Monitoring modalities and assessment of fluid status: A practice management guideline from the Eastern Association for the Surgery of Trauma

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BACKGROUND: Fluid administration in critically ill surgical patients must be closely monitored to avoid complications. Resuscitation guided by invasive methods are not consistently associated with improved outcomes. As such, there has been increased use of focused ultrasound and Arterial Pulse Waveform Analysis (APWA) to monitor and aid resuscitation. An assessment of these methods using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework is presented.

METHODS: A subsection of the Surgical Critical Care Task Force of the Practice Management Guideline Committee of EAST conducted two systematic reviews to address the use of focused ultrasound and APWA in surgical patients being evaluated for shock. Six population, intervention, comparator, and outcome (PICO) questions were generated. Critical outcomes were prediction of fluid responsiveness, reductions in organ failures or complications and mortality. Forest plots were generated for summary data and GRADE methodology was used to assess for quality of the evidence. Reviews are registered in PROSPERO, the International Prospective Register of Systematic Reviews (42015032402 and 42015032530).

RESULTS: Twelve focused ultrasound studies and 20 APWA investigations met inclusion criteria. The appropriateness of focused ultrasound or APWA-based protocols to predict fluid responsiveness varied widely by study groups. Results were mixed in the one focused ultrasound study and 9 APWA studies addressing reductions in organ failures or complications. There was no mortality advantage of either modality versus standard care. Quality of the evidence was considered very low to low across all PICO questions.

CONCLUSION: Focused ultrasound and APWA compare favorably to standard methods of evaluation but only in specific clinical settings. Therefore, conditional recommendations are made for the use of these modalities in surgical patients being evaluated for shock. (*J Trauma Acute Care Surg.* 2018;84: 37–49. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Systematic Review, level II.

KEY WORDS: Focused ultrasound; arterial pulse waveform analysis; shock; resuscitation; critical care; organ failure.

Liberal fluid administration can be associated with pulmonary dysfunction, organ failures, coagulopathy, and infectious complications.[1] Evidence neither supports central venous pressure (CVP) measurements,[2,3] nor the necessity for the pulmonary artery catheter to safely guide resuscitation.[4–6] There has been a shift to less invasive dynamic measures to monitor fluid status.[7–9] However, many of these modalities have not undergone comparison.[10] Administering a "fluid challenge" remains variable and frequently ill-advised.[11] Guidelines for early goal-directed therapy in sepsis call for frequent fluid assessments but do not specify methodology.[12] There is a need for tools to guide resuscitations. Using the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) process,[13] we performed a systematic review to define the role of focused ultrasound and Arterial Pulse Waveform Analysis (APWA) for surgical patients in shock.

Focused Ultrasound

Focused ultrasound is common in critical care.[14,15] It is used for risk stratification,[16] shock in the emergency department (ED),[17] treatment of sepsis[18] and trauma resuscitation.[19,20] Variations include, limited transthoracic echocardiogram ("LTTE"),[21] rapid ultrasound in shock-velocity time integral,[22] and Bedside Echocardiographic Assessment in Trauma/Critical Care.[23] In all variants,[24] the test is clinician performed for a specific problem, with a limited number of potential diagnoses, and can include noncardiac images. Expert reviews have recommended focused ultrasound to monitor resuscitation in various shock states.[15,24,25] However, other technologies exist,[26] previous strong recommendations are not specific to surgical resuscitations and are based on variable data. The optimal method for hemodynamic monitoring remains elusive[24] despite growing acceptance of

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focused ultrasound. Further, a large international evidence based review urged caution for the use of focused ultrasound to predict fluid responsiveness despite advocating for wider use.[14]

Arterial Pulse Waveform Analysis

Wesseling et al.[27] described a method to predict aortic flow, stroke volume variation (SVV) and, therefore, fluid responsiveness, using APWA. The Vigileo, FloTrac device (Edwards Lifesciences, Irvine, CA) utilizes algorithms to determine SVV, from standard deviations of the pulse pressure. The Pulse Contour Cardiac Output system ("PiCCO"; Pulsion SG, Munich), renders cardiac output (CO) by measuring the area of the systolic waveform and aortic impedance. This system also provides for calibration of CO via transpulmonary thermodilution. The LiDCO device (LiDCO Ltd, Cambridge) renders CO derived from pulse power analysis with lithium indicator method calibration. With an increasing permeation of these devices, clinicians require an awareness of their indications and limitations.[26]

Six population [P], intervention [I], comparator [C], and outcome [O] (PICO) questions[13] are addressed in this guideline:

PICO question 1:

In surgical patients being evaluated for shock [P], should a protocol that includes focused ultrasound [I] be utilized versus a standard protocol [C] to predict fluid responsiveness [O]?

PICO 2:

In surgical patients being resuscitated from shock [P], should a protocol that includes focused ultrasound [I] be utilized versus a standard protocol [I] to reduce organ failures or complications [O]?

PICO 3:

In surgical patients being resuscitated from shock [P], should a protocol that includes focused ultrasound [I] be utilized versus a standard protocol [C] to reduce mortality [O]?

PICO question 4:

In surgical patients being evaluated for shock [P], should a protocol that includes APWA [I] be utilized versus a standard protocol [C] to predict fluid responsiveness [O]?

PICO question 5:

In surgical patients being resuscitated from shock [P], should a protocol that includes APWA [I] be utilized versus a standard protocol [C] to reduce organ failures or complications [O]?

PICO question 6:

In surgical patients being resuscitated from shock [P], should a protocol that includes APWA [I] be utilized versus a standard protocol [C] to reduce mortality [O]?

INCLUSION AND EXCLUSION CRITERIA

Study Types

We included prospective randomized trials, case control studies, prospective observational studies, retrospective observational trials, and cohort studies with comparator groups.

Participant and Setting Types (Population, P)

We included adult surgical patients being evaluated for shock. This included hemodynamic instability or other indications for which fluid administration was considered. We also included studies of nonsurgical populations if the predominant diagnosis was severe sepsis, but downgraded the evidence for indirectness.[26] We restricted our settings to the ED, the intensive care unit (ICU) and the operating room. However, since resuscitation from shock should be rare in the elective operative setting, we downgraded the level of evidence in these studies.[28]

Intervention Type(s) (I)

We included studies addressing the use of focused ultrasound or APWA for resuscitative guidance. We excluded studies addressing focused assessment with sonography for trauma or pulse pressure variation (PPV) as we considered these discrete modalities.

Comparison Type(s) (C)

Studies comparing focused ultrasound or APWA to static variables (CVP, pulmonary artery occlusion pressure [PAOP], vital signs) were included in quantitative analysis. We included studies where the comparator was "standard management" but downgraded for bias concerns since protocols were inconsistently defined. We included studies where the comparator was PPV. We excluded comparisons of focused ultrasound to APWA.

Outcome Measure Types (O)

In accordance with GRADE,[13] critical outcomes of mortality, fluid responsiveness and organ failure were selected by the working group. Fluid responsiveness was assessed by CO, stroke volume or any determinant, such as velocity time integrals (VTI). We analyzed organ failures and complications in aggregate since there were a low number of studies that addressed organ failures alone.[29] We then downgraded the evidence for this surrogate outcome.[28]

METHODS

Search Strategy

Two searches of PubMed, MEDLINE and the Cochrane Register of Controlled Trials for articles published from January 1, 1992, to December 31, 2016, were performed. The focused ultrasound search included the terms: *Bedside Ultrasound, Hemodynamic Ultrasound, focused ultrasound, Point of Care Ultrasound, ICU ultrasound, Limited Ultrasound, Fluid responsiveness, Resuscitation, and Echocardiography.* The APWA search included the terms: *Arterial waveform analysis, Stroke Volume Variation, Systolic Pressure Variation, noninvasive monitoring, Arterial Pressure Waveform Analysis, Pulse Power Analysis, Pulse Contour Analysis, Transpulmonary Thermodilution, LiDCO, PiCCO, FloTrac, and fluid responsiveness.* The "related articles" function and manual review of bibliographies were used to broaden the search.

Study Selection

A team member (D.S.P.) accessed all abstracts and assessed general relevance to our review. A second team member (D.Y.K.) reviewed the determinations. A third team member was available for disagreements. Reviews, case reports, technical papers, letters to the editor, and non-English language publications were excluded. Abstracts were distributed among team members and full text articles were accessed if considered appropriate.

Data Extraction and Management

Data including methodology, population, and outcome, was entered into Review Manager (RevMan) (Version 5.3: Cochrane Collaboration, Oxford). Forest plots were generated when appropriate. The data for fluid responsiveness were used to generate evidence tables.

Assessment of Methodological Quality and Recommendations

Data were entered into GRADEpro (Version 3.2, Cochrane Collaboration, Oxford) to generate quality of evidence tables. However, since the quality of studies evaluating diagnostic test (DTA) accuracy differ; the QUADAS-2 tool[30] was implemented in RevMan to assess methodological quality for fluid responsiveness studies. QUADAS-2 addresses bias and applicability concerns as "low," "unclear," or "high" across relevant domains. We also considered the risk-benefit of using the modalities and potential patient and clinician preferences. We prefaced strong recommendations with "we recommend," and weak recommendations with "we conditionally recommend."[31]

Data Synthesis and Statistical Analysis

We performed a meta-analysis where adequate data were reported to calculate incidence of our outcomes for comparison. In accordance with recommendations of Cochrane reviews of DTA, pooled sensitivities were not calculated.[32]

RESULTS: FOCUSED ULTRASOUND

Search Results

A total of 151 abstracts were identified (Fig. 1A). After eliminating duplicates, 135 were screened. After exclusions, 47 full text articles were reviewed with 12 studies meeting inclusion criteria.

Results for the Use of Focused Ultrasound for Fluid Responsiveness (PICO 1)

Nine studies (73%), reported on fluid responsiveness with most of the population (540 [61%]) from a single multicenter ICU study[10] (Table 1A). Three studies were conducted in medical ICUs in patients with severe sepsis. Only one of these studies and three studies in mixed ICUs reported the percentage of surgical patients (32% and 25%–53%). Two studies relate to surgical subspecialties (Neurosurgery and Cardiothoracic) while the remaining study, with 50% incidence of septic shock, was conducted in an ED. Three studies, one in the ED,[38] and two ICU studies[36,40] addressed nonintubated spontaneously breathing patients. Eight studies measured changes in IVC measurements (by TTE), whereas one study measured SVC (by transesophageal echocardiography) as the index test.[39] Three studies compared focused ultrasound to CVP.

Determinants of fluid responsiveness included increases in CO or VTI. However, one study measured systolic blood pressure response and was downgraded for bias concerns.[38] The reference standards (CO, CI, or VTI) were measured by TTE in six studies, TEE in one study, and by transpulmonary thermodilution[35] in the remaining study. All assigned ideal cutoff points after data collection and analysis, incurring additional bias concerns.

One study[37] did not report sensitivities; therefore, only eight studies are included to generate forest plots. Focused ultrasound (Fig. 2A) generally outperformed CVP measures (Fig. 2b). However, four of the nine studies failed to predict fluid responsiveness to predefined tolerance. One of these, in postoperative cardiac patients, showed that focused ultrasound was equivalent to CVP.[37] The three remaining studies that did not demonstrate superiority for focused ultrasound were in spontaneously breathing patients.[36,38,40] In addition, the sensitivities and specificities of the largest study[10] noticeably underperformed compared to smaller previous investigations.

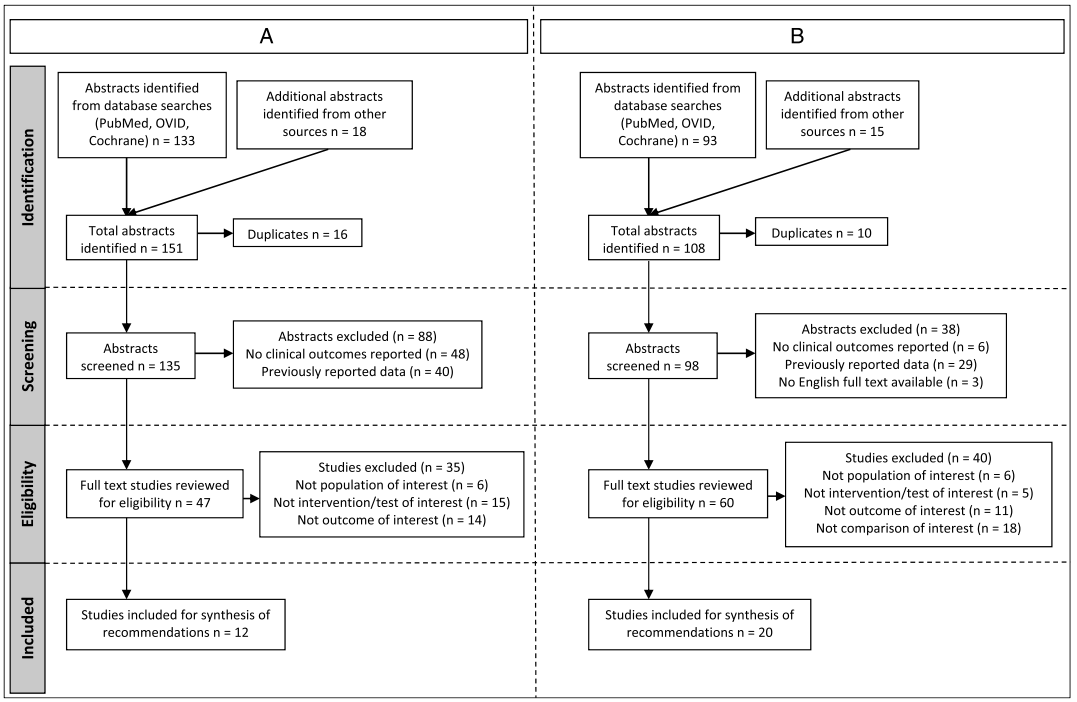

Figure 1. Prisma diagram for systematic review. (*A*) Prisma diagram of focused ultrasound studies. (*B*) Prisma diagram of arterial pulse waveform studies.

TABLE 1. Characteristics of Studies Predicting Fluid Responsiveness

Study	Population	No. Patients	Method	Bolus	Response	Predictor	ROC	Sensitivity	Specificity
(A) Focused ultrasound Studies									
Feissel et al., 2004[33] Prospective	MV Medical ICU-sepsis	39	TTE	8 mL/kg 6% hydroxyethyl 20 minutes	CO ≥ 15%	ΔdIVC 12%	NR	87%	97%
Barbier et al., 2004[34] Prospective	MV Medical ICU-sepsis or ALI	20	TTE	7 mL/kg 4% modified fluid gelatin	CO ≥ 15%	dIVC 18%	0.91	90%	90%
						CVP 7 mmHg	0.57	40%	80%
Moretti and Pizzi, 2010[35] Prospective	MV SAH	20	TTE	7 mL/kg 6% hydroxyethyl over 30 minutes	CI ≥ 15%	dIVC 16%	0.90	71%	100%
						SVV	0.78	NR	NR
						CVP	0.67	59%	50%
Muller et al., 2012[36] Prospective	SB Mixed ICU (88% sepsis, 52% abdominal sepsis or bleeding postoperative or trauma)	40	TTE	500 mL 6% hydroxyethyl over 15 minutes	VTI ≥ 15%	cIVC 40%	0.77	70%	80%
Sobczyk et al., 2015[37] Prospective	MV post-CABG	50	TTE	NR	VTI ≥ 15%	CVP IVCmax dIVC cIVC	NR No difference between responders and nonresponders. Dynamic measures and CVP not useful in this population.	NR	NR
deValk et al., 2014[38] Prospective	SB shock ED (50% sepsis)	45	TTE	500 mL NS over 15 minutes	SBP ≥ 10%	IVC-CI 36.5%	0.741	83%	67%
Vieillard-Baron et al, 2004[39] Prospective	MV Medical ICU-sepsis (32% surgical)	66	TEE	10 mL/kg 6% hydroxyethyl over 30 minutes	VTI ≥ 10%	SVC-CI 36%	0.99	90%	100%
Airapetian et al., 2015[40] Prospective	SB Mixed ICU shock (42% surgical)	59	TTE	PLR and 500 mL NS over 15 minutes	VTI ≥ 10%	cIVC 42%	0.62	31%	97%
Vignon et al., 2016[10] MCPT	MV Mixed ICU shock (75% sepsis, 25% surgical)	540	TTE and TTE	PLR and various	LV VTI ≥ 10%	ΔSVC21%	0.775	61%	84%
						ΔIVC8%	0.635	55%	70%
(B) APWA studies									
Angappan et al., 2015[41]	ICU severe sepsis (surgery % NR)	n = 45 R: 29 NR: 16	FloTrac (third-generation)	500 mL 6% hydroxyethyl starch over 30 minutes	CI ≥ 15% by FloTrac	SVV ≥ 13%	0.72	78%	89%
						CVP (NR)	0.56	NR	NR
Biais et al., 2008[42]	ICU liver transplant patients	n = 35 R:17 NR: 18	FloTrac (second-generation)	20 mL × BMI 4% Albumin	CO ≥ 15% by TTE VTI	SVV ≥ 10%	0.95	94%	94%
						CVP ≥ 3	0.64	58%	50%
						PAOP (NR)	0.60	NR	NR
Cecconi et al., 2012[43]	ICU postoperative major elective GI surgery	n = 31 R: 12 NR: 19	LiDCO plus	250 mL colloid	SV ≥ 15% by LiDCO	SVV ≥ 12.5%	0.84	75%	83%
						CVP (NR)	0.62	NR	NR

Continued next page

Khwannimit and Bhurayanontachai, 2012[44]	ICU septic shock (surgery % NR)	n = 42 R: 24 NR: 18	FloTrac (third-generation)	500 mL 6% hydrocyethyl starch	SVI ≥ 15% by FloTrac	SVV ≥ 10% PPV ≥ 12%	0.92 0.92	92% 83%	83% 83%
Li et al., 2013[45]	Intraoperative elective GI surgery	n = 50 R: 30 NR: 20	FloTrac (third-generation	7 mL/kg hydroxyethyl starch	SVI ≥ 25% by FloTrac	LoTV SVV 9.5% HiTV SVV 9.5% LoTV CVP (NR) HiTV CVP (NR)	0.814 0.85 0.40 0.43	91% 100% NR NR	71% 57% NR NR
Zhao et al. 2015[46]	Intraoperative management of obstructive jaundice	n = 25 R: 12 NR: 13	FloTrac (second-generation)	250 mL 6% hydroxyethyl starch	SVI ≥ 10% by FloTrac	SVV ≥ 10% PPV ≥ 8% CVP (NR)	0.96 0.86 0.52	100% 92% NR	92% 69% NR

ALI, acute lung injury; CABG, Coronary Artery Bypass Graft; CI, Cardiac Index, IVC-CI (caval index); IVCe-IVCi/IVCe; ΔdIVC, IVC max-IVCmin/(IVCmax + IVCmin/2), dIVC (distensibility index) = Dmax-Dmin/Dmin, cIVC (collapsibility index) = Dmax-Dmin/Dmax; MCPT, multicenter prospective trial; MV, mechanically ventilated; NR, "not reported"; PLR, passive leg raise; SB, spontaneously breathing; SAH, subarachnoid hemorrhage; SV, stroke volume; SVI, Stroke Volume Index, SBP, systolic blood pressure; SVC-CI, SVCe-SVCi/SVCe; ΔSVC, SVCe-SVCi/SVCe.

Grading the Evidence PICO Question 1

As per QUADAS 2, risk of bias and applicability concerns were generally "unclear" to "high," and therefore the overall quality of the evidence as it pertains to PICO 1 is considered low.

Recommendations for the Use of Focused Ultrasound for Fluid Responsiveness (PICO 1)

We conditionally recommend the use of focused ultrasound to determine fluid responsiveness in the management of a mixed population of surgical patients being evaluated for shock. There is a lack of clear superiority of focused ultrasound for this outcome. Focused ultrasound is only useful for the clinician with the training and maintenance of the skill to correctly perform the examination and demonstrates an understanding of the populations of patients that are appropriate for this modality.

Results for the Use of Focused Ultrasound to Reduce Complications and Organ Failures and Complications (PICO 2)

An observational cohort in a mixed ICU of mechanically ventilated patients with undifferentiated shock, assessed organ failures or complications.[37] There was a marked increase in stage III acute kidney injury with standard treatment. Focused ultrasound studies were performed by an American College of Cardiology Level II credentialed intensivist. The protocol was based upon "eyeball" assessments of LV function and IVC fluctuations driving resuscitative decisions.

Grading the Evidence PICO Question 2

There was serious risk of bias in this one qualifying study for the use of historical controls and for the ill-defined "eye ball" protocol. Additionally, since the number of surgical patients was not reported, there were indirectness concerns. Although the magnitude of effect appears significant, one could not upgrade this single study. The overall quality of the evidence for PICO 2 is very low (Table 2A).

Recommendations for the Use of Focused Ultrasound to Reduce Organ Failures and Complications (PICO 2)

We conditionally recommend the use of focused ultrasound to decrease organ failures and complications in surgical patients being treated for shock. This is based on a lack of high-quality studies that assess organ failures, whereas the single included study had serious methodological concerns. Dependence on focused ultrasound for the purposes of reductions in complications and organ failure should be discouraged outside of an overall protocol.

Results for the Use of Focused Ultrasound to Reduce Mortality (PICO 3)

Mortality was an outcome in three (25%) studies.[21,47,48] Two were prospective randomized trials while the third was that described for PICO 2.[47] Jones et al[48] randomized ED patients in shock to early versus late focused ultrasound and found that the number of potential diagnoses were lower earlier in the treatment group. However, this did not result in a mortality difference. A trauma study[21] assigned patients in shock to LTTE versus no

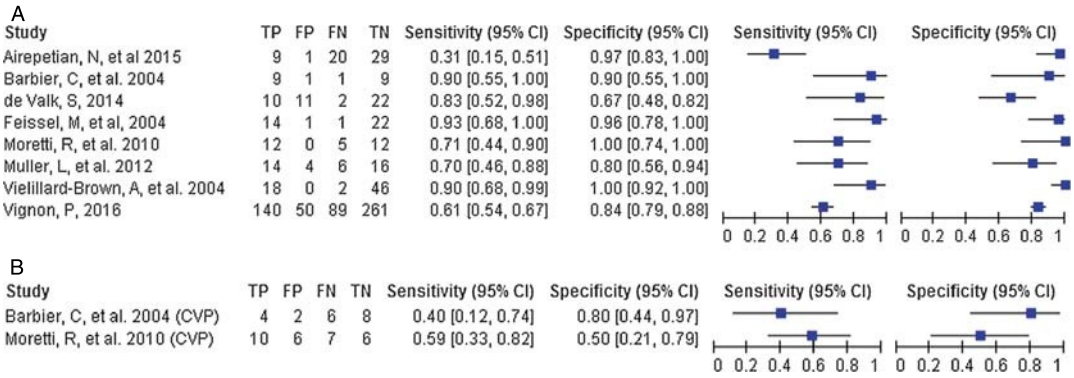

Figure 2. Predictive performance of focused ultrasound versus standard measures to predict fluid responsiveness. (*A*) Sensitivity and specificity of focused ultrasound to predict fluid responsiveness. (*B*) Sensitivity and specificity of CVP to predict fluid responsiveness.

LTTE to assess cardiac function and hypovolemia and guide resuscitation. However, no specific protocols were reported. Mortality trended toward significance but was noteworthy in traumatic brain injury (14.7% vs. 39.5%, $p = 0.03$). Given the low number of heterogeneous studies, no forest plots were generated for this PICO.

Grading the Evidence PICO Question 3

Risk of bias was serious. Only Jones et al.[48] randomized with a computer-generated sequence while others assigned by day of admission[21] or used historical controls.[47] Only one study[21] relates to the population of interest, and one other study did not address the comparison of interest. Therefore, quality was assessed as very low (Table 2B).

Recommendations for the Use of Focused Ultrasound to Reduce Mortality (PICO 3)

We conditionally recommend the use of focused ultrasound to reduce mortality in surgical patients in shock. This is based on the very low quality of studies related to this outcome. Further, focused ultrasound is only one contributor in an overall protocol designed to improve outcomes; however, protocols were not clearly articulated.

DISCUSSION: FOCUSED ULTRASOUND

The lack of randomized trials, heterogeneity and indirectness of included studies contributed to our weak recommendations regarding focused ultrasound. A demonstrable cause and effect relationship is lacking. The use of CVP and other static measures (suboptimal resuscitative tools) as the comparator may also artificially skew evidence in favor of focused ultrasound. The risk of faulty interpretation of the focused ultrasound findings can be high[10,24,49] and can lead to medicolegal consequence.[50] Focused ultrasound has a narrow application profile; having been shown to be inaccurate in the setting of arrhythmias, other cardiac dysfunction, early hemorrhage, and spontaneous breathing.[36–38,40,51–53] Despite these limitations, we would presume that some patients and clinicians may prefer a noninvasive means of monitoring. However, an absolute requirement for the use of focused ultrasound is the appropriate training and maintenance of skill needed to perform the examination, interpret the results and understanding of the limitation of the modality.

Application to Clinical Practice

Since this test is operator-dependent, we would recommend enrolling in any of the professional society courses available. Additionally, one could consider ultrasound certification after demonstrating proficiency in logged cases. Thereafter, the clinician would incorporate focused ultrasound into an existing or new protocol and frequently reassess with ongoing QI. The protocol would vary by patient population and clinical circumstance; however, focused ultrasound can be associated with improved performance in the setting of controlled ventilation in the absence of vasopressors or dysrhythmias.

Future Directions

Further study of the use of focused ultrasound in the resuscitation of surgical patients is critical particularly in acute undifferentiated shock and as an adjunct to subsequent resuscitations. Credentialing and certifications in specific technologies is common (eg, mechanical ventilation, fluoroscopy) and will likely apply to focused ultrasound in the future.

RESULTS: ARTERIAL PULSE WAVEFORM ANALYSIS

Search Results

A total of 108 abstracts were identified (Fig. 1B). After eliminating duplicates, 98 were screened. After exclusions, 60 full text articles were reviewed with 20 studies meeting inclusion criteria.

Results for the Use of APWA to Predict Fluid Responsiveness (PICO 4)

Six studies (30%) addressed fluid responsiveness (Table 1B). Three compare SVV with CVP, whereas one compared SVV with CVP and PAOP.[42] The remaining two compared SVV to PPV. Four ICU studies addressed liver transplant patients,[42] postoperative major GI surgery,[43] and septic shock patients.[41,44] The number of surgical patients was not reported in either of these two septic shock studies. Li et al[45] studied the effect of third-generation FloTrac on intraoperative management of major elective GI surgery, whereas Zhao et al.[46] performed an intraoperative analysis of patients with obstructive jaundice. Three studies assessed third-generation FloTrac, two studies evaluated second-generation FloTrac,[42,46] and the remaining

TABLE 2. Quality Assessment of Studies for Organ Failure or Complications (A) and Mortality (B) Outcomes With Use of Focused Ultrasound

Quality Assessment							No. Patients		Effect			
No. Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	A Focused Ultrasound Guided Protocol	A Standard Protocol	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Organ failures or complications (A)												
1	Observational studies	Serious*	Not serious	Serious**	Not serious	None	65 (68.4%) of 95	88 (94.6%) of 93	OR 0.12 (0.05 to 0.33)	268 fewer per 1,000 (from 93 fewer to 478 fewer)	⊕○○○ VERY LOW	CRITICAL
Mortality (B)												
3	Randomized trial†	Serious‡	Not serious	Very serious§	Serious	None	63 (21.7%) of 290	86 (26.1%) of 329	OR 0.73 (0.49 to 1.09)	56 fewer per 1,000 (from 17 more to 114 fewer)	⊕○○○ VERY LOW	CRITICAL

CI, confidence interval; OR, odds ratio.
*Screening criteria not reported. Unable to blind treatment arm.
**75% sepsis. Number of surgical patients not reported.
†Kanji et al. is a case control study. Ferrada et al. and Jones et al. are prospective randomized studies.
‡Unable to blind treatment arm. Atypical randomization by day of admission. Unclear of consecutive patients were evaluated or enrolled.
§Treatment arms are varied. Protocols not uniformly reported. Technical aspects of the intervention vary. Not clearly populations of interest. Intervention not clearly consistent with PICO question.

referenced the LiDCO device. All patients were mechanically ventilated.

Biais et al.[42] was the only study that used a separate modality (TTE) to measure the reference standard (increases in CO by VTI). The remaining studies utilized FloTrac and LiDCO plus, the study modalities of interest, to measure both the index test and the reference standard introducing unknown confounding. One study compared the APWA device in patients ventilated with traditional versus low tidal volumes showing no difference.[45]

Only one study reported the ideal cutoff for CVP for comparisons.[42] APWA-derived variables generally outperformed non-APWA measures. Forest plots for SVV by APWA and for combined CVP and PPV comparison studies are depicted in Figure 3.

Grading the Evidence PICO Question 4

The quality of evidence domains using QUADAS-2[30] was generally "low" to "unclear." Further, there was high risk of selection bias in two studies where patients were identified on subjective measures for varied indications.[42,44] Applicability concerns were high risk in four (67%) studies. Additionally, unknown confounding is introduced when the same technology is used as the index test and to define the reference standard.

Recommendation for the Use of APWA to Predict Fluid Responsiveness (PICO 4)

We conditionally recommend the use of APWA to predict fluid responsiveness in surgical patients being evaluated for shock. This is based on the concern for applicability and, thus, low quality of the evidence. Similarly, APWA devices should only be used by the clinician who understands its indications and limitations.

Results for the Use of APWA for Reducing Organ Failure and Complications (PICO 5)

Nine (45%) studies referenced organ failures or complications. All were prospective randomized studies except for one retrospective analysis.[54] Seven (78%) investigations were in the intraoperative or early postoperative setting. The remaining were ICU studies. Most studies (55%) analyzed patients undergoing major elective GI surgery while other groups included liver transplant, cardiac surgery, burn and the critically ill patients with severe sepsis. All patients were mechanically ventilated but only three studies reported settings. Two were conventional[55,56] and one utilized "lung protective" modes.[57] Three studies reported organ failures, four reported complications; the remaining reported both. Four reported SOFA scores.

Results are mixed (Fig. 4). Two major elective GI surgery intraoperative studies (second-generation FloTrac) and one elective cardiac intraoperative study (calibrated PiCCO) favored APWA. The remaining studies showed no significant outcome improvement[54,58,59] with two showing a significant disadvantage with APWA.[60,61] Meta-analysis favored APWA, however high heterogeneity ($I^2 = 69\%$) is demonstrated (Fig. 4a). Further, the four studies that reported SOFA scores trended in favor of standard management (Fig. 4b). Investigations showing no advantage to APWA included "atypical" populations [high-risk

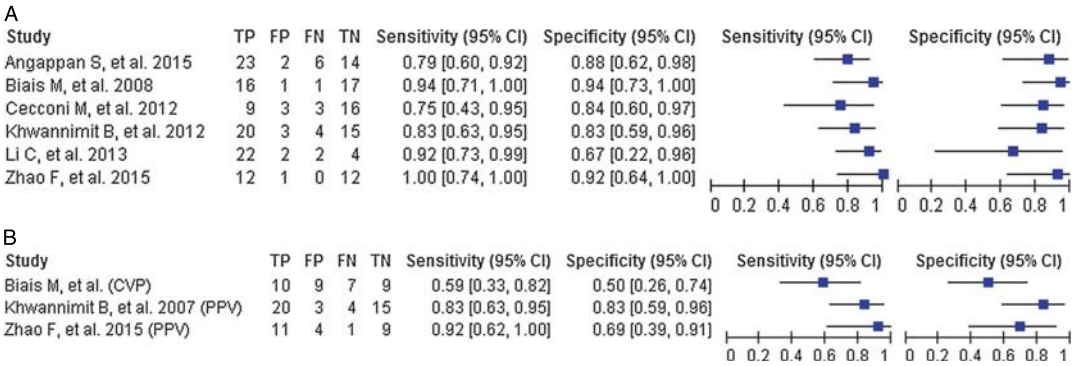

Figure 3. Predictive performance of focused ultrasound versus standard measures to predict fluid responsiveness. (*A*) Sensitivity and specificity of APWA to predict fluid responsiveness. (*B*) Sensitivity and specificity of CVP or PPV to predict fluid responsiveness.

emergency surgery,[60] sepsis with ARDS,[61] liver transplant,[54] burn resuscitations,[56]] and/or the use of an uncalibrated device.[58,59]

Grading the Evidence PICO Question 5

The quality of the evidence was assessed as "low" for this outcome (Table 3A). Results varied across patient populations and the device used, thus indirectness was a significant concern. Studies were small and confidence intervals were wide.

Recommendation for Use of APWA for Reducing Complications and Organ Failures (PICO 5)

We conditionally recommend the use of APWA to decrease complications or organ failures in surgical patients being

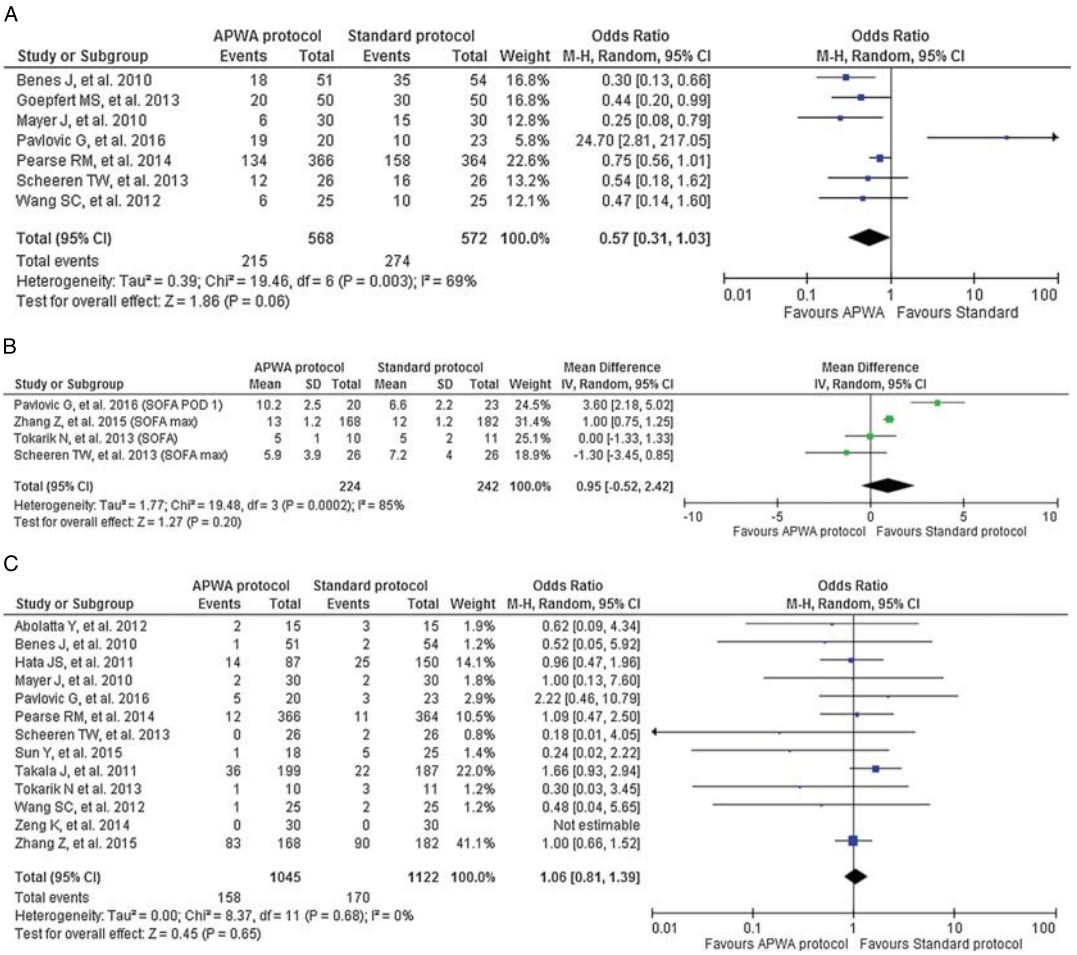

Figure 4. Comparison of APWA versus standard protocols for organ failure, complications and mortality. (*A*) Comparison of APWA versus standard protocols to reduce organ failures or complications. (*B*) Comparison of mean difference of SOFA scores associated with APWA versus standard protocols. (*C*) Comparison of APWA versus standard protocols to reduce mortality.

TABLE 3A. Quality Assessment for Complications and Organ Failure Outcomes (a) and Mortality (b) With the Use of APWA Measurements

Quality Assessment							No. Patients		Effect			
No. Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	A Focused Ultrasound Guided Protocol	A Standard Protocol	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Organ failures or complications												
9	Randomised trials*	Not serious**	Very serious†	Serious‡	Not serious§	Strong association	215 (37.9%) of 568	274 (47.9%) of 572	OR, 0.57 (0.31–1.03)	135 fewer per 1,000 (from 7 more to 257 fewer)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment for organ failures or complications.
*All studies were prospective randomised except for one retrospective study. (Wang et al., 2012).
**Blinding was difficult across all studies due to the nature of the interventions. However, this outcome was generally predefined or assessed by objectively by SOFA scores.
†Results were varied across studies for this outcome. Heterogeneity was high (66% and 85%).
‡Most studies involved intraoperative management while only a small number were in the ICU setting. Composite outcome of complications and organ failures used as a surrogate outcome for organ failures alone.
§Although study size was suboptimal, findings generally were supported by previous data for patient populations.

treated for shock. This is based on the widely varied results across different populations. Although APWA is favored in select patients yielding meta-analysis results that appear favorable, this should be approached with caution given a low number of high-quality studies. However, patients and clinicians may prefer a less-invasive option with a strong understanding of the limitations.

Results for the Use of APWA Devices to Reduce Mortality (PICO 6)

Thirteen (65%) studies reported mortality outcomes. The majority were prospective randomized trials (77%). Nine (75%) were conducted, at least partially, in the ICU while the remaining were intraoperative studies.[55,59,60,62] Of the six intraoperative studies, five involved major elective GI surgery. Six of the nine ICU studies addressed surgical patients exclusively. The remaining studies were conducted in the setting of acute pancreatitis[63] and severe sepsis.[61,64] All patients were mechanically ventilated. No study showed a significant difference for this outcome with APWA or comparator (Fig. 4C).

Grading the Evidence PICO Question 6

Overall grade of the evidence was low (Table 3B). There was concern for indirectness since 50% of studies were conducted intraoperatively or were in the setting of medical critical illness or a low percentage of surgical patients.

Recommendation for the Use of APWA Devices to Decrease Mortality (PICO 6)

We conditionally recommend the use of APWA to reduce mortality. This is based on results that essentially show equivalence to comparators. Any use of APWA mandates a thorough understanding of the narrow clinical application profile supported by published data.

DISCUSSION: APWA

Our recommendations are based on the low quality of the evidence and varied results across populations showing no clear superiority for APWA. The APWA-derived measures may be inaccurate and trend toward inferiority in certain subgroups. Unfortunately, these groups define patients where resuscitative guidance is critical. These include higher acuity abdominal and emergency surgery patients,[58,60,65] severe sepsis,[66–69] burn resuscitations,[56] pressure support ventilation,[68] or any condition where vascular tone is altered due to disease or vasopressors.[54,70–73] APWA is associated with narrow applicability parameters in an acutely unstable mixed population of critically ill.[74] In addition, uncalibrated devices appear to be more prone to error. Further, there is an unknown risk of bias in the many investigations that utilize the same APWA modality to administer the index test as well as to define the reference standard.

Application to Clinical Practice

The technology should be integrated within a resuscitative protocol directed by a clinician who can assimilate the measurements for improved outcomes in the appropriate populations. The new protocol should then undergo ongoing reassessment.

TABLE 3B. Quality Assessment for Complications and Organ Failure Outcomes (a) and Mortality (b) With the Use of APWA Measurements

Quality Assessment							No. Patients		Effect			
No. Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	A Focused Ultrasound Guided Protocol	A Standard Protocol	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Mortality												
13	Randomized trials*	Not serious	Not serious	Serious**	Serious†	None	158/1045 (15.1%)	170/1122 (15.2%)	**OR 1.06** (0.81 to 1.39)	**8 more per 1,000** (from 25 fewer to 47 more)	⊕⊕◯◯ LOW	CRITICAL

Quality assessment for mortality.
*With the exception of Hata et al., Sun et al., and Wang et al. that were retrospective case control studies.
**More than half of studies were intraoperative or were conducted in the setting of medical patients with a very low number of patients with a surgical diagnosis.
†Most studies were small with wide CIs.

TABLE 4. Summary of Recommendations

PICO questions 1, 2, and 3:

In surgical patients being evaluated or treated for shock, we conditionally recommend a protocol that includes Focused ultrasound be utilized versus a standard protocol to predict fluid responsiveness, to reduce complications and organ failures and to reduce mortality.

PICO question 4, 5, and 6:

In surgical patients being evaluated or treated for shock, we conditionally recommend a protocol that includes APWA derived variables be utilized versus a standard protocol to predict fluid responsiveness, to reduce complications and organ failures and to reduce mortality.

Future Directions

Despite an increasing permeation of these devices, the evidence does not clearly support utilization in surgical patients. Further study is essential particularly in higher acuity patients with ongoing comparison of APWA device types.

CONCLUSIONS

Our review reflects the importance of patient selection for focused ultrasound and APWA. Since treatment algorithms were not consistently defined, it was difficult to compare relative performance of focused ultrasound or APWA as diagnostic studies alone or in the context of a treatment protocol. The use of focused ultrasound or APWA requires training and understanding of the measurements as it relates to the specific populations being treated.

A potential weakness of our review is that the acknowledged variability in study types and populations and broad definitions of outcomes make it difficult to address specific knowledge gaps. However, as evidenced by the multitude of focused ultrasound and APWA-based protocols and their use in undifferentiated shock, the review team elected to include the multiple potential roles for these modalities as applied to a broad definition of shock across many populations to identify favorable clinical applications.

Our recommendations are summarized in Table 4. Neither focused ultrasound nor APWA is patently superior to standard protocols in a general population of surgical patients in shock. Therefore, reliance on either or both technologies is not clearly supported for general use. However, with training in identification of appropriate subpopulations, procedural details and interpretation of data, focused ultrasound or APWA can be associated with favorable outcomes when compared with traditional management.

AUTHORSHIP

V.B. participated in the critical revision. W.C. participated in the taskforce leader, review design, critical revision. S.M.G. participated in the review design, critical revision, writing. M.E.H. participated in the review design, critical revision. U.K. participated in the critical revision. D.Y.K. participated in the review design, data collection, critical revision. D.S.P. is the team leader, and participated in the review design, data collection, writing. A.S.R. participated in the review design, critical revision, writing. B.R.H.R. is the chairperson, and participated in the review design, critical review. S.A.T. participated in the review design, critical revision. J.W. participated in the critical revision. B.W. is the taskforce leader and participated in the critical revision.

DISCLOSURE

The authors declare no conflicts of interest.

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