SHOCK, Vol. 46, No. 2, pp. 132–138, 2016

OPEN

CARDIAC OUTPUT MONITORING MANAGING INTRAVENOUS THERAPY (COMMIT) TO TREAT EMERGENCY DEPARTMENT PATIENTS WITH SEPSIS

Peter C. Hou,[*] Michael R. Filbin,[†] Anthony Napoli,[‡] Joseph Feldman,[§] Peter S. Pang,[||] Jeffrey Sankoff,[¶] Bruce M. Lo,[#] Howard Dickey-White,[**] Robert H. Birkhahn,[††] and Nathan I. Shapiro[‡‡§§]

[*]Department of Emergency Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [†]Department of Emergency Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; [‡]Department of Emergency Medicine, Brown University School of Medicine, Providence, Rhode Island; [§]Department of Emergency Medicine, Hackensack University Medical Center, Hackensack, New Jersey; [||]Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, Indiana; [¶]Department of Emergency Medicine, Denver General Hospital, Denver, Colorado; [#]Department of Emergency Medicine, Eastern Virginia Medical School/Sentara Norfolk General, Norfolk, Virginia; [**]Department of Emergency Medicine, HMHP/Mercy Health, Northeast Ohio Medical University (NEOMED), Rootstown, Ohio; [††]Department of Emergency Medicine, New York Methodist Hospital, Brooklyn, New York; [‡‡]Department of Emergency Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts; and [§§]The Center for Vascular Biology Research, Division of Molecular and Vascular Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Received 30 Oct 2015; first review completed 16 Nov 2015; accepted in final form 7 Jan 2016

ABSTRACT—**Objective:** Fluid responsiveness is proposed as a physiology-based method to titrate fluid therapy based on preload dependence. The objectives of this study were to determine if a fluid responsiveness protocol would decrease progression of organ dysfunction, and a fluid responsiveness protocol would facilitate a more aggressive resuscitation. **Methods:** Prospective, 10-center, randomized interventional trial. Inclusion criteria: suspected sepsis and lactate 2.0 to 4.0 mmol/L. Exclusion criteria (abbreviated): systolic blood pressure more than 90 mmHg, and contraindication to aggressive fluid resuscitation. Intervention: fluid responsiveness protocol using Non-Invasive Cardiac Output Monitor (NICOM) to assess for fluid responsiveness (>10% increase in stroke volume in response to 5 mL/kg fluid bolus) with balance of a liter given in responsive patients. Control: standard clinical care. Outcomes: primary—change in Sepsis-related Organ Failure Assessment (SOFA) score at least 1 over 72 h; secondary—fluids administered. Trial was initially powered at 600 patients, but stopped early due to a change in sponsor's funding priorities. **Results:** Sixty-four patients were enrolled with 32 in the treatment arm. There were no significant differences between arms in age, comorbidities, baseline vital signs, or SOFA scores ($P > 0.05$ for all). Comparing treatment versus Standard of Care—there was no difference in proportion of increase in SOFA score of at least 1 point (30% vs. 33%) (note bene underpowered, $P = 1.0$) or mean preprotocol fluids 1,050 mL (95% confidence interval [CI]: 786–1,314) vs. 1,031 mL (95% CI: 741–1,325) ($P = 0.93$); however, treatment patients received more fluids during the protocol (2,633 mL [95% CI: 2,264–3,001] vs. 1,002 mL [95% CI: 707–1,298]) ($P < 0.001$). **Conclusions:** In this study of a "preshock" population, there was no change in progression of organ dysfunction with a fluid responsiveness protocol. A noninvasive fluid responsiveness protocol did facilitate delivery of an increased volume of fluid. Additional properly powered and enrolled outcomes studies are needed.

KEYWORDS—Fluid resuscitation, sepsis, shock, stroke volume, volume responsiveness

INTRODUCTION

Patients with infection-related conditions, in particular sepsis, commonly present to the emergency department (ED) (1, 2). Furthermore, sepsis is often a rapidly progressing syndrome where deterioration to severe illness may occur during the first few hours of the disease. Therefore, definitive diagnosis coupled with timely and appropriately aggressive treatment is critical to ensure optimal patient outcome.

The fluid responsiveness approach to guiding resuscitation is an approach where one evaluates preload dependence by *dynamic* means (i.e., measuring the stroke volume or cardiac output response to increased preload) (3–6). This contrasts with traditional *static* measures of volume status such as central venous pressure (CVP). The concept is to augment preload (volume challenge) until cardiac stroke volume (or cardiac output) no longer increases, thus signifying that the plateau of the Frank-Starling curve has been reached. This approach has

Address reprint requests to Nathan I. Shapiro, MD, MPH, Beth Israel Deaconess Medical Center, 1 Deaconess Road, CC2-W, Boston, MA 02215.
E-mail: nshapiro@bidmc.harvard.edu

Authors contributions: All investigators participated in the original study conception and approval of the protocol. All authors recruited patients into the study at their study sites. NIS led the initiative and conducted the primary data analysis and interpretation. PCH and NIS drafted the primary manuscript and all authors reviewed the manuscript and gave critical input.

This study was sponsored by Cheetah Medical, Tel Aviv, Israel. The study investigators had primary input into the study design, data collection form creation, performed the analysis, and both drafted the primary manuscript and had final editorial decision-making. As the sponsor, Cheetah Medical had also input into the study design, assisted with data collection, and reviewed the final manuscript. They did not dictate journal submission.

The author reports no conflicts of interest. Since this was an industry sponsored trial, all authors received research funding from Cheetah medical (as described above).

DOI: 10.1097/SHK.0000000000000564

Copyright © 2016 by the Shock Society. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0, where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

been historically limited by the impractical nature of traditional cardiac output monitoring techniques (i.e., pulmonary arterial catheter) in the ED. Novel technologies now enable noninvasive assessment of stroke volume and cardiac output, thus making fluid responsiveness approaches feasible in the ED setting (7). In this trial, we use the Non-Invasive Cardiac Output Monitor (NICOM), a noninvasive device that uses bioreactance (a methodology that measures phase shift of an electrical current) and estimates hemodynamic parameters such as stroke volume and cardiac output based on changes in signal during the cardiac cycle.

Since at the time we conducted the study, early goal-directed therapy (EGDT) was the accepted therapy for patients with overt shock, we turned our attention to a group of patients presenting to the ED with earlier stages of the disease, namely confirmed infection without evidence of severe hypoperfusion or shock. This population has been previously described as the preshock population (8). The ability to identify and intervene in patients with occult hypoperfusion has the potential to curtail the progression to septic shock. In this study, we attempted to define a new fluid responsiveness protocol in a ''preshock'' population. We set out to test the hypothesis that a fluid administration protocol guided by noninvasive hemodynamic assessment of fluid responsiveness would reduce the incidence of progressive organ dysfunction (defined by the worsening of Sepsis-related Organ Failure Assessment [SOFA] score) within 72 h of enrollment. The secondary hypothesis was that a fluid responsiveness protocol guided by noninvasive hemodynamic monitoring would facilitate a more aggressive resuscitation (higher volume of crystalloid delivered).

MATERIALS AND METHODS

Study design

This was a prospective, multicenter, nonblinded randomized-controlled trial that enrolled ED patients at 10 participating centers. Patients meeting entry criteria were randomized (1:1, stratified by site, in permutation blocks of 4 to ''Intervention'' or ''Standard Care'' arms). ''Intervention'' patients were treated with a stroke volume (SV)-guided fluid administration protocol (see Fig. 1), whereas ''Standard of Care'' (SOC) patients received care as dictated by the clinical team. The intervention consisted of up to four fluid bolus cycles, after which routine care was resumed. The study was registered on clinical trials.gov (NCT01484106, registered November 28, 2011), and all patients were enrolled with a written informed consent overseen study-wide by the Beth Israel Deaconess Committee on Clinical investigations, with each institution's human subjects committees approving the study locally. This study was sponsored by Cheetah Medical.

Study setting and population

The study recruited ED patients from participating centers who met study entry criteria. The study *inclusion criteria* were as follows: adult patients at least 18 years old with suspected or confirmed infection; at least two of the following four criteria (systemic inflammatory response syndrome): temperature more than 38°C or less than 36°C, heart rate more than 90 beats/min, respiratory rate more than 20 breaths/min or $PaCO_2$ less than 32 mmHg, white blood cell count more than 12,000 or less than 4,000 per mm^3; or more than 10% bandemia; lactate at least 2.0 mmol/L but less than 4.0 mmol/L; and enrollment within 4 h of ED presentation and within 2.5 h of meeting eligibility criteria. The exclusion criteria were as follows: age less than 18 years; on vasopressor therapy; systolic blood pressure less than 90 mmHg (fluid responsive hypotension was permitted); receipt of more than 3 L of crystalloid before randomization; the presence of any of the following: pulmonary edema, acute coronary syndrome, new onset cardiac arrhythmia, trauma, acute burn, emergent operative diagnosis, stroke, end-stage renal disease on renal replacement therapy, known pregnancy, treatment with immunosuppressive therapy for organ transplant, end-stage liver disease with ascites, active gastrointestinal bleeding, toxic ingestion or drug overdose, left ventricular assist device, advanced directive of ''Do-Not-Treat'' or ''Comfort care only.''

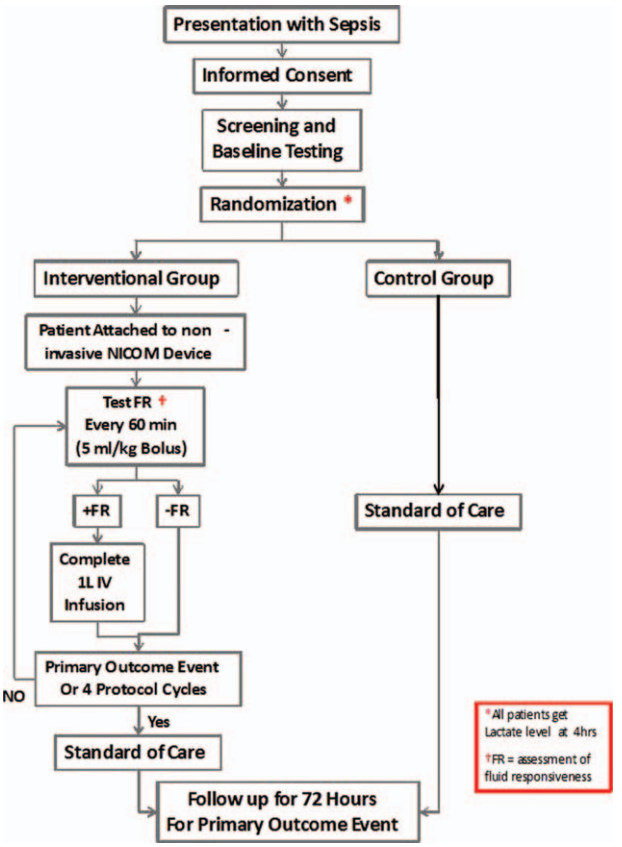

Fig. 1. **Study procedures.** Patients were randomized to invention or standard of care. The information provided by the NICOM in response to a test bolus of crystalloid 5 mL/kg over approximately 10 min (maximum infusion volume 500 mL in a 100 kg or greater person) was used to assess whether the subject was ''fluid responsive.'' A subject was considered ''fluid responsive'' if his/her stroke volume increased by at least 10% by the end of or within 5 min of the fluid challenge. Per protocol, patients who were ''fluid responsive'' received additional crystalloid to complete a 1-L infusion over a 30- to 60-min period. The intervention protocol stopped after four cycles or the primary outcome was met (e.g., SOFA score increased due to worsening respiratory status or new hypotension/vasopressor use), and then patients were returned to standard care. Of note, patients with a negative fluid responsiveness assessment were reassessed at the next cycle and remained eligible for protocol-driven fluid administration if a subsequent FR assessment was positive. All patients had a serum lactate measured at 4 h, and were followed for 72 h. FR indicates fluid responsiveness; NICOM, Non-Invasive Cardiac Output Monitor; SOFA, Sepsis-related Organ Failure Assessment.

Study protocol

Intervention arm patients received care according to a noninvasive fluid responsiveness algorithm (Fig. 1) where a Bioreactance-based noninvasive cardiac output monitor (NICOM, Cheetah Medical Inc, Portland, OR) was used to measure cardiac stroke volume in response to fluid challenges administered during the 4-h treatment algorithm (Fig. 1). The information provided by the NICOM in response to a test bolus of crystalloid 5 mL/kg over approximately 10 min (maximum infusion volume 500 mL in a 100 kg or greater person) was used to assess whether the subject was ''fluid responsive.'' A subject was considered ''fluid responsive'' if his/her stroke volume increased by at least 10% by the end of or within 5 min of the fluid challenge. Per protocol, patients who were ''fluid responsive'' received additional crystalloid to complete a 1 L infusion over a 30- to 60-min period.

For example, a 70-kg individual would receive a 350-mL test bolus over an approximately 10-min period. If SV increased by at least 10%, then an additional 650 mL over the following 50 min was infused. If the patient was

fluid nonresponsive, the protocol dictated that crystalloid was to be given at a rate to keep the vein open. At the end of the first cycle of the protocol (generally 1 h), the second cycle was initiated with another 5 mL/kg (maximum 500 mL) crystalloid bolus to guide further crystalloid administration during that cycle depending on the SV response, as detailed above. If a patient was fluid nonresponsive for two successive challenges, then the protocol was halted.

Patients were examined at the end of each fluid bolus for clinical signs of fluid overload (e.g., new crackles on lung ascultation, increasing shortness of breath, decreasing O_2 saturation); if such signs developed, fluid resuscitation was halted. The protocol also allowed physicians to suspend the protocol in the treatment group to perform additional diagnostic and/or therapeutic procedures. Once the off-protocol procedure or treatment was completed, the fluid responsiveness algorithm resumed at the point where it was suspended. The fluid bolus sequence was carried out for a minimum of four cycles at hours 0, 1, 2, and 3, at which point the protocol was considered completed.

The "SOC" group received treatment entirely at the discretion of the treating team and did not receive any hemodynamic monitoring. Both study groups had a repeat serum lactate measured at the 4-h mark.

Measurements

We collected pertinent vital signs, demographics, comorbidities, as well as fluid administration data and details of the protocol implementation. A lactate level was obtained at 4 h in both groups to assess lactate clearance, and this result was available to the clinical team. In both groups, the hospital chart was examined for 72 h following enrollment to assess organ dysfunction on days 1, 2, and 3. If the patient was discharged from the hospital before the 72-h time point, the patient was called at 72 h to make sure that he/she was not readmitted to another hospital.

Key outcome measures

Primary outcome: The primary outcome was a worsening of the SOFA score over the first 72 h, defined as a change in the SOFA score by greater than 1 point. *Secondary outcomes*: Secondary outcomes (defined *a priori*) were as follows: volume of fluids administered during the protocol; change in lactate level at 4 h (a serum lactate was drawn in both groups at 4 h after protocol initiation); ICU admission; and length of hospital stay. Serious related adverse events were defined as protocol-related events requiring intervention: intubation, noninvasive mechanical ventilation, or diuretic administration.

Data analysis

The primary hypothesis tested was that patients who were randomized to fluid responsiveness guided fluid management would have less frequent progression of organ dysfunction. The secondary hypothesis was that patients in the intervention group would receive more fluid as compared with the SOC group. Both were assessed using a Fisher exact test, with α set for significance at 0.05. Secondary endpoints that were proportions were assessed using Fisher exact test; those with continuous endpoints were assessed for normality and compared using either a Wilcoxon rank-sum test or *t* test, as appropriate.

Sample size

For purposes of initial sample size calculation, it was assumed that the proportion of patients in the control group who would progress to meet the primary endpoint of an increase in SOFA score would be 30%, and we powered the study to detect an absolute reduction in rate of progression by 10% (33% relative risk reduction) in the treatment group. On the basis of these two assumptions, 294 patients were required in each group to provide 80% power to detect a statistically significant difference (α set at 0.05) in the primary outcome between groups. Thus, assuming a 2% dropout rate, the study was initially planned to enroll a total of 600 patients. However, the sponsor terminated the study early (after 65 patients) because of a change in corporate management and funding priorities. The data saturation monitoring board had no clinical concerns before or after stopping the study.

RESULTS

Characteristics of study subjects

There were a total of 65 patients enrolled in the study before early study termination by the sponsor. One patient in the treatment group withdrew due to patient preference and was withdrawn from the study at the patient request, so 64 patients were included in the analysis. Overall, 19 (30%) patients reached the primary outcome of increase in SOFA score of 1 point or more. There was one nonsepsis-related death and one patient received mechanical ventilation, both in the SOC group.

Main results

Demographics and organ dysfunction—There were no significant differences between arms in age, comorbidities, baseline vital signs, or SOFA scores (Table 1). Please note that the primary outcome comparison is significantly underpowered, but we report them nonetheless to add perspective and inform future investigations. Comparing intervention arm to SOC, there was no difference in increase in SOFA at least 1 (30% vs. 33%; $P = 1.0$). The average lactate level was similar at 4 h (1.6 ± 0.7 vs. 1.6 ± 0.7; $P = 1.0$). There was no difference in the length of stay or ICU admission rate (Table 2).

Fluid management—In regards to fluid administration, the volume of fluid received by patients before enrollment was similar: 1,050 mL (95% confidence interval [CI]: 786–1,314 mL) vs. 1,032 mL (95% CI: 741–1,325 mL), $P = 0.93$ (Table 3). However, during the protocol the intervention group received more fluids: 2,633 mL (95% CI: 2,264–3,001) vs. 1,002 mL (95% CI: 707–1,298), $P < 0.001$ (Fig. 2). The mean

Table 1. **Demographics**

	SOC, n = 32	Treatment, n = 32
Demographics		
Age (mean years ± SD)	58.8 ± 19.9	60.6 ± 12.1
Male sex	15 (47%)	15 (47)%
Race: White	21 (66%)	27 (84%)
Race: Black	11 (34%)	5 (16%)
Weight (mean lbs ± SD)	185 ± 52.5	196.3 ± 60.3
Health history, n (%)		
None	7 (21.9%)	8 (25%)
CHF	3 (9.4%)	3 (9.4%)
CAD	3 (9.4%)	3 (9.1%)
MI	1 (3.1%)	2 (6.3%)
COPD	2 (6.3%)	7 (21.9%)
DM	9 (28.1%)	13 (40.6%)
Hypertension	20 (62.5%)	14 (43.8%)
Liver disease	2 (6.3%)	2 (6.3%)
Stroke/TIA	3 (9.4%)	2 (6.3%)
Vital signs		
SBP, mmHg)	134.7 ± 26.7	128 ± 21.6
DBP, mmHg	76.5 ± 22	69.8 ± 13.5
Temp, °F	98.3 ± 11.5	97.9 ± 11.1
HR, beats/min	106.5 ± 20.5	102.7 ± 17.4
RR, breaths/min	20.6 ± 5.1	20.9 ± 5.1
SAO_2, %	97.7 ± 2.3	97.1 ± 2.5
Labs and severity		
Lactate, mmol/L	2.5 ± 0.4	2.7 ± 0.4
Creatinine, mmol/L	1.2 ± 0.6	1.2 ± 0.6
SOFA score	1.0 ± 1.6	1.2 ± 1.5
APACHE II score	9 ± 4.7	10 ± 5.7
Pre-enrollment fluids		
Normal saline, mL	972 ± 765	945 ± 669
Medications, mL	60 ± 90	105 ± 154
Total, mL	1,032 ± 804	1,050 ± 742

CAD indicates coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HR, heart rate; MI, myocardial infarction; RR, respiratory rate; SAO_2, oxygen saturation; SBP, systolic blood pressure; SOC, Standard of Care; SOFA, Sepsis-related Organ Failure Assessment; Temp, temperature; TIA, transient ischemic attack.

TABLE 2. **Follow-up characteristics**

Outcome	SOC, n = 32	Treatment, n = 32	*P*
Any SOFA increase ≥1 point	9 (29%)	10 (31%)	1.0
SOFA organ-specific increase ≥1			
SOFA respiratory	3 (9.4%)	2 (6.3%)	1.0
SOFA cardiac	6 (19%)	7 (22%)	1.0
SOFA coagulation	4 (13%)	3 (9.4%)	1.0
SOFA liver	0 (0.0%)	1 (3.1%)	1.0
SOFA neurologic	2 (6.3%)	0 (0.0%)	0.49
SOFA renal	5 (16%)	1 (3.1%)	0.20
Vasopressor use	0 (0%)	0 (0%)	1.0
Change in lactate level over 4 h (mmol/L), mean (SD)	−0.91 (±0.69)	−1.2 (±0.65)	0.20
Mechanical ventilation	1 (3.4%)	0 (0%)	1.0
Death	1 (3.4%)	0 (0%)	1.0
Peak creatinine change over 72 h, mean (SD)	−0.15 (±0.56)	−0.12 (±0.26)	0.78
Hospitalization	26 (81%)	31 (97%)	0.10
Hospital LOS (median)	4 (3–5)	3 (2–5)	0.70
ICU admission	5 (17%)	4 (13%)	1.0

ICU indicates intensive care unit; LOS, length of stay; SOC, Standard of Care; SOFA, Sepsis-related Organ Failure Assessment.

amount of fluid administered from time of protocol completion (or at 3 h in the control group) to 24 h was higher in the SOC group (851 vs. 1,727 mL), $P < 0.01$ (Table 3). We also show the distribution of the fluids administered to the two groups during the protocol, after the protocol period, and overall during the first 72 h (Fig. 3). Among the patients who received a volume responsiveness challenge, they were largely responsive at each time point (Table 4). Overall, 28 of 33 (85%) patients were fluid responsive to one of the fluid challenges. The total amount of fluid given as a function of the number of positive fluid challenges is shown, with the expected relationship between number of positive tests and total volume of fluid (Table 5).

Adverse events—In terms of serious adverse events, there was one patient who received mechanical ventilation as an inpatient in the SOC group. No patients in either group developed vasopressor-dependent hypotension. There were two patients in the treatment group who developed signs and/or symptoms that may have been due to volume overload, and subsequently received furosemide and oxygen via nasal cannula but no other interventions. There was one unrelated (cancer complications) death in the SOC group.

DISCUSSION

Although the COMMIT study was prematurely halted due to termination of financial support by the sponsor, we submit that this study serves as an important proof-of-concept for the potential of fluid responsiveness-guided resuscitation in the ED. We hope that these data may be used to guide future initiatives. Although the fluid responsiveness protocol guided by noninvasive hemodynamic monitoring did not demonstrate a reduction in our *a priori* primary outcome of organ dysfunction, this assessment was significantly underpowered. However, our protocol did facilitate an earlier and more vigorous fluid resuscitation. In addition, we demonstrate that the majority (85%) of ''preshock'' patients were fluid responsive to at least one volume challenge.

Debate remains about the ideal amount of fluid to give in patients who present to the ED with sepsis, as well as whether a ''fluid-restrictive'' or a ''fluid-liberal'' approach is optimal as there continues to be a lack of solid evidence to guide clinicians. However, regardless of whether one takes a ''fluid restrictive'' or ''fluid liberal'' approach, giving a patient additional fluid when they are no longer fluid responsive is less likely to be of benefit. A fluid responsiveness approach may offer a more effective means of implementing early fluid resuscitation in these patients, and we have demonstrated that this approach provides a feasible means of fluid titration that accounts for an individual's unique physiology. Our findings support the hypothesis that SV-guided fluid resuscitation in the ''preshock'' patient will result in more aggressive volume expansion in the early setting.

Although the notion of using physiologic measurements to guide resuscitation is certainly commonplace, the ideal measure for this purpose remains controversial. The most notable measure beyond heart rate and blood pressure is CVP, a primary component of EGDT (9). Although CVP may be useful at extreme values (low or high), the limitations and pitfalls of using CVP are well described (10, 11). Although a low CVP is typically indicative of volume depletion, normal or high values may be indicative of decreased cardiac compliance rather than adequate volume repletion or volume overload. CVP should certainly be interpreted with caution, and the search for alternative indices of volume status is certainly warranted.

The use of stroke volume and cardiac output as a dynamic measure to guide fluid resuscitation is reasonably well accepted. It has gained the most recognition in the ICU and the perioperative setting, where initial studies have demonstrated outcomes benefit (6). An advantage of SV-guided fluid challenge approach is that it measures the ''dynamic'' response to a relevant physiologic perturbation, namely preload augmentation via a fluid bolus. Initial studies in the perioperative setting demonstrated decreased mortality rates with guided therapy. Although large-scale validation in the perioperative setting has questioned definitive benefit (12), implementation remains commonplace and the preponderance of evidence still suggests benefit. Outcomes data in the ICU setting are less definitive, but SV-guided fluid resuscitation is certainly prevalent (4).

TABLE 3. **Fluids administration**

Time period	SOC, n = 32, mean (95% CI)	Treatment, n = 32, mean (95% CI)	*P*
Pre-enrollment	1,032 mL (741–1,325)	1,050 mL (786–1,314)	0.93
Protocol	1,002 mL (707–1,298)	2,633 mL (2,264–3,001)	<0.001
Protocol end to 24 h	1,842 mL (1,366–2,319)	906 mL (540–1,272)	<0.001
Total fluids	3,876 mL (3,156–4,479)	4,588 mL (3,891–5,285)	0.23

CI indicates confidence interval; SOC, Standard of Care.

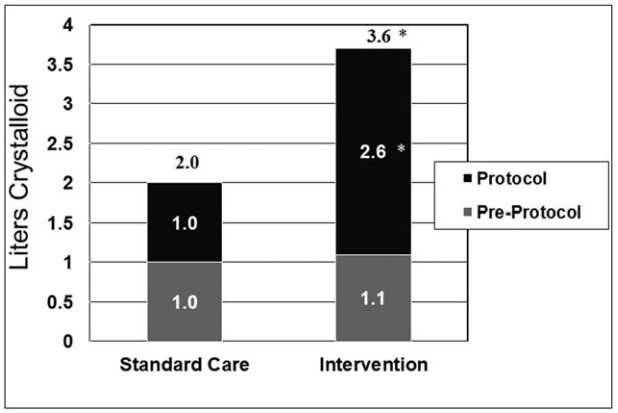

Fig. 2. **Amount of fluids received in the ED.** The mean volume of fluid received by patients before enrollment was similar: 1,050 mL (95% CI: 786–1,314 mL) vs. 1,032 mL (95% CI: 741–1,325 mL), $P = 0.93$. However, during the protocol the intervention group received more fluids: 2,633 mL (95% CI: 2,264–3,001) vs. 1,002 mL (95% CI: 707–1,298), $P < 0.001$. ED indicates emergency department.

In the design and implementation of this investigation, there are a number of considerations that we made whose discussion might be valuable in designing future studies. For example, we selected a "preshock" population as opposed to an overtly hypotensive population, based on literature suggesting that downstream decompensation is not an uncommon event, and the notion that early intervention might prevent decompensation (13). Thus, these findings do not necessarily apply to a population in overt shock. We were surprised to find that no patient in either group went on to develop vasopressor-dependent hypotension; thus, the studied population was less ill than anticipated. Second, we chose a change in SOFA score more than 1 as our primary outcome measure. The most common change was an increase in the cardiac component of the SOFA score from 0 to 1, which was transient hypotension that resolved with fluid therapy, so not very clinically significant. Third, we also chose to use a fluid challenge approach where we used a 5-mL/kg bolus; a larger bolus may have made a difference. The passive leg raise technique may also have been a better option to administer a fluid challenge (14). In our subsequent experience we found that the passive leg raise was easier to implement and more reproducible, and this should be a consideration in future studies (7). Fourth, we used a practical approach of finishing out a liter if the patient was fluid responsive as opposed to a strict mL/kg protocol. Fifth, we

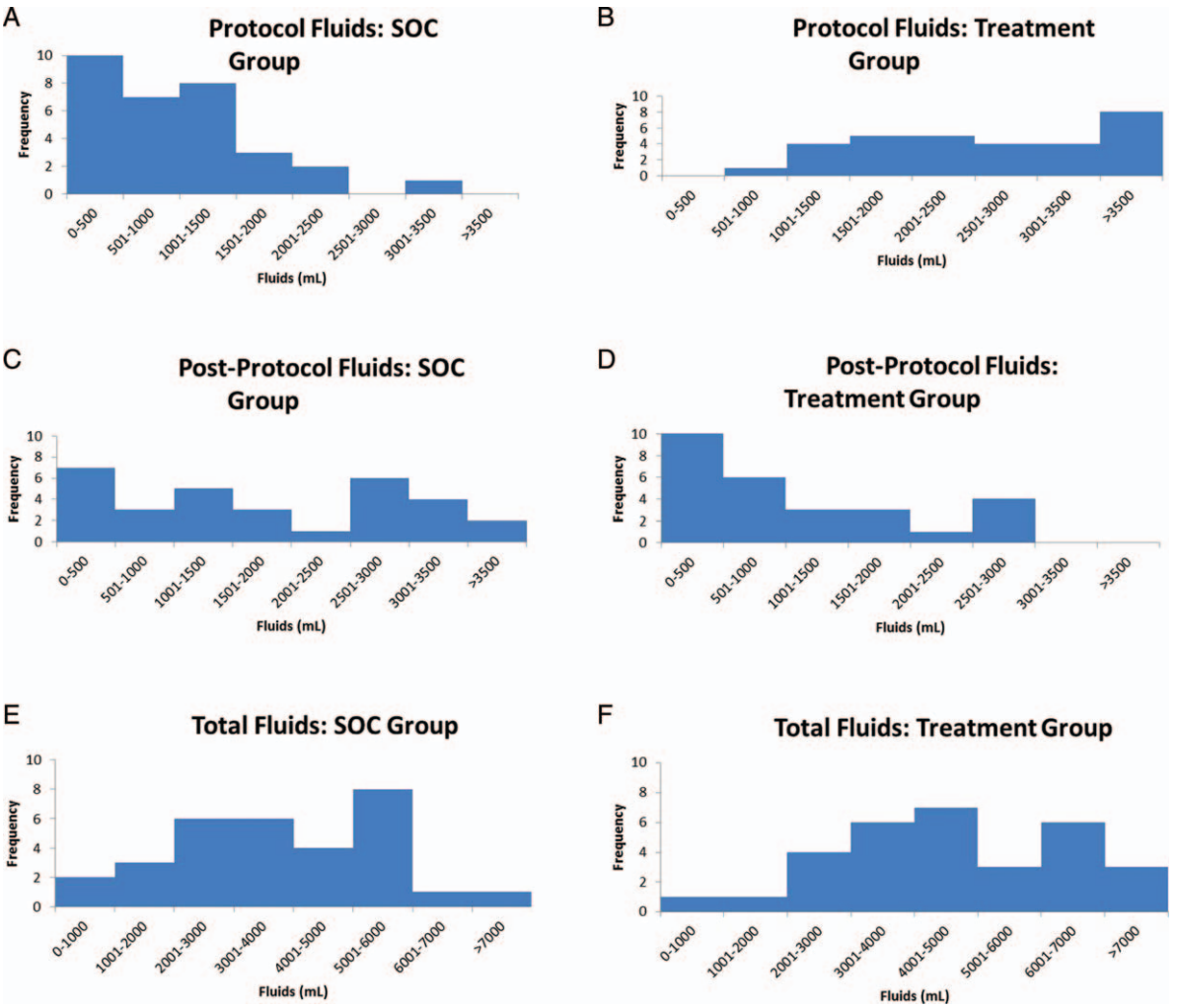

Fig. 3. **Fluid administration histogram.** This figure is a histogram of the amount of fluids received, stratified by treatment or standard of care group during the (A) protocol period, (B) postprotocol period, and (C) in total.

Table 4. **Stroke volume and average responsiveness at each assessment**

Cycle no.	No. of patients assessed	Average baseline stroke volume	Change in stroke volume to bolus, %	No. of fluid responsive, n (%)
1	32	63.6	12.9	15 (47)
2	30	63.9	15.4	19 (63)
3	24	67.4	16.1	15 (63)
4	23	64.2	13.6	11 (48)

Table 5. **Fluid administration by fluid responsiveness episodes**

No. of times fluid responsive	N (%)	Mean, mL	95% CI, mL	Min, mL	Max, mL
0	4 (13)	1,803	(695–2,912)	1,300	2,150
1	11 (34)	1,905	(1,488–2,323)	750	2,800
2	8 (25)	2,558	(1,951–3,165)	1,500	3,400
3	3 (9)	3,543	(3,162–3,924)	3,400	3,705
4	6 (19)	4,024	(3,797–4,253)	3,700	4,300

CI indicates confidence interval.

selected to use the NICOM to guide the fluid therapy, whereas other more invasive approaches such as esophageal Doppler, LIDCO, or PICO monitors may have been acceptable choices (15). Finally, we limited our protocol to four cycles which was about 3 h, whereas continuing for a longer period may have yielded better results.

Future studies may consider adopting some of the alternatives listed above, with the obvious additional consideration of an appropriately powered study. For example, perhaps a passive leg raised based protocol of patients with overt shock may demonstrate outcomes benefit. Using patient-oriented outcomes such as mechanical ventilation or organ dysfunction, or mortality if feasible, would certainly be informative. Given the debate about fluid restrictive and fluid liberal approaches, incorporation of vasopressors earlier in the protocols may be a logical alternative approach. Although our study was sepsis based, perhaps a resuscitation protocol for any etiology of shock may be another way forward.

There are a number of limitations to this study, the most obvious being its early stoppage. This led to an underpowered investigation for the primary endpoint; however, findings pertaining to the secondary hypothesis around fluid resuscitation are worth reporting. In addition to the lack of power to properly assess our stated primary outcome, our investigation may also be underpowered to detect meaningful adverse events. Our choice of SOFA score is not necessarily a ''patient-oriented outcome'' and may have been overly sensitive. Our outcomes in both groups were quite favorable, so although our protocol facilitated a larger volume of fluid administered within the first 4 h, we cannot truly comment on the ultimate impact on patient survival. Finally, this was largely an efficacy study where the intervention was typically delivered by a study team carefully monitoring the patients, which may not be generalizable to a routine clinical care environment.

In this abbreviated study in a ''preshock'' population, there was no change in progression of organ dysfunction with a fluid responsiveness protocol guided by noninvasive hemodynamic monitoring; however, our study was underpowered to address the primary endpoint. Importantly, we did find that a noninvasive fluid challenge-guided approach facilitated more aggressive fluid resuscitation in the ED. This type of approach holds promise as a standardized method to titrate fluid resuscitation to an individual patient's physiologic response. Future studies on a larger population of ''preshock'' patients, as well as more acutely ill populations, using a similar noninvasive approach, are warranted to determine if reductions in morbidity and mortality can be achieved.

ACKNOWLEDGMENTS

The authors thank the clinical teams and study teams at all sites for their participation and support of this project; Drs Deborah Diercks, Judd Hollander, and Alan Jones for their participation on the Data Safety Monitoring Board; and also Amanda Milgram, Dr Yoav Avidor, and Dr Daniel Burkhoff for their work on this project.

REFERENCES

1. Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, Sicignano A, Palazzo M, Moreno R, Boulme R, et al.: Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med* 28(2):108–121, 2002.
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR: Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 29(7):1303–1310, 2001.
3. Teboul JL, Monnet X: Prediction of volume responsiveness in critically ill patients with spontaneous breathing activity. *Curr Opin Crit Care* 14(3):334–339, 2008.
4. Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, Teboul JL: Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med* 34(5):1402–1407, 2006.
5. Monnet X, Dres M, Ferre A, Le Teuff G, Jozwiak M, Bleibtreu A, Le Deley MC, Chemla D, Richard C, Teboul JL: Prediction of fluid responsiveness by a continuous non-invasive assessment of arterial pressure in critically ill patients: comparison with four other dynamic indices. *Br J Anaesth* 109(3):330–338, 2012.
6. McKendry M, McGloin H, Saberi D, Caudwell L, Brady AR, Singer M: Randomised controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimisation of circulatory status after cardiac surgery. *BMJ* 329(7460):258, 2004.
7. Duus N, Shogilev DJ, Skibsted S, Zijlstra HW, Fish E, Oren-Grinberg A, Lior Y, Novack V, Talmor D, Kirkegaard H, et al.: The reliability and validity of passive leg raise and fluid bolus to assess fluid responsiveness in spontaneously breathing emergency department patients. *J Crit Care* 30(1):217e1–217e5, 2015.
8. Arnold RC, Sherwin R, Shapiro NI, O'Connor JL, Glaspey L, Singh S, Medado P, Trzeciak S, Jones AE, Emergency Medicine Shock Research Network Investigators. Multicenter observational study of the development of progressive organ dysfunction and therapeutic interventions in normotensive sepsis patients in the emergency department. *Acad Emerg Med* 20(5):433–440, 2013.

9. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345(19):1368–1377, 2001.
10. Marik PE, Baram M, Vahid B: Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest* 134(1):172–178, 2008.
11. Marik PE, Cavallazzi R: Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med* 41(7):1774–1781, 2013.
12. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, Grocott MP, Ahern A, Griggs K, Scott R, et al.: Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *JAMA* 311(21):2181–2190, 2014.
13. Glickman SW, Cairns CB, Otero RM, Woods CW, Tsalik EL, Langley RJ, van Velkinburgh JC, Park LP, Glickman LT, Fowler VG Jr, et al.: Disease progression in hemodynamically stable patients presenting to the emergency department with sepsis. *Acad Emerg Med* 17(4):383–390, 2010.
14. Jabot J, Teboul JL, Richard C, Monnet X: Passive leg raising for predicting fluid responsiveness: importance of the postural change. *Intensive Care Med* 35(1):85–90, 2009.
15. Marik PE: Noninvasive cardiac output monitors: a state-of the-art review. *J Cardiothorac Vasc Anesth* 27(1):121–134, 2013.