



Does Point-of-Care Ultrasonography Improve Clinical Outcomes in Emergency Department Patients With Undifferentiated Hypotension? An International Randomized Controlled Trial From the SHoC-ED Investigators

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Study objective: Point-of-care ultrasonography protocols are commonly used in the initial management of patients with undifferentiated hypotension in the emergency department (ED). There is little published evidence for any mortality benefit. We compare the effect of a point-of-care ultrasonography protocol versus standard care without point-of-care ultrasonography for survival and clinical outcomes.

Methods: This international, multicenter, randomized controlled trial recruited from 6 centers in North America and South Africa and included selected hypotensive patients (systolic blood pressure <100 mm Hg or shock index >1) randomized to early point-of-care ultrasonography plus standard care versus standard care without point-of-care ultrasonography. Diagnoses were recorded at 0 and 60 minutes. The primary outcome measure was survival to 30 days or hospital discharge. Secondary outcome measures included initial treatment and investigations, admissions, and length of stay.

Results: Follow-up was completed for 270 of 273 patients. The most common diagnosis in more than half the patients was occult sepsis. We found no important differences between groups for the primary outcome of survival (point-of-care ultrasonography group 104 of 136 patients versus standard care 102 of 134 patients; difference 0.35%; 95% binomial confidence interval [CI] -10.2% to 11.0%), survival in North America (point-of-care ultrasonography group 76 of 89 patients versus standard care 72 of 88 patients; difference 3.6%; CI -8.1% to 15.3%), and survival in South Africa (point-of-care ultrasonography group 28 of 47 patients versus standard care 30 of 46 patients; difference 5.6%; CI -15.2% to 26.0%). There were no important differences in rates of computed tomography (CT) scanning, inotrope or intravenous fluid use, and ICU or total length of stay.

Conclusion: To our knowledge, this is the first randomized controlled trial to compare point-of-care ultrasonography to standard care without point-of-care ultrasonography in undifferentiated hypotensive ED patients. We did not find any benefits for survival, length of stay, rates of CT scanning, inotrope use, or fluid administration. The addition of a point-of-care ultrasonography protocol to standard care may not translate into a survival benefit in this group. [Ann Emerg Med. 2018;72:478-489.]

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INTRODUCTION

Background

Patients who present to the emergency department (ED) with nontraumatic hypotension or shock have high mortality

rates and pose both diagnostic and therapeutic challenges for the emergency physician.^{1,2} Early recognition and appropriate initial empiric treatment aimed at avoiding prolonged hypotension and tissue hypoxia has been shown to decrease morbidity and mortality in patients with undifferentiated and septic shock.³⁻⁷ Point-of-care ultrasonography can

Editor's Capsule Summary*What is already known on this topic*

Using point-of-care ultrasonography in the assessments of patients with undifferentiated hypotension can improve diagnostic accuracy and influence initial management, but has yet to be shown to improve outcomes.

What question this study addressed

Using a multicenter randomized controlled trial, the authors examined outcomes among 270 hypotensive patients who were evaluated with point-of-care ultrasonography compared with those not evaluated with it.

What this study adds to our knowledge

The use of point-of-care ultrasonography had no effect on important outcomes for patients with undifferentiated hypotension, including overall survival (difference 0.35%), length of stay (difference 0.12 days), inotrope use (difference 3.6%), or fluid administration (difference 74 mL).

How this is relevant to clinical practice

Study findings suggest that although point-of-care ultrasonography may improve diagnostic accuracy among patients with undifferentiated hypotension, it has little effect on final outcomes.

support clinicians in the initial diagnosis and management of patients with undifferentiated hypotension in the ED.^{2,8}

Diagnostic accuracy for patients with undifferentiated shock improved from 60.6% to 85.0% with the use of a structured point-of-care ultrasonography protocol,² affecting initial management in 24% to 50% of patients.^{2,8} Point-of-care ultrasonography has also been shown to rapidly diagnose common conditions that may cause shock, such as cardiac dysfunction^{9,10} and ruptured aortic aneurysm¹¹ and to evaluate the fluid status of the patient with shock.¹² Despite reported diagnostic benefits and improved timing of critical interventions in patients with both traumatic and nontraumatic hypotension,^{2,8,13-19} to our knowledge there are no prospective comparative studies examining patient-centered outcomes, such as survival for point-of-care ultrasonography protocols in hypotensive emergency patients.

There is some evidence that individual point-of-care ultrasonography components improve clinical outcomes in select patient populations. Limited point-of-care

ultrasonography-guided management after early resuscitation is associated with improved survival, less fluid, and increased inotropic prescription in hypotensive ICU patients.²⁰ Point-of-care ultrasonography has also been shown to decrease time to the operating room and the rate of computed tomography (CT) scanning in trauma patients.²¹ Although there is evidence to support clinically relevant treatment improvements for these individual point-of-care ultrasonography components, for patients with undifferentiated nontraumatic shock in the ED there is little evidence to date to support any added patient-oriented outcome benefits for the use of protocols such as Abdominal and Cardiothoracic Evaluation with Sonography in Shock or Rapid Ultrasound for Shock and Hypotension that combine these components.²²⁻²⁴

Importance

Although the argument that reduced time to diagnosis and improved accuracy of diagnosis should lead to improved outcomes is valid, to our knowledge this logic has not yet been tested in a prospective controlled comparative study. The current literature addressing the use of point-of-care ultrasonography in undifferentiated hypotension is unclear in relation to any true influence on patient-oriented outcomes.

Goals of This Investigation

This trial, from the Sonography in Hypotension and Cardiac Arrest in the Emergency Department series, was an international, multicenter, randomized controlled trial that assessed the effect of a standardized point-of-care ultrasonography protocol on clinical outcomes for selected patients presenting to the ED with undifferentiated hypotension. The primary outcome measure was survival to 30 days or hospital discharge. Secondary outcome measures included initial treatment (inotrope and intravenous fluid administration), investigations (rates of CT use), admissions rates (hospital and ICU), and length of stay (hospital and ICU). The study is part of a series of investigations aiming to provide a clearer understanding of how the use of point-of-care ultrasonography directly affects clinically important patient outcomes for patients presenting to the ED with hypotension or in cardiac arrest.

MATERIALS AND METHODS**Study Design and Setting**

We completed an international, multicenter, randomized controlled trial of patients who presented to the ED with undifferentiated (ie, without a clearly evident cause) nontraumatic hypotension or shock. Recruitment occurred in 3 centers in North America and 3 in South Africa. The

North American centers were large tertiary referral and teaching centers, staffed by accredited emergency physicians with active point-of-care ultrasonography programs. The South African centers consisted of a large district hospital, a large regional hospital, and a tertiary academic center based in the greater Cape Town area, including the largest low-income informal housing settlement, and were also staffed by accredited emergency physicians with active point-of-care ultrasonography programs. All ultrasonographic scans were performed by physicians who had demonstrated training and competency in point-of-care ultrasonography. Any scans performed by residents were supervised by certified emergency physicians with competencies as described above. Principal investigators at each site agreed on standards of competency required to undertake scanning. Several of the North American investigating physicians visited South Africa, and vice versa, to confirm that the competency standards were comparable at all locations. For all sites, recruitment and enrollment was performed as a convenience sample of eligible patients when appropriately trained staff were immediately available in the ED. The point-of-care ultrasonography protocol used during the study was clearly defined and was based on previously published protocols for hypotension and shock.^{23,24} It consisted of cardiac, lung, inferior vena cava, abdominal aortic, abdominal, and pelvic views. Specific questions to be answered included the effectiveness of the “pump,” using subxiphoid, parasternal, and apical cardiac views relating to left and right ventricular size, contractility, and evidence of pericardial fluid; the “tank,” relating to the size and collapsibility of the inferior vena cava and pleural, peritoneal, and pelvic fluid; and the “pipes,” relating to evidence of aortic disease or central signs of thromboembolism (Figure 1).

Selection of Participants

All adult patients were screened after triage by trained staff to identify 2 parameters: a sustained systolic blood pressure less than 100 mm Hg or a shock index greater than 1.0. Shock index is defined as pulse rate over systolic blood pressure. Inclusion criteria for study enrollment were aged 19 years or older, presentation with a sustained initial systolic blood pressure less than 100 mm Hg, or a shock index greater than 1.0 (with systolic blood pressure <120 mm Hg).

Exclusion criteria were pregnancy known at presentation or discovered during initial screening, the necessity of cardiopulmonary resuscitation or other advanced cardiac life support interventions (eg, defibrillation, emergency pacing, insertion of ventricular assist device) before screening or enrollment, a history of significant trauma in the past 24 hours, a 12 lead ECG diagnostic of acute myocardial infarction, an evident clear mechanism or cause

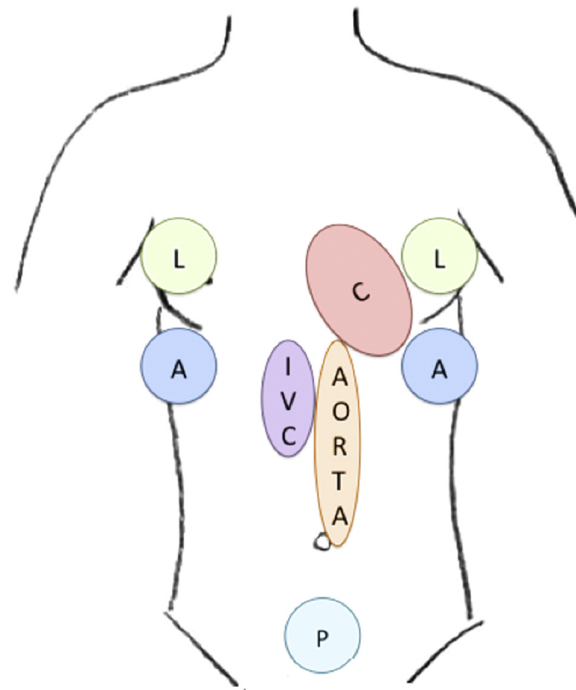


Figure 1. The point-of-care ultrasonography protocol used for the Sonography in Hypotension and Cardiac Arrest in the Emergency Department trial consisted of a standardized shock-hypotension protocol based on a combination of the core components of the Abdominal and Cardiothoracic Evaluation with Sonography in Shock and Rapid Ultrasound for Shock and Hypotension protocols and was followed uniformly at all of the investigating sites. Cardiac (C) views included subxiphoid, parasternal long, parasternal short, and apical. The presence or absence of pericardial fluid was noted, as was left and right ventricular function and size. Base-of-lung (thoracic) scans (L) were performed on the left and right side of the chest to look for the evidence of lung sliding to tension pneumothoraces, and both pleural spaces were examined for pleural effusions. The right and left upper quadrants of the abdomen (A) were examined for free fluid in the hepatorenal and splenorenal regions. The inferior vena cava (IVC) was examined for size and collapsibility. The aorta was measured in a transverse and longitudinal plane to ascertain whether an abdominal aneurysm was present. The pelvic views (P) were performed in the transverse and longitudinal planes to determine whether free fluid was present in the peritoneal space, as well as to determine an estimate of bladder filling.

for the hypotension or shock (ie, in which an obvious cause for the shocked state, such as gastrointestinal bleeding or ruptured aortic aneurysm, was immediately identifiable by the treating physician and therefore the patient did not have undifferentiated shock), a previously known diagnosis from another hospital (for transferred patients), a vagal episode (as cause of hypotension), and low blood pressure considered to be nonpathologic (normal variant or other).

Interventions

ED clinical staff, including physicians and nurses, identified potential candidates for the study and flagged their patient records or triage notes to notify the attending physician. A standardized patient preinclusion form was used to ensure that these parameters were correctly recorded and reviewed. Emergency physicians trained on the study point-of-care ultrasonography protocol (Figure 1) proceeded to review the inclusion and exclusion criteria and obtained written or witnessed verbal consent to participate in the study. The study point-of-care ultrasonography protocol consisted of a standardized shock-hypotension protocol based on a combination of the core components of the Abdominal and Cardiothoracic Evaluation with Sonography in Shock and Rapid Ultrasound for Shock and Hypotension protocols and was followed uniformly at all of the investigating sites. For patients with altered mental status or who presented unconscious, consent was waived according to the study protocol.

This study used randomized convenience-sampling blocks by site, and allocation concealment was performed at each site. QuickCalcs Random Numbers (version 2011; GraphPad Software, La Jolla, CA) was used to randomly assign either control (no point-of-care ultrasonography) or intervention (point-of-care ultrasonography protocol) documents to batches of 100 envelopes (50 of each group were assigned at each site), which were sealed, ensuring concealment of allocation. On completion of review of inclusion and exclusion criteria, and after obtaining consent, the physician retrieved a numbered sealed envelope that contained randomization details and the case report form. Randomization was also protected by the following measures: Researchers were provided with sequentially numbered prerandomized envelopes, which were opaque and matched for size and weight to ensure that it was impossible to discern between an intervention and control envelope. All locations had site-specific prefixes to the envelope numbers.

Case report forms included step-by-step instructions for performing, and fields for recording, ultrasonographic and clinical data. For patients randomized to the point-of-care ultrasonography group, physicians performed their normal initial clinical assessment and then completed the required point-of-care ultrasonography scans within the first 60 minutes of the patient visit, recording their data after each step. Patients in the control group received usual care without any point-of-care ultrasonography in the ED. Physicians recorded data after their initial clinical assessment without using point-of-care ultrasonography. In both groups, physicians performed a secondary clinical assessment and recorded their revised impressions at 60 minutes.

Methods of Measurement

Demographics, clinical details, and study findings, including ultrasonographic findings and clinical impressions, were collected prospectively. Initial and secondary diagnoses were recorded at 0 and 60 minutes, with ultrasonography performed in the point-of-care ultrasonography group before secondary assessment. Any missing information, including vital signs, was collected by a research coordinator by chart review and entered into a master study spreadsheet (MS Excel, version 15; Microsoft, Redmond, WA). Local principal investigators were responsible for ensuring appropriate training and monitoring of standards at their center.

Outcome Measures

The primary outcome of this study was 30-day or discharge survival of selected patients presenting to the ED with undifferentiated shock. This was defined as survival to hospital discharge, or to 30 days if the patient remained in the hospital. Subgroup analysis was performed for the primary outcome by continent.

Secondary clinical outcomes included volume of intravenous fluid administered in the ED, rate of inotrope administration, rate of CT scanning, hospital and ICU admission rates, and lengths of stay.

Reported diagnoses were grouped under general diagnostic categories for ease of comparison. The diagnosis category list was adapted from Jones et al,¹ with the addition of a category for malignancy-related illness. Categories of shock and diagnoses were established by independent chart review by 2 clinicians, blinded to the initial sonographer, point-of-care ultrasonography findings, arm of study, and initial and revised diagnoses. A third clinician was available to adjudicate for any disagreements.

Primary Data Analysis

We provide percentages and binomial confidence intervals (CIs) for categorical data, and medians and interquartile ranges (IQRs) for continuous data. Results are presented in terms of differences in proportion or median between experimental and control groups, along with a binomial CI for the observed differences.

The study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov), and all sites received local research ethics board approval. All study subject information collected was kept confidential and was password protected. All identifiable patient data and scan records were removed from the source documents and replaced by study-specific numbers that were known only by the data collector and site investigator. The study was conducted in accordance with the International Conference on Harmonization for Good Clinical Practice²⁵ and the

appropriate regulatory requirements. Witnessed verbal or written informed consent (if the patient was able to provide it), delayed consent (if the patient recovered sufficiently), and waiver of consent were obtained from the patient or next of kin before enrollment commenced. The decision to randomize patients to a control arm not receiving point-of-care ultrasonography in the ED was agreed to by all research ethics boards because the use of point-of-care ultrasonography was deemed not to be standard of care for patients at the enrolling sites, where the provision of point-of-care ultrasonography depended on the presence of a physician trained in point-of-care ultrasonography. A sample size of 400 patients would have provided at least 80% power to detect a reduction in mortality of 10%, at $\alpha=.05$ for our primary endpoints (survival to 30 days or hospital discharge), assuming mortality of 30% in the control group. At interim analysis, the research ethics board advised stopping recruitment at the point reported (after

inclusion of 270 patients) because of slow recruitment and the perceived futility of continuing.

RESULTS

From September 2012 to December 2016, 273 patients were enrolled across the 6 study sites. Data were collected for 270 patients, with 3 being lost to follow-up. The participant CONSORT flow sheet is shown in Figure 2. Of those enrolled, 135 participants were randomized to the control group and 138 to the point-of-care ultrasonography group. Baseline demographics are shown in Table 1. Randomization was successful, with the groups being adequately matched for baseline demographics and vital signs. Baseline vital signs confirmed selection of patients with hypotensive shock, with an overall median systolic blood pressure of 91.6 mm Hg (IQR 90.1 to 93.3 mm Hg) and a median pulse rate of 109.2 beats/min (IQR 106.2 to 112.8 beats/min). Categories of final

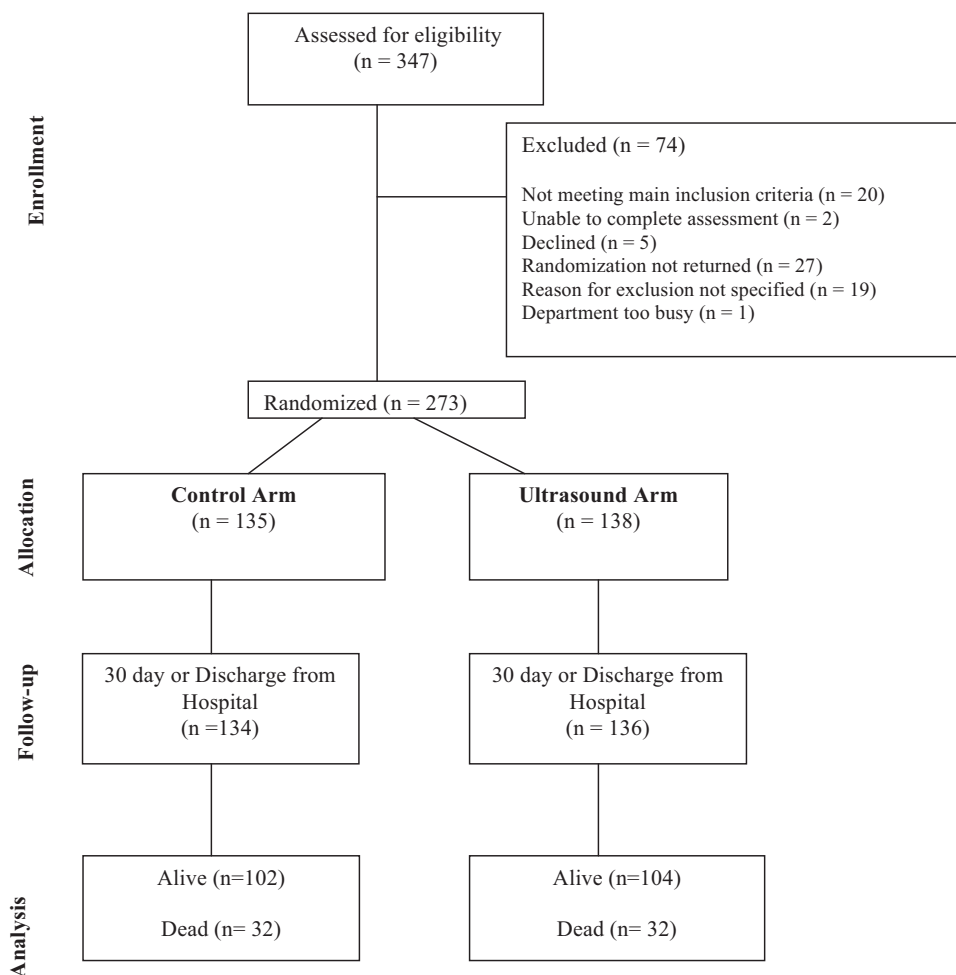


Figure 2. CONSORT flow diagram.

Table 1. Baseline demographic profile of study participants.

Group	PoCUS	Control
Total participants (n)	138	135
North America, No. (%; binomial 95% CI)	90 (65.2; 56.6–73.1)	89 (65.9; 57.2–73.8)
South Africa, No. (%; binomial 95% CI)	48 (34.8; 26.8–43.3)	46 (34.1; 26.1–42.7)
Men, No. (%; binomial 95% CI)	73 (52.9; 44.2–61.4)	65 (48.1; 39.4–56.9)
Age, median (IQR), y	56 (53.4–59.8)	58.5 (56.2–62.1)
Systolic blood pressure, median (IQR), mm Hg	91.0 (88.5–94.2)	91.8 (89.1–94.8)
Pulse rate, median (IQR), beats/min	106.5 (102.4–111.8)	111.4 (105.8–116.5)
Respiration, median (IQR), breaths/min	24.3 (22.3–26.0)	23.9 (22.8–25.6)
Temperature, median (IQR), °C / F	36.7 (36.5–36.9) / 98.1 (97.7–98.4)	36.8 (36.6–37.0) / 98.2 (97.9–98.6)
Category of shock, No. (%; binomial 95% CI)		
Cardiogenic	15 (10.8; 6.2–17.3)	13 (9.6; 5.2–15.9)
Noncardiogenic	121 (87.6; 81.0–92.6)	118 (87.4; 80.6–92.5)
Both	1 (0.7; 0.0–3.9)	0 (0.0; 0.0–2.7)
Uncertain	1 (0.7; 0.0–3.9)	4 (3.0; 0.8–7.4)

PoCUS, Point-of-care ultrasonography.

shock diagnosis based on blinded chart review (Table 1) and diagnoses (Table 2) were similar in both groups. The majority of cases (87.6%) were categorized as noncardiogenic, with sepsis the most common diagnosis, making up 52% of cases overall. There was heterogeneity between sites, although not between study groups. South African sites had a higher incidence of sepsis, whereas North American sites had a higher rate of severe dehydration (Table 2).

One hundred thirty-eight patients in the point-of-care ultrasonography group received a standardized point-of-care ultrasonography protocol. All patients had cardiac, base of lung, inferior vena cava, aorta, abdominal, and pelvic scans attempted. Commonly reported abnormal findings included small-volume inferior vena cava (71; 55%), collapsing inferior vena cava (65; 50%), hyperdynamic left ventricular function (60; 44%), pericardial effusion (24; 18%), noncollapsing inferior vena cava (19; 15%), pleural fluid (19; 14%), hypodynamic left ventricular function (17; 13%), peritoneal fluid (13; 9%), and abdominal aortic aneurysm (5; 4%). Ultrasonographic findings are further described in detail in Table E1, available online at <http://www.annemergmed.com>.

We found no important difference between groups for the primary outcome of survival to 30 days or hospital discharge for the 270 patients (98.9%) for whom follow-up

was complete. One hundred four of 136 patients (76.5%; 95% CI 68.4% to 83.3%) in the point-of-care ultrasonography group survived compared with 102 of 134 patients (76.1%; 95% CI 68.0% to 83.1%) in the control group (difference 0.35%; 95% CI –10.2% to 11.0%) (Table 3).

Subgroup analysis by recruitment site showed a lower survival rate overall at South African centers, with 58 of 93 patients (62.4%; 95% CI 51.7% to 72.2%) surviving compared with 148 of 177 (83.6%; 95% CI 77.3% to 88.7%) at North American centers (Table 3). However, there was no survival difference between the point-of-care ultrasonography and control groups at either group of sites; 76 of 89 patients survived in the North American point-of-care ultrasonography group compared with 72 of 88 in the control group, a difference of 3.6% (95% CI –8.1% to 15.3%), whereas 28 of 47 survived in the South African point-of-care ultrasonography group compared with 30 of 46 in the control group, a difference of –5.6% (95% CI –26.0% to 15.2%).

The median volume of intravenous fluid administered during the 4-hour ED resuscitation phase was similar in each group (point-of-care ultrasonography 1,611 mL [IQR 1,467 to 1,883 mL] versus control 1,676 [IQR 1,402 to 1,926 mL]) from 255 patients when data were available.

After final chart review, data on inotrope administration were available for 271 patients (134 patients in the control group, 137 in the point-of-care ultrasonography group). Rates were similar in each group, with 17 of 132 patients (12.9%; 95% CI 8.3% to 20.1%) in the point-of-care ultrasonography group and 12 of 129 (9.3%; 95% CI 5.4% to 16.3%) in the control group receiving inotropes (difference 3.6%; 95% CI –4.1% to 11.2%).

Data on CT scanning were available for 271 patients. Rates of CT scanning did not differ significantly between groups, with 36 of 137 patients (26.3%; binomial 95% CI 20.4% to 33.6%) receiving CT in the point-of-care ultrasonography group compared with 32 of 134 (23.9%; binomial 95% CI 18.2% to 28.7%) in the control group (difference 2.4%; 95% CI –7.9% to 12.7%).

Hospital admission rates did not differ significantly between groups, with 113 of 138 patients (81.8%; binomial 95% CI 74.4% to 87.9%) admitted in the point-of-care ultrasonography group compared with 113 of 135 patients (83.7%; binomial 95% CI 76.3% to 89.5%) in the control group (difference 1.9%; 95% CI –7.7% to 11.3%). Admissions directly to a higher level of care (ICU/high-dependency-level bed or operating room) did not differ meaningfully between groups, with 21 patients in the point-of-care ultrasonography group (18.5%; binomial 95% CI 11.9% to 26.9%) and 16 patients in the control

Table 2. Diagnostic category list: final diagnoses based on blinded independent chart review.

Final Diagnosis (Total and by Region)	Ultrasonography (n/138) (%; Binomial 95% CI)	Control (n/135) (%; Binomial 95% CI)
Sepsis		
Total	74 (53.6; 40.9–62.1)	68 (50.4; 37.6–59.1)
North America	38 (42.2; 31.8–53.1)	37 (41.5; 31.2–52.5)
South Africa	36 (75; 60.4–86.3)	31 (67.3; 51.9–80.4)
Severe dehydration		
Total	17 (12.3; 7.3–19.0)	20 (14.8; 9.3–21.9)
North America	17 (18.9; 11.4–28.5)	17 (19.1; 11.5–28.8)
South Africa	0 (0; 0–7.4)	3 (6.5; 1.3–17.9)
Left ventricular failure/myocardial ischemia		
Total	10 (7.2; 3.5–12.9)	12 (8.9; 4.6–15.0)
North America	7 (7.7; 3.1–15.3)	8 (9.0; 4.0–16.9)
South Africa	3 (6.2; 1.3–17.2)	4 (8.7; 2.4–20.8)
Abdominal inflammation and infection		
Total	8 (5.8; 2.5–11.1)	11 (8.1; 4.1–14.1)
North America	6 (6.6; 2.5–14.0)	9 (10.1; 4.7–18.3)
South Africa	2 (4.1; 0.5–14.2)	2 (4.3; 0.5–14.8)
Autonomic dysfunction		
Total	3 (2.1; 0.4–6.2)	7 (5.2; 2.1–10.4)
North America	2 (2.2; 0.2–7.8)	6 (6.7; 2.5–14.1)
South Africa	1 (2.1; 0–11.0)	1 (2.1; 0–11.5)
Occult hemorrhage bleeding		
Total	3 (2.1; 0.4–6.2)	6 (4.4; 1.6–9.4)
North America	3 (3.3; 0.7–9.4)	6 (6.7; 2.5–14.1)
South Africa	0 (0; 0–7.4)	0 (0; 0–7.7)
Venous thromboembolic disease		
Total	6 (4.3; 1.6–9.2)	1 (0.74; 0.02–4.1)
North America	4 (4.4; 1.2–11.0)	1 (1.1; 0–6.1)
South Africa	2 (4.1; 0.5–14.2)	0 (0; 0–7.7)
Dysrhythmia		
Total	4 (2.9; 0.8–7.2)	1 (0.74; 0.02–4.1)
North America	3 (3.3; 0.7–9.4)	1 (1.1; 0–6.1)
South Africa	1 (2.1; 0–11.0)	0 (0; 0–7.7)
Neurogenic shock		
Total	1 (0.7; 0–4.0)	2 (1.5; 0.1–5.3)
North America	1 (1.1; 0–6.0)	1 (1.1; 0–6.1)
South Africa	0 (0; 0–7.4)	1 (2.1; 0–11.5)
Anaphylaxis		
Total	1 (0.7; 0–4.0)	1 (4.4; 1.6–9.4)
North America	1 (1.1; 0–6.0)	1 (1.1; 0–6.1)
South Africa	0 (0; 0–7.4)	0 (0; 0–7.7)
Occult medication error/overdose		
Total	1 (0.7; 0–4.0)	0 (0; 0–2.7)
North America	1 (1.1; 0–6.0)	0 (0; 0–4.0)
South Africa	0 (0; 0–7.4)	0 (0; 0–7.7)
Mesenteric ischemia		
Total	0 (0.7; 0–4.0)	1 (4.4; 1.6–9.4)
North America	0 (0; 0–4.0)	1 (1.1; 0–6.1)
South Africa	0 (0; 0–7.4)	0 (0; 0–7.7)
Aneurysm/aortic dissection		
Total	2 (1.4; 0.1–5.1)	0 (0; 0–2.7)
North America	2 (2.2; 0.2–7.8)	0 (0; 0–4.0)
South Africa	0 (0; 0–7.4)	0 (0; 0–7.7)
Tension pneumothorax		
Total	1 (0.7; 0–4)	0 (0; 0–2.7)
North America	0 (0; 0–4.0)	0 (0; 0–4.0)
South Africa	1 (2.1; 0–11.0)	0 (0; 0–7.7)
Cardiac tamponade/effusion		
Total	1 (0.7; 0–4.0)	1 (4.4; 1.6–9.4)
North America	1 (1.1; 0–6.0)	1 (1.1; 0–6.1)
South Africa	0 (0; 0–7.4)	0 (0; 0–7.7)

Table 2. Continued.

Final Diagnosis (Total and by Region)	Ultrasonography (n/138) (%; Binomial 95% CI)	Control (n/135) (%; Binomial 95% CI)
Other		
Total	4 (3.0; 0.8–7.3)	3 (2.2; 0.4–6.3)
North America	3 (3.3; 0.7–9.4)	0 (0; 0–4.0)
South Africa	1 (2.1; 0–11.0)	3 (6.5; 1.3–18.0)
Lost to follow-up/incomplete		
Total	2 (1.4; 0.1–5.1)	1 (4.4; 1.6–9.4)
North America	1 (1.1; 0–6.0)	0 (0; 0–4.0)
South Africa	1 (2.1; 0–11.0)	1 (2.1; 0–11.5)

group (14.1%; binomial CI 8.3% to 22%), a difference of 4.4% (95% CI –6.1% to 14.8%).

The overall hospital length of stay was similar in each group, with a median of 9.59 days (IQR 8.15 to 10.86 days) in the point-of-care ultrasonography group compared with 9.71 days (IQR 7.84 to 12.26 days) in the control group, a difference of 0.12 days (IQR –1.74 to 2.36 days). The ICU length of stay was also similar in each group, with a median of 7.16 days (IQR 4.68 to 10.62 days) in the point-of-care ultrasonography group compared with 5.14 days (IQR 3.68 to 8.66 days) in the control group, a difference of 2.02 days (IQR –0.85 to 4.63 days).

Table 3 summarizes all primary and secondary outcomes.

LIMITATIONS

This remains a small study, with a significant number of exclusion criteria. We had initially planned to recruit 400 patients; however, because of the slowing rate of recruitment, concerns about randomization to the control group from physicians, and the perceived futility of continuing at interim analysis as we approached two thirds of anticipated numbers of patients, the research ethics

board advised stopping recruitment at the point reported. Despite the smaller final sample size, study power should not be a major concern. The actual observed difference in survival, the absolute risk reduction, is 0.35% (binomial 95% CI –10.2% to 11.0%). The associated number needed to benefit would be 285 (binomial 95% CI –10.2% to 9.5%, or number needed to benefit 9.5 to infinity, and number needed to harm 10.2 to infinity). As such, we cannot say with 95% certainty whether point-of-care ultrasonography is harmful, has no effect, or is beneficial compared with control, consistent with the research ethics board declaration of futility.

During the study design phase, because point-of-care ultrasonography had become more commonly used in EDs, there were initial ethical concerns about randomizing certain patients to the control group and restricting their access to point-of-care ultrasonography during their assessment. This led the study group to exclude pregnant patients with possible ruptured ectopic pregnancies and those with a high clinical suspicion for abdominal aortic aneurysm. In addition, patients with ST-segment elevation myocardial infarction on ECG and those with a “clear mechanism” of shock were also excluded. This resulted in

Table 3. Outcomes postintervention.

Group	PoCUS	Control	Difference in Proportion/Median, % (95% CI)
Total patients randomized, n	138	135	
Overall survival to 30 days/discharge, n*	104/136	102/134	0.35 (–10.2 to 11.0)
Survival North America, n	76/89	72/88	3.6 (–8.1 to 15.3)
Survival South Africa	28/47	30/46	5.6 (–15.2 to 26.0)
Intravenous fluid administered, median (IQR), mL	1,609 (1,412 to 1,816)	1,683 (1,456 to 1,924)	74 (–50.8 to 196.2)
Patients receiving inotropes, n	17/132	12/129	3.6 (–4.6 to 11.8)
CT scans performed, n	36/137	32/134	2.4 (–8.4 to 13.1)
Hospital admission, n	113/138	113/135	1.8 (–7.7 to 11.2)
Hospital length of stay, median (IQR), days	9.59 (8.15 to 10.86)	9.71 (7.84 to 12.26)	0.12 (–1.74 to 2.36)
ICU admissions, n	21/113	16/113	4.4 (–5.9 to 14.6)
ICU length of stay, median (IQR), days	7.16 (4.68 to 10.62)	5.14 (3.68 to 8.66)	2.018 (–0.85 to 4.63)
Lost to follow-up, n	2/138	1/135	0.06 (–2.9 to 4.4)

*Primary outcome.

randomizing only patients with truly undifferentiated or occult shock. The exclusion of these obvious suspected pathologies requiring critical therapeutic interventions may have detracted from any potential survival benefit with point-of-care ultrasonography use. The early adoption of point-of-care ultrasonography into emergency medicine before the completion of randomized controlled trials has limited the scope of this trial and any potential future comparative trials for point-of-care ultrasonography.

Making the diagnosis of occult sepsis (the ultimate diagnosis of more than half of the patients recruited) during initial resuscitation in the ED is difficult because such patients can have myriad point-of-care ultrasonography findings, depending on their premorbid status and their unique response to sepsis. The result is a spectrum of nonspecific point-of-care ultrasonography findings ranging from hyperdynamic to hypodynamic left ventricular function with variable inferior vena cava calibers, in addition to any preshock findings such as ascites or pleural effusions. In such settings, point-of-care ultrasonography may enable one to rule out critical diagnoses such as tamponade and abdominal aortic aneurysm, but may fall short of delivering the specific diagnosis.

In terms of sonographer skill levels, this study represents actual standards. All physicians performing point-of-care ultrasonography were trained, and each site had used local processes to confirm credentialing, qualifications, and skill level for ultrasonography. However, as demonstrated in Table E1 (available online at <http://www.annemergmed.com>), some physicians were at times not able to generate a complete point-of-care ultrasonography protocol with conclusive views. This could have negated any potential benefit in the point-of-care ultrasonography group, an issue that is difficult to resolve without all sites being fully staffed with ultrasonography experts, and one likely to reflect actual practice. Future work would benefit from storage of ultrasonography video clips for review and quality assurance. Having limited numbers of trained staff resulted in slower recruitment at some sites in particular.

Baseline characteristics were similar between the control and intervention groups for age and presenting vital signs, although there was significant heterogeneity between the North American and Southern African sites, with higher rates of sepsis in South Africa and more severe dehydration in North America, in addition to higher mortality overall at South African sites. Although this may limit the generalizability of the results, there was still no important outcome difference when point-of-care ultrasonography was compared with the control group at any site or when Southern African cohorts were compared with North American ones.

Finally, our point-of-care ultrasonography protocol did not include specific interrogation for anterior pneumothorax, interstitial syndrome, or consolidation, although it did not prohibit looking for these and did use base-of-lung ultrasonography to look for fluid. As point-of-care ultrasonography use develops, perhaps a future comparative study could include these parameters, as outlined in the recently published International Federation for Emergency Medicine - Sonography in Hypotension and Cardiac Arrest consensus statement.²⁶

DISCUSSION

In this international randomized controlled trial, we found no important benefit with the addition of a point-of-care ultrasonography protocol for our primary outcome of survival to 30 days or hospital discharge for patients presenting to the ED in shock with undifferentiated hypotension. The findings are similar to those of a previous comparative trial of a point-of-care ultrasonography protocol versus standard care in trauma patients,²¹ in which there was also no significant survival benefit for patients in the point-of-care ultrasonography group. Our study showed no important difference in the clinical secondary outcomes, with similar admission rates, need for ICU care and length of stay in both groups. There was also no important difference in the amount of intravenous fluids administered, inotrope use, or CT scans ordered.

These results suggest that despite the additional information provided by the point-of-care ultrasonography protocol for patients in the intervention group, and without any point-of-care ultrasonography performed in the control group, all patients ultimately received similar care and had similar outcomes. Point-of-care ultrasonography is not a therapeutic intervention, and as such it may be unrealistic to expect the addition of this diagnostic tool to affect clinical outcomes such as length of stay or survival. There are several hypotheses that may explain this further.

First, it is possible that although point-of-care ultrasonography provides a high rate of abnormal findings, these pathologies are equally detectable by standard methods, without the use of point-of-care ultrasonography. As demonstrated by use of CT scanning in both groups, the comparison was not to discriminate between diagnostic point-of-care ultrasonography and no investigations, but rather between point-of-care ultrasonography and usual standard of care, which often included comprehensive laboratory and advanced imaging resources. However, there was no apparent advantage for patients in the point-of-care ultrasonography group in South Africa, where it could be argued that any benefit would be most apparent because of

the nature of the underresourced public health care setting, and with delayed access to advanced imaging.

Second, it is possible that the average emergency clinician is already adept at managing patients with undifferentiated shock. Perhaps careful clinical evaluation, review of standard investigations, and reassessment of the patient promptly after initial interventions (as was done in the study) would have an effect similar to that of performing a bedside ultrasonography protocol.

Of course, this does not detract from the potential benefits of point-of-care ultrasonography in the prompt diagnosis of certain critical conditions such as pericardial tamponade or aortic aneurysm, when early diagnosis and rapid management are essential. However, these reversible “point-of-care ultrasonography–dependent” pathologies were rare in our series; thus, the incidence may be insufficient to provide the point-of-care ultrasonography group with any advantage. One might argue that even a single unanticipated emergency procedure would justify the use of point-of-care ultrasonography in critically ill patients.

This study was shaped by and contributes to the evolving definition of the patient with undifferentiated shock. By the very nature of the inclusion and exclusion criteria, how a clinician determines undifferentiated shock necessarily changes when point-of-care ultrasonography equipment is at the ready. For example, patients with suspected abdominal aortic aneurysm or ruptured ectopic pregnancy remained undifferentiated in EDs for hours until the integration of point-of-care ultrasonography in modern practice. Contrast this with our study, in which such patients were deemed ineligible for randomization because inclusion in the non–point-of-care ultrasonography (control) arm would have denied them the previously reported benefit from resuscitative point-of-care ultrasonography.^{27,28} At what point a suspicion for a given diagnosis becomes high remains undefined and will be a potential source of contention facing future studies in this field. If a patient in shock arrives with lower limb immobilization, one could argue that an obstructive process (massive pulmonary embolism) is more likely and thus the patient is likely to benefit from rapid identification of acute right ventricular strain. These examples raise questions in regard to the threshold for presumptive diagnoses in shock and hypotension. On one hand, one could make the argument that until some clear diagnostic marker is obtained (ECG, blood glucose level, chest radiograph, or point-of-care ultrasonography), the majority of shock patients are undifferentiated until proven otherwise. If this is the case, designing randomized controlled trials will prove challenging because clinicians may struggle with the implications of not using point-of-care ultrasonography

early in the assessment of these patients. On the other hand, as is the case in this study, attempts can be made to designate a proportion of shock patients as truly undifferentiated. In this study, through the use of ECG, history, and patient demographics, several potential patients became no longer undifferentiated despite that a solid diagnosis had yet to be established. This may have had a significant effect on the study results. For example, more than half of all patients enrolled eventually received a diagnosis of occult sepsis as a cause of shock. It is unknown whether this high prevalence of occult sepsis is actually representative of patients with undifferentiated shock or whether this is more a reflection of our stringent inclusion and exclusion criteria, which excluded patients in whom a clear underlying cause was suspected at presentation. We do know that similar numbers were found in a Cochrane review,²⁹ which showed that 60% of patients with undifferentiated shock who were admitted to the ICU were ultimately found to have occult sepsis. This implies that the study inclusion and exclusion criteria had a significant effect on screening out patients with other forms of shock, almost on par with a complete preadmission evaluation. In doing so, the study may have excluded patients who might have received benefits from point-of-care ultrasonography because of other causes of shock. Furthermore, with such a high predominance of occult sepsis in patients with undifferentiated shock, it may have been beneficial for the study to incorporate serial ultrasonographic scans in the point-of-care ultrasonography protocol arm, especially when the secondary outcome for intravenous fluid use was examined. One might argue that serial volume assessments in septic shock might have a direct correlation to mortality.

Our findings may reflect that the use of point-of-care ultrasonography should be targeted to answer specific clinical questions that are relevant to each particular patient, rather than following a one-size-fits-all protocol. We, along with other members of the International Federation for Emergency Medicine Ultrasound Interest Group, have begun work on creating and validating such a targeted approach that promotes the use of ultrasonography to help categorize the type of shock, assess fluid requirement, and rule out critical diagnoses relevant to each patient’s risk profile.²⁶

Because there is no evidence of harm, point-of-care ultrasonography protocols can continue to be safely integrated into clinical use as an extension of the physical examination and a guide to patient management.

To our knowledge, this is the first randomized controlled trial to compare point-of-care ultrasonography with standard care for undifferentiated hypotensive ED patients. We did not find any important survival benefits

with the use of a point-of-care ultrasonography protocol, although a larger study including more point-of-care ultrasonography-sensitive diagnoses is required to confirm these findings. We found no important differences in ICU admission rates, hospital lengths of stay, rates of inotrope use, volumes of intravenous fluid administered, or rates of use of advanced investigations.

Although point-of-care ultrasonography may have early diagnostic accuracy for specific pathologies and may provide a noninvasive way to assess cardiovascular status, these may not translate directly into differences in treatment and ultimately into a survival benefit effect for ED patients with undifferentiated hypotension who are undergoing a point-of-care ultrasonography shock protocol.

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centers and patients and managed the data, including quality control. GS and PA provided statistical advice on study design and analyzed the data. PA, DL, DAL, MP, LT, and LR drafted the manuscript, and all authors contributed substantially to its revision. PA takes responsibility for the paper as a whole.

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