 7	8 ± 12	3 ± 4	4 ± 6	1 ± 1	2 ± 2 [a]	
	300-Baseline	0.4 ± 6.2 [b]	2.4 ± 3.8 [b]	-3 ± 6	11 ± 14 [a]	4 ± 5	6 ± 6	2 ± 2	3 ± 2 [a]	
	400-Baseline	0.2 ± 6.8 [b]	2.3 ± 6.3 [b]	-3 ± 7	10 ± 17	5 ± 5 [a]	7 ± 7 [a]	3 ± 3 [a]	3 ± 1 [a]	
	500-Baseline	-1.9 ± 8.6 [b]	1.3 ± 5.9 [b]	-3 ± 8	15 ± 18 [a]	5 ± 5	8 ± 8 [a]	3 ± 3 [a]	3 ± 2 [a]	

[a] *P*<0.05 between baseline and volume expansion from 100 mL to 500 mL in subgroup; [b] *P*<0.05 between responders and nonresponders.

Physiological variables change with mini-fluid challenge

Baseline and changes on physiological variables are explained in detail in the Table 5 and Table 6. In R and NR, the baseline $ScvO_2$ was 71.2 ± 10.7% and 72.5 ± 11.5%, and the baseline SvO_2 was 68.2 ± 9.0% and 70.7 ± 10%. After mini-fluid challenge, $ScvO_2$ and SvO_2 gradually increased. There were no significant differences between the R and NR. Pcv-aCO_2 at baseline in R and NR were 4 mmHg (3–6) versus 5 mmHg (4–6), and there were no significant differences between R and NR. Pcv-aCO_2 did not change significantly with any amount of mini-fluid challenge. ΔDO_2I increased from 13 ± 32 (mL/min/m^2) to 46 ± 41(mL/min/m^2) in R, while decreasing from − 13 ± 45 (mL/min/m^2) to -56 ± 53 (mL/min/m^2) in NR. There were significant differences between the R and NR ($p < 0.05$).

Table 5
Hemoglobin and physiological variables before and after fluid challenge in R and NR

Group	Infusion (mL)	HBG (g/dL)	Hct (%)	$ScvO_2$ (%)	SvO_2 (%)	DO_2I (mL/min/m^2)	VO_2I (mL/min/m^2)	Pcv-aCO_2 (mmHg)	Pv-aCO_2 (mmHg)
Responders	Baseline	9.5 ± 2.6	26 ± 9	71.2 ± 10.7	68.2 ± 9.0	412 ± 144	103 ± 39	4 (3–6)	5 (3–6)
(n = 36)	100	9.3 ± 2.5 [a]	25 ± 8 [a]	72.1 ± 9.4	68.5 ± 8.2	425 ± 154 [a b]	102 ± 39	5 (3–6)	5 (3–6)
	200	9 ± 2.4 [a]	24 ± 8 [a]	72.0 ± 9.6	69.5 ± 7.9	439 ± 156 [a b]	106 ± 39	4 (2–7)	4 (3–6)
	300	8.8 ± 2.3 [a]	23 ± 8 [a]	73.6 ± 9.0 [a]	71.1 ± 7.9 [a]	445 ± 149 [a b]	102 ± 36	5 (2–6)	4 (3–6)
	400	8.7 ± 2.4 [a]	23 ± 8 [a]	74.3 ± 9.3 [a]	72 ± 7.6 [a]	448 ± 157 [a b]	99 ± 38	4 (2–7)	4 (3–5)
	500	8.5 ± 2.2 [a]	23 ± 7 [a]	72.7 ± 10.7	70.8 ± 8.7 [a]	458 ± 147 [a b]	107 ± 39	5 (2–5)	4 (2–5)
Nonresponders	Baseline	9.5 ± 2.6	27 ± 7	72.5 ± 11.5	70.7 ± 10	535 ± 203	120 ± 30	5 (4–6)	5 (4–7)
(n = 11)	100	9.1 ± 2.5[a]	25 ± 7 [a]	72.8 ± 10.5	71.9 ± 9.6	522 ± 199 [a b]	119 ± 34 [a]	5 (3–6)	4 (3–6)
	200	8.9 ± 2.5[a]	25 ± 7 [a]	75.1 ± 11.0	73.4 ± 10.1	488 ± 178 [a b]	101 ± 38 [a]	5 (3–6)	4 (4–5)
	300	8.6 ± 2.4[a]	23 ± 6 [a]	75.4 ± 10.5[a]	74.2 ± 10.1	487 ± 170 [a b]	102 ± 36 [a]	5 (4–5)	5 (4–6)
	400	8.6 ± 2.5[a]	24 ± 7 [a]	75.1 ± 11.5	73.3 ± 11.1	486 ± 183 [a b]	100 ± 37 [a]	5 (3–6)	4 (3–5)
	500	8.7 ± 2.3[a]	23 ± 6 [a]	74.8 ± 11.3	71.8 ± 10.4	478 ± 179 [a b]	99 ± 37 [a]	5 (4–5)	5 (4–6)

Abbreviations: HBG, hemoglobin; Hct, hemotocrit; $ScvO_2$, central venous oxygen saturation; SvO_2, mixed venous oxygen saturation; DO_2I, Oxygen delivery index; VO_2I, oxygen consumption index; Pcv-aCO_2, central venous-to-arterial carbon dioxide partial pressure; Pv-aCO_2, mixed venous-to-arterial carbon dioxide partial pressure.

[a] $P<0.05$ between baseline and volune expansion from 100 mL to 500 mL in subgroup; [b] $P<0.05$ between responders and nonresponders.

Table 6
Changes in hemoglobin and physiological variables between R and NR

Group		ΔHBG (g/dL)	ΔHct (%)	$\Delta ScvO_2$ (%)	ΔSvO_2 (%)	ΔDO_2I (mL/min/m^2)	ΔVO_2I (mL/min/m^2)	$\Delta Pcv\text{-}aCO_2$ (mmHg)	$\Delta Pv\text{-}aCO_2$ (mmHg)
Responders (n = 36)	100-Baseline	-0.2 ± 0.5	-1 ± 1	0.9 ± 4.8	0.2 ± 4.5	13 ± 32 [b]	-2 ± 22	0 (-2-1)	0 (-2-1)
	200-Baseline	-0.5 ± 0.5 [a]	-2 ± 2 [a]	0.8 ± 6.0	1.3 ± 4.8 [a]	27 ± 38 [a b]	3 ± 23 [b]	-1 (-2-2)	0 (-3-1)
	300-Baseline	-0.7 ± 0.5 [a]	-3 ± 2 [a]	2.4 ± 6.9[a]	2.9 ± 5.5 [a]	33 ± 30 [a b]	-1 ± 28	0 (-1-2)	-1 (-2-1)
	400-Baseline	-0.9 ± 0.6 [a]	-3 ± 2 [a]	3.0 ± 8.8[a]	3.8 ± 5.3 [a]	36 ± 38 [a b]	-4 ± 33	0 (-2-2)	0 (-2-1)
	500-Baseline	-1. 0 ± 0.6 [a]	-3 ± 2 [a]	1.5 ± 6.5	2.6 ± 6.2 [a]	46 ± 41 [a b]	5 ± 27 [b]	0 (-2-1)	-1 (-3-1)
Nonresponders (n = 11)	100-Baseline	-0.4 ± 0.5	-1 ± 2	0.3 ± 2.6	1.2 ± 4.2	-13 ± 45 [b]	-6 ± 14	0 (-1-0)	-1 (-3-1)
	200-Baseline	-0.6 ± 0.6	-2 ± 2	2.6 ± 5.7	2.7 ± 4.4	-47 ± 52 [a b]	-19 ± 21 [a b]	0 (-3-1)	-1 (-2-0)
	300-Baseline	-0.9 ± 0.6 [a]	-3 ± 2 [a]	2.9 ± 4.1[a]	3.5 ± 5.9	-49 ± 36 [a b]	-18 ± 16 [a]	0 (-2-1)	0 (-2-1)
	400-Baseline	-0.8 ± 0.5 [a]	-3 ± 2 [a]	2.6 ± 5.8	2.6 ± 7.4	-48 ± 36 [a b]	-19 ± 23 [a]	1 (-2-1)	-1 (-3-1)
	500-Baseline	-0.8 ± 0.7 [a]	-3 ± 3 [a]	2.3 ± 5.1	1.1 ± 4.5	-56 ± 53 [a b]	-21 ± 28 [a b]	-1 (-2-1)	0 (-3-1)

[a] *P*<0.05 between baseline and volume expansion from 100 mL to 500 mL in subgroup; [b] *P*<0.05 between responders and nonresponders.

Predictive value of mini-fluid challenge

The correlation between ΔCO_{100mL} and ΔCO_{500mL} was negative (r = 0.26, $p = 0.08$), whereas ΔCO_{200mL} and ΔCO_{500mL}, ΔCO_{300mL} and ΔCO_{500mL}, ΔCO_{400mL} and ΔCO_{500mL} were all positive (r = 0.57, r = 0.73, r = 92; $p < 0.05$) respectively. ROC of ΔCO% after every 100 mL fluid bolus were analyzed for predicting FR (Fig. 5). The AUROC were calculated and compared separately (Table 7). In this study, a mini fluid of 100 mL had a poor predictive ability (AUC = 0.67, $p > 0.05$). ΔCO_{200mL} demonstrated a predictive value for FR with an AUC of 0.93 (95% CI: 0.84–1.00, $p < 0.05$). The best cutoff value of $\Delta CO_{200mL}$was 1.9%, which was lower than the reproducibility of any kinds of CO measurements (sensitivity of 97.2% and specificity of 81.8%). Taking reproducibility and reliability into account, the best cutoff value was 5.2%, with a sensitivity of 83.3%, and a specificity of 90.9%. The AUC of ΔCO_{300mL} and ΔCO_{400mL} were 0.95 and 0.97 ($p < 0.05$) There was no difference between the predictive abilities between the ΔCO_{200mL}, ΔCO_{300mL} and ΔCO_{400mL} compared with the ΔCO_{500mL}.

Table 7
The predictive characteristics of the increase in CO in mini-fluid challenge for a response of CO > 10% over 500 mL of fluid infusion

Fluid bloused	AUC	*P*	95% CI	Cut off value,%	Sensitivity (%)	Specificity (%)	Y	Difference between areas	*P*	r_s	$P(r_s)$
100	0.67	0.11	0.52–0.80	NA	NA	NA	NA	0.33	< 0.05	0.26	0.08
200	0.93	< 0.05	0.82–0.99	1.9	97.2	81.8	0.79	0.06	0.16	0.57	< 0.05
300	0.96	< 0.05	0.85–0.99	4.8	100	90.9	0.91	0.04	0.32	0.73	< 0.05
400	0.97	< 0.05	0.87-1.000	6.2	97.2	90.9	0.88	0.03	0.20	0.92	< 0.05

Abbreviations: AUC, area under the curve; CI, confidence interval; Y Youden index; r_s, Spearman's correlation.

MAP < 61 mmHg at baseline was able to predict a fluid response (AUC = 0.71, 95%CI $p < 0.05$) with a sensitivity and specificity of 100% and 100% (Fig. 6).

ΔDO_2I has predictive ability after bolus of 200 mL, the AUROC of $\Delta DO_2I_{200mL-base}$ to $\Delta DO_2I_{500mL-base}$ were individual around 0.93 to 0.94 ($p < 0.05$), and the cut-off was around 2.5–3.5% (Fig. 7,8, Table 8)

Table 8
The predictive characteristics of the increase in ΔDO_2I in mini-fluid challenge for a response of CO > 10% over 500 mL of fluid infusion

	Mean ± SD		P	AUC	P	95%CI	Cut-off (g/L)	Sensitivity(%)	Specificity(%)
	R (n = 35)	NR (n = 11)							
$\Delta DO_2I_{100mL-base}$ (mL/min/m^2)	13 ± 32	-13 ± 45	< 0.05	0.68	0.07	0.49–0.87	NA	NA	NA
$\Delta DO_2I_{200mL-base}$ (mL/min/m^2)	27 ± 38 [a]	-47 ± 52 [a]	< 0.05	0.94	< 0.05	0.88-1.0	2.5	71.4	100
$\Delta DO_2I_{300mL-base}$ (mL/min/m^2)	33 ± 30 [a]	-49 ± 36 [a]	< 0.05	0.93	< 0.05	0.80-1.0	3.5	82.9	90.0
$\Delta DO_2I_{400mL-base}$ (mL/min/m^2)	36 ± 38 [a]	-48 ± 36 [a]	< 0.05	0.97	< 0.05	0.94-1.0	3.5	85.7	100
$\Delta DO_2I_{500mL-base}$ (mL/min/m^2)	46 ± 41 [a]	-56 ± 53 [a]	< 0.05	0.94	< 0.05	0.83-1.0	2.5	82.9	90.9

Abbreviation: DO_2I, Oxygen delivery index

[a] $P<0.05$ between baseline and volume expansion from 100 mL to 500 mL in subgroup; [b] $P<0.05$ between responders and nonresponders.

$ScvO_2$, SvO_2, $Pcv\text{-}aCO_2$, $\Delta ScvO_2$, ΔSvO_2, $\Delta Pcv\text{-}aCO_2$ were not able to predict a positive fluid response with any amount of mini-fluid challenge in this study (Table 9).

Table 9
Relationship between baseline and change after 500 mL FC $ScvO_2$, SvO_2, Pcv-aCO2and Pv-aCO_2 levels and changes in cardiac output (ΔCO%) in all patients and the AUC of each indicators

	r_s	$P(r_s)$	AUC	*P*	95%CI
ScvO2	-0.18	0.22	0.46	0.65	0.26–0.65
SvO2	-0.33	< 0.05	0.45	0.63	0.26–0.65
Pcv-aCO2	0.07	0.67	0.43	0.48	0.25–0.61
Pv-aCO2	0.22	0.14	0.43	0.48	0.25–0.61
$\Delta ScvO_{2\ (500-base)}$	-0.04	0.69	0.48	0.85	0.29–0.68
$\Delta SvO_{2\ (500-base)}$	0.27	0.08	0.56	0.59	0.37–0.74
$\Delta Pcv\text{-}aCO_{2\ (500-base)}$	-0.06	0.80	0.51	0.94	0.32–0.69
$\Delta Pv\text{-}aCO_{2\ (500-base)}$	0.26	0.07	0.57	0.49	0.37–0.77

Abbreviations: AUC, area under the curve; CI, confidence interval; r_s, Spearman's correlation.

Discussion

Optimizing CO by increasing preload is based on the assumption that increased blood volume may subsequently promote stroke volume (SV) as described by the Frank-Starling law. Predicting fluid responsiveness is to test whether the patient was in the ascending part of the Frank-Starling curve (preload dependence state) and may benefit from fluid treatment[24, 27–30]. Although numerous measurements can predict FR, the fluid challenge is a gold standard for assessing FR and is widely used. The new concept of mini-fluid challenge is to use a minimun amount of fluid to avoid overload risk, whereas a median volume of 500 mL has been used before.[14, 31, 32]. A metanalysis demonstrated that a mini volume of 100 mL could predict preload responsiveness, the pooled AUC was 0.91 (95%CI 0.85–0.97), with a pooled sensitivity of 0.82 (95%CI 0.76–0.88) and specificity of 0.83 (95%CI 0.77–0.89)[33]. No similar findings were found in our study: the predictive power of 100 mL is disappointing with an AUROC of 0.69.

The main reason for these differences may be the difference in the study population. Our study focused on septic shock patients, whose cardio-vascular system has undergone major perturbations and profound alterations to the endothelium. Capillary leakage caused by epithelial barrier dysfunction occurs, as a consequence, the intravascular volume is insufficient and unstressed volume substantially reduced[34]. The adjustment and shift between unstressed volume and stressed volume introduce a role for volume expansion that is not simply to increase CO but rather to ensure reserves[35]. In these patients, a larger dose may be required for an effective test, whereas 100 mL of fluid seemed too little to predict the FR. Among the previous 7 studies, only 1 mini-fluid study focused on septic shock. Wang's study showed a similar result to ours that the predictive power with 100 mL was less satisfying. In other mini-fluid challenge investigation, the study population was perioperative patients in a stable hemodynamic state. In this study, we chose colloid of gelatin to perform the fluid challenge, which can stay in vascular longer and may increase CO more than crystalloid. The marked change, however, showed in 200 mL.

In spite of the effect of heterogeneity of study population, Aya et al[22]. and Smoerenberg et al[16]. were unable to reproduce similar results as well, who showed the predicted minimal volume is 4 mL/kg to defined FC (CO measured by LiDCO*plus* monitor), or minimal volume of 150 mL CO measured by Modelflow^R COm and 200 mL by PulseCO^{R}COIi. These two studies implied a negative predictive value of a minimum dose of 100 mL to reliably assess FR even in a fairly homogeneous sample of postoperative cardiac surgery patients. It suggests that the specificity and sensitivity values of mini fluid challenge may change depending on the device used to measure the CO. To the best of our knowledge, CO measurements including thermodilution (PAC), pulse index continuous CO, Doppler echocardiography (TTE or TEE) and Fick techniques, have been most commonly used to assess FR in recent decades. In the mini fluid challenge, pulse contour CO was used in 4 out of the 7 cases, and TTE was used in 2 out of the 7 cases, while PAC, as a standard clinical reference method for CO monitoring was not used in the above studies.

However, the CO measurements by Doppler echocardiography (we have discussed only the VTi method, which is the most popular and presented in recent studies) have been validated for a long time for its noninvasive, but its accuracy is limited by the devices and technicians. In method of echocardiography, SV is affected by VTi and the aortic valve area. When estimating the changes in SV, the value of VTi is the main component of the SV calculation whereas the aortic valve area is supposed to be constant. It is well known that either the quality and

sharpness of image or the process of technician may have an influence on the value of VTi. Moreover, Gorassi et al.[36] demonstrated that pulsed Doppler has limitations in detecting high cardiac output values when the blood flow velocity is greater than 2 m/sm, especially in septic shock patients who showed the greatest variability in CO. What is more, the CO measured by PAC integrated over several heartbeats, while the VTi was measured on a beat-to-beat basis, and then calculates CO by the products of SV and HR, which may increase the potential error of CO estimation. VTi seemed to be more likely influenced by heart-lung interaction than PAC, and previous studies have shown that CO is more reliable on an average of serial measurements[37]. Based on the published studies evidences, the accuracy of PAC is higher than that of the transthoracic echocardiography[23, 36, 38].

At the same time, the precision of new generation CO measurement, especially methods coupled with thermodilution and pulse contour analysis, such as Pulse index Continuous Cardiac Output combination (PiCCO), is also unclear, because more variables will affect the estimation of CO. Pulse contour analysis measures CO indirectly by integrating a variety of characteristics of the pressure waveform to calculate stroke volume. In the equation of CO = SV × HR, SV is calculated from area under systolic portion of arterial waveform trace and aortic impedance, in which the arterial pressure waveform is complex and aortic impedance varies between individuals and within individuals, especially in septic shock patients whose hemodynamic state is characterized by distributive shock and the vascular impedance is unpredictable. Although the pulse contour analysis has been calibrated by trans-cardiopulmonary thermodilution to overcome some limitations, the analysis remains potential inaccuracy due to multitude of variables in the equation of CO calculation. A great deal of studies and meta-analysis have been done to compare the precision of new generation measurements of CO with PAC, but why not perform a mini-fluid challenge in classic thermodilution by PAC.

In addition to taking the mini-volume into fluid challenge, the threshold of predictive value is also a controversial topic. In most clinical practice, and even in most studies, the definition of FR is based on the assumption that thermodilution is the only method validated to detect a 10–15% increase in CO[23]. This consensus was originally derived from the understanding of the sources of errors of PAC, that is, three measurements are sufficient if the CO differs by 10% or less. On the contrary, if the CO difference exceeds 10%, the measurements are considered unreliable[39]. It is worth noting that these technique errors were mostly introduced by the measurement of injecting iced water while CO was measured[38–41]. Our application for CO measurement by PAC (Swan-Ganz CCOmbo CCO/SvO_2, Vigilance II™ monitor, Edwards Lifesciences, Irvine, CA, USA) in this study is automatic heating, and iced water injection is no longer needed. The sources of error including temperature of iced water, volume of injection and even injection speed will not affect the CO measurement accuracy during this protocol. In order to avoid measurement errors and enhance the reproducibly of the results, we took an average CO value of 3 measurements at each point in time as a CO determination. In this study, the best cutoff value of 1.9% was an inferior threshold to the interobserver variability of PAC. Thus, considering both clinical feasibility and reproducibility, the cutoff value was 5.2%, with a specificity of 83.3% and 90.9%, respectively. An increase in CO greater than 5.2% after 200 mL may be more clinically relevant. The correlation between ΔCO_{200mL} and ΔCO_{500mL} suggests that the greater the increase in ΔCO_{200mL}, the more we can expect a similar increase in ΔCO_{500mL}. If we accepted CO > 10% in mini-FC, both the sensitivity and specificity were too low (60.7% and 73.7%) to predict FR, and up to 32% of R may possibly be misclassified as NR (Fig. 9).

In the design of this study, we attempted to find a surrogate of CO, which can evaluate FR simply and practically when there is no CO monitoring available or inconvenient. SvO_2 and $ScvO_2$ are a pair of parameters wildly used in clinical practice to assess whether CO and oxygen delivery (DO_2) are sufficient to meet the patient's need and to guide fluid resuscitation[42]. The well-known study by Rivers et al.[43] indicated that targeting a $ScvO_2$ > 70% in the early stage of resuscitation may improve outcomes. In our study, both in R and NR, the mean value of $ScvO_2$ were higher than 70% while that of SvO_2 were higher than 65%. Neither the actual value of $ScvO_2$ and SvO_2 nor the $\Delta ScvO_2$ and ΔSvO_2 were meaningless to predict FR. In fact, $ScvO_2$ and SvO_2 can be influenced by oxygen extraction. We confirmed the result of Velissaris et al[42] that a high level of $ScvO_2$ and SvO_2 levels did not exclude FR. In this study, there were 17 cases out of 37 (45.9%) with $ScvO_2$ were greater than 70%, and 20 cases out of 37 (54.1%) with $ScvO_2$ greater than 65% in FR. Based on the same theory, Pcv-aCO_2 are considered as alternative markers of tissue hypoperfusion and are used to guide treatment for shock. However, there was no difference between R and NR before and after FC. For the indicators we simply used in clinical practice, MAP < 61 mmHg before FC is a strong indicator for FR, with a sensitivity and specificity of 100% and 100%. Although ΔDO_2I exhibited predictive power in this study, it correlated to the changes of CO and could not be used as a surrogate of CO.

Several limitations of this study need to be discussed. First, as we discussed before, the accuracy varies with different hemodynamic techniques. With the development of techniques in assessing the circulatory function, the new generation measurements noted by less or non-invasive, such as TEE, bio-impedance and TTE are more likely to be applied in recent decade[36, 44]. Our findings depend on PAC to monitor CO, and the results may not be extrapolated to other techniques used to monitor CO. Second, 77% of the patients responded to fluid administration after a total volume of 500 mL gelatin, and the proportion of responders (PR) was higher than in other studies. Our FC was completed within 40 minutes from the first bolus. Theoretically, PR decreases with a long infusion time, as described by Toscani et al.[45],

but our results are just the opposite. We compared the similar results of high PR, which appeared in Smorenberg's study, with a PR of 71% at the end of FR. These trials shared two same points, one was that patients subsequently received a 500 mL volume expansion by several intravenous boluses, and the other was that both used the colloid in FC. So, a reasonable question is whether the high PR may be due to the accumulative of fluid or the colloid, which supposed to remain in the intravascular compartment longer. To answer this question, we need to further study the pharmacodynamic outcomes and its effect on different approaches of FC. Third, we did not find a meaningful surrogate of CO that can predict FR and guide fluid therapy. In future study, a feasible and simple clinical indicator for predicting FR needs to be found. Above all, future research may be conducted to investigate the diagnostic value of the mini-FC using crystalloids, and the accuracy grey zone to detect CO changing by using different CO monitor. Furthermore, pharmacodynamic and pathophysiology mechanisms FC need to be studied.

Conclusions

A mini-fluid challenge of 200 mL colloid can predict fluid responsiveness in septic shock patients. ΔCO% greater than 5.2% after a mini-volume of 200 mL 4% gelatin is a good predictor. Further studies are needed to confirm this result and detect the predictive value of mini fluid by using crystalloids.

List Of Abbreviations

AUC	Area under curve
CO	Cardiac output
CVP	Central venous pressure
DO_2	Oxygen delivery
DBP	Diastolic blood pressure
DO_2I	Oxygen delivery index
FC	Fluid challenge
FR	Fluid responsiveness
HR	Heart rate
Hb	Hemoglobin
ICU	Intensive care unit
Lac	Lactate
MAP	Mean arterial pressure
Min	Minute
N	Nonresponder
R	Responder
ROC	Receiver operator characteristic
PAC	Pulmonary artery catheter
Pmsf	Mean systemic filling pressure
PC/VC	Pressure control/Volume control
Pcv-aCO_2	Central venous-to-arterial carbon dioxide partial pressure
SV	Stroke volume
SVR	Systemic vascular resistance
ScvO_2	Central venous oxygen saturation
SvO_2	Mixed venous oxygen saturation
SBP	Systolic blood pressure

Declarations

Ethics approval

Ethical approval for the study was provided by the Ethical Committee of Peking Union Medical College Hospital (ZS-1085). Written informed consent was obtained from all patients or their legal representative.

Consent for publication

Not applicable.

Availability of data and materials

All data generated and/or analyzed during this study are included in this published article (and its supplementary information files).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TY is the chief investigator of this study in designing and conducting the study, also participated in data acquisition and analysis, drafted the manuscript. BD is made a significant contribution to the design and supervised the analyses. LW, WJ, CYW, JMP and XYH are co-applicants and site principal investigators and made a significant contribution to conduct of the study. TY and SL are responsible for day to day study management. All authors commented critically on the manuscript and reviewed and approved the final manuscript.

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Figures

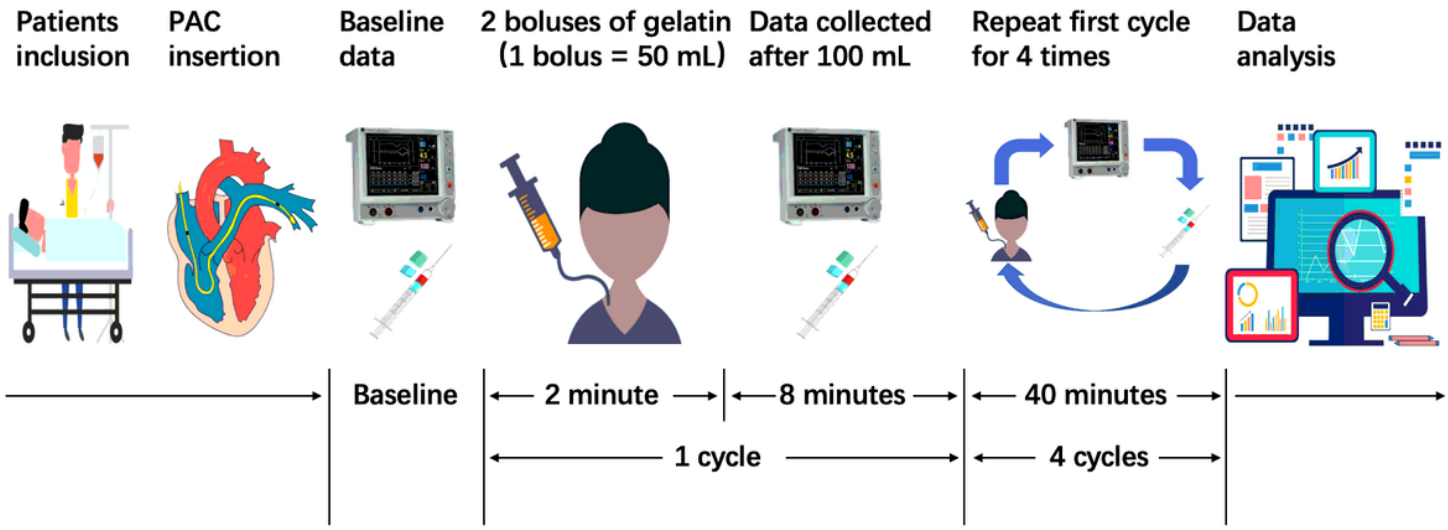

Fig.1 Study design.

Figure 1

Study Design

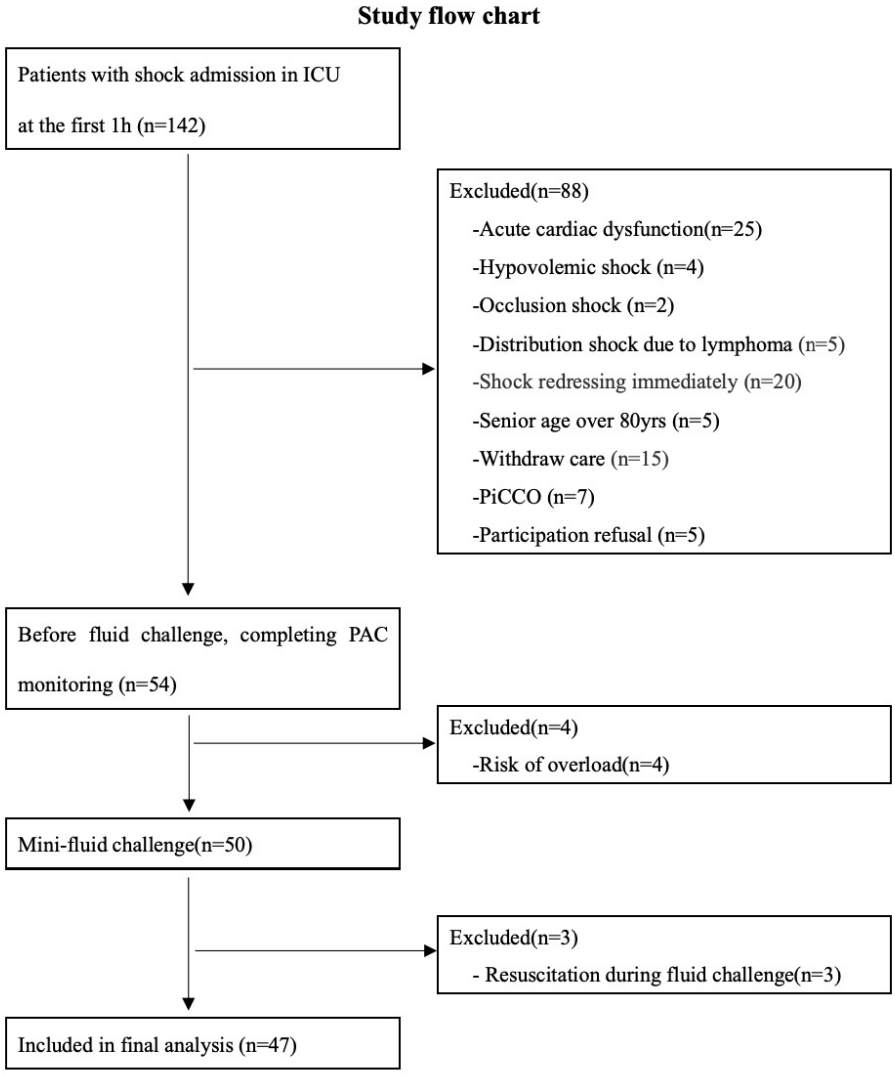

Fig. 2 Study flow chart

Figure 2

Study Flow

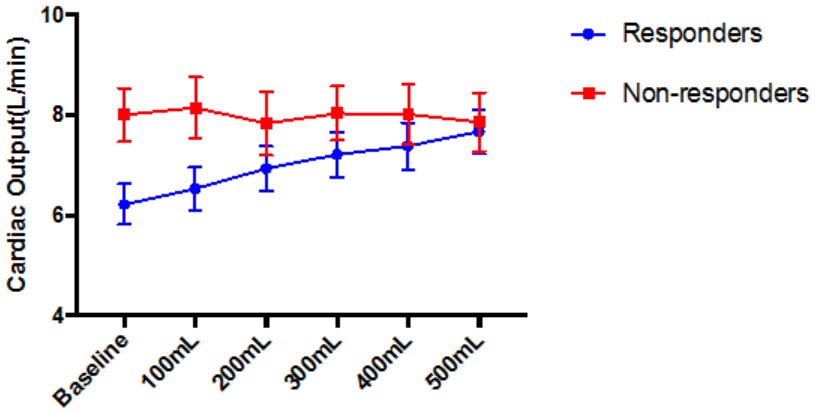

Figure 3

The tendency of CO after mini-fluid challenge in positive and negative responders.

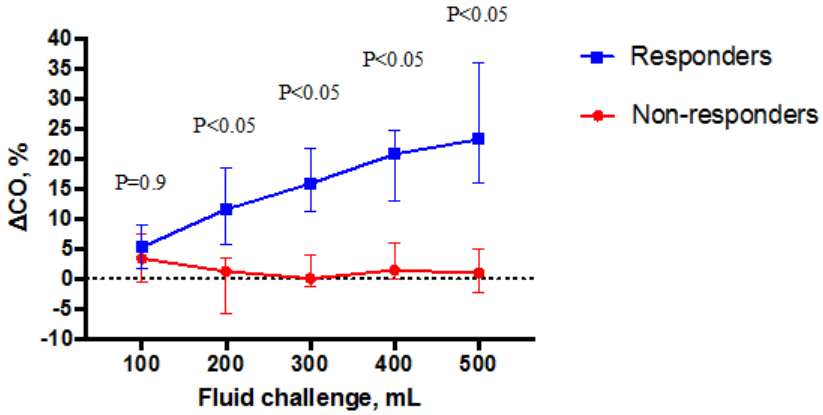

Figure 4

The median increase in cardiac output according to a fluid response defined by an increase in CO ≥ 10% after 500 mL fluid infusion with P values (Mann-Whitney U test).

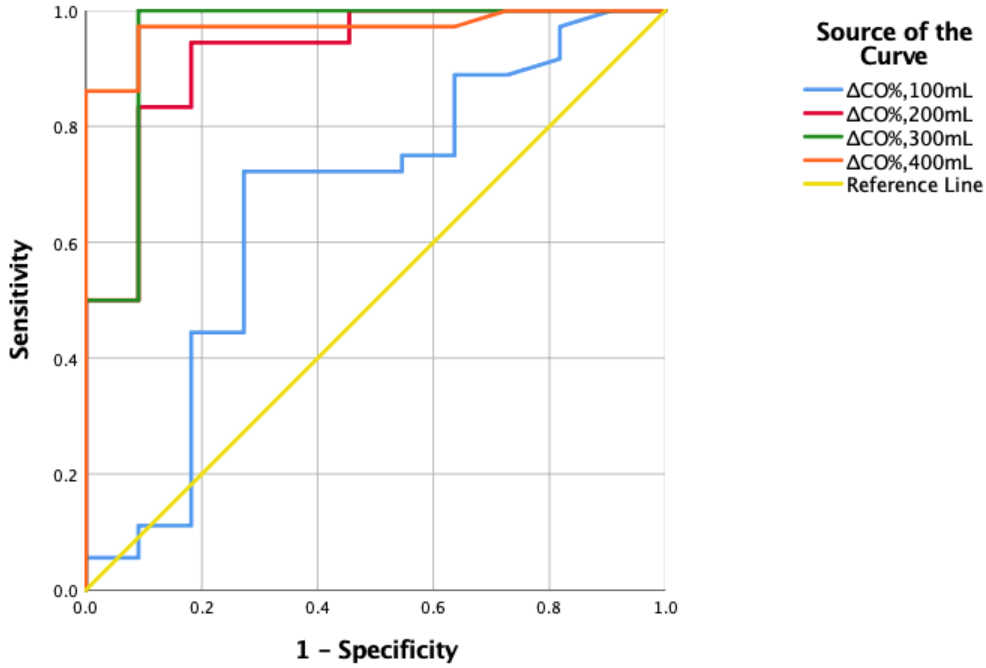

Figure 5

Receiver operating characteristics curves generated for mini-fluid challenge. ΔCO%,100 mL (changes in cardiac output induced by a rapid 100 mL volume expansion). ΔCO%, 200 mL (changes in cardiac output induced by an accumulative of 200 mL volume expansion). ΔCO%, 300 mL and ΔCO%, 400 mL in the same definition showing its abilities to predict positive fluid responsiveness. Positive fluid challenge was defined as an increase in cardiac output greater than 10% from baseline after an infusion of 500 mL.

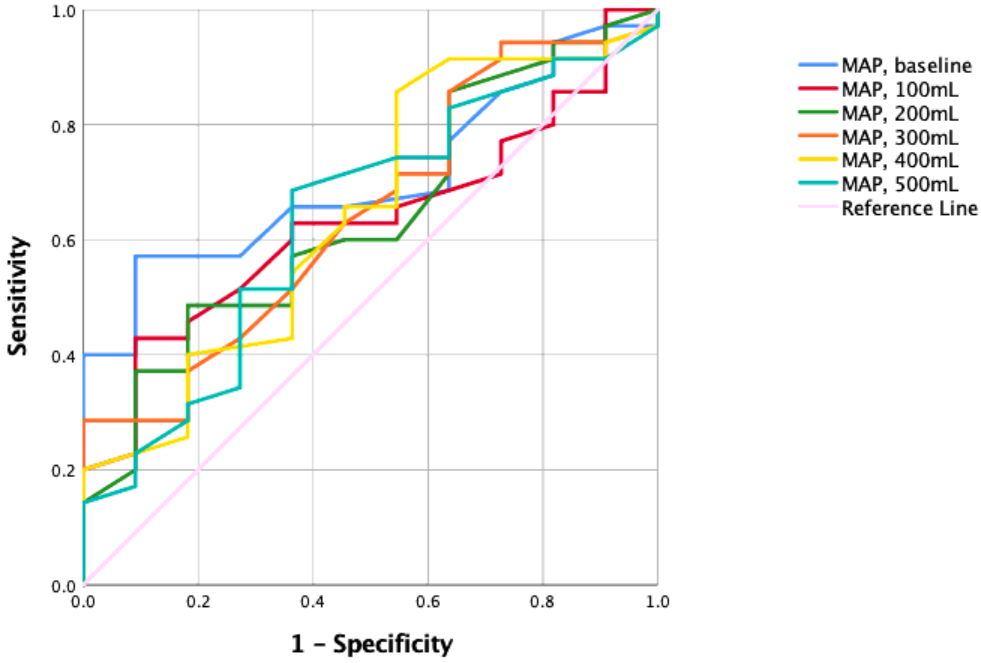

Figure 6

Receiver operating characteristic curve of MAPbaseline, MAP100, MAP200, MAP300, MAP400 MAP500 to predict fluid responsiveness. MAP at baseline has predictive power with AUC 0.71($p < 0.05$, 95%CI: 0.56-0.86), the best cut-off is 61mmHg with a sensitivity and specificity of 100% and 100%.

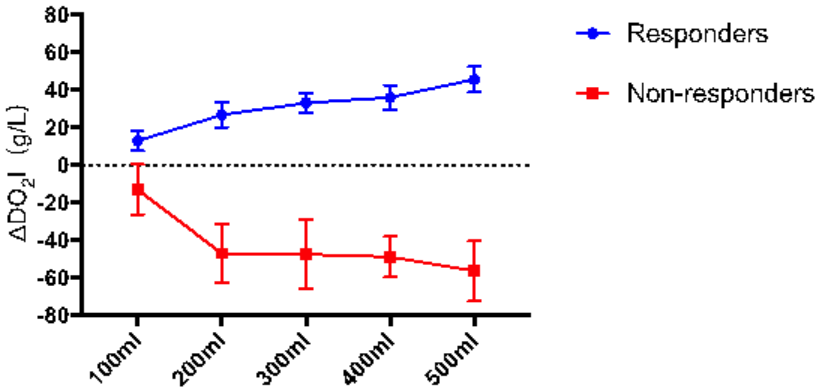

Figure 7

The tendency of ΔDO2I after mini-fluid challenge in R and NR.

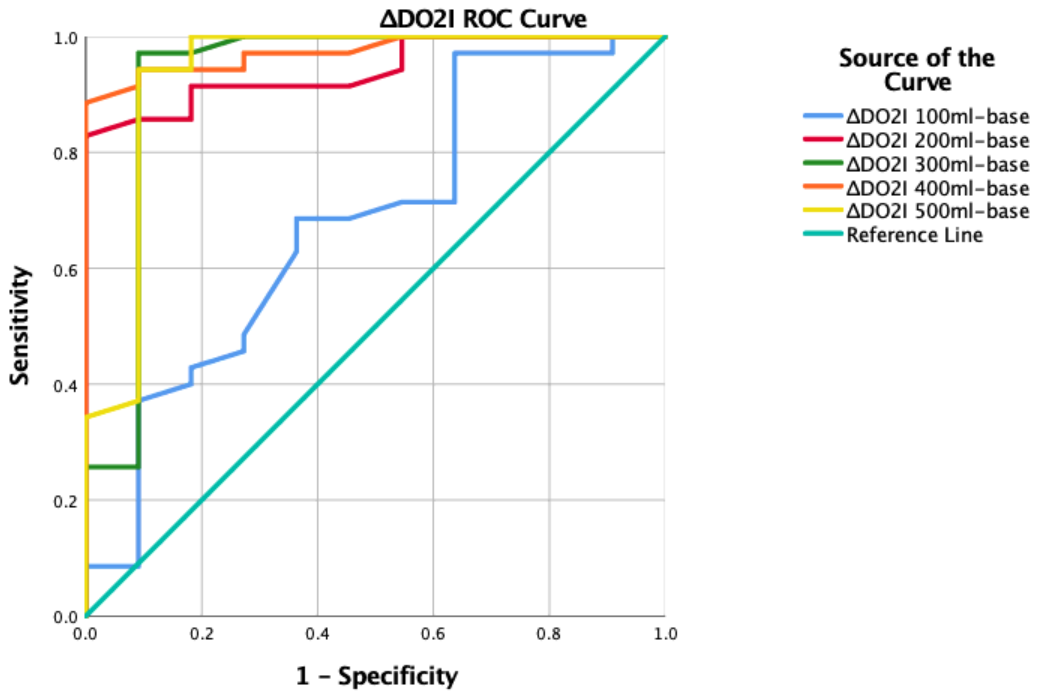

Figure 8

Receiver operating characteristic curve of ΔDO2I100, ΔDO2I200, ΔDO2I300, ΔDO2I400 ΔDO2I500 to predict fluid responsiveness

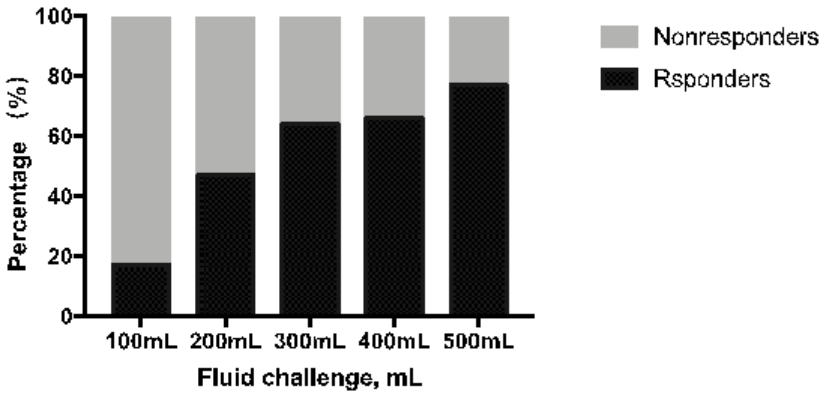

Figure 9

FR were defined as CO > 10% at each volume of FC, proportion of responders increased with the amount used for a fluid challenge. Proportions were compared across different volume of colloid with a chi-square statistic. The P values was significantly different ($p < 0.05$).