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Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids?

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IMPORTANCE Fluid overload occurring as a consequence of overly aggressive fluid resuscitation may adversely affect outcome in hemodynamically unstable critically ill patients. Therefore, following the initial fluid resuscitation, it is important to identify which patients will benefit from further fluid administration.

OBJECTIVE To identify predictors of fluid responsiveness in hemodynamically unstable patients with signs of inadequate organ perfusion.

DATA SOURCES AND STUDY SELECTION Search of MEDLINE and EMBASE (1966 to June 2016) and reference lists from retrieved articles, previous reviews, and physical examination textbooks for studies that evaluated the diagnostic accuracy of tests to predict fluid responsiveness in hemodynamically unstable adult patients who were defined as having refractory hypotension, signs of organ hypoperfusion, or both. Fluid responsiveness was defined as an increase in cardiac output following intravenous fluid administration.

DATA EXTRACTION Two authors independently abstracted data (sensitivity, specificity, and likelihood ratios [LRs]) and assessed methodological quality. A bivariate mixed-effects binary regression model was used to pool the sensitivities, specificities, and LRs across studies.

RESULTS A total of 50 studies (N = 2260 patients) were analyzed. In all studies, indices were measured before assessment of fluid responsiveness. The mean prevalence of fluid responsiveness was 50% (95% CI, 42%-56%). Findings on physical examination were not predictive of fluid responsiveness with LRs and 95% CIs for each finding crossing 1.0. A low central venous pressure (CVP) (mean threshold <8 mm Hg) was associated with fluid responsiveness (positive LR, 2.6 [95% CI, 1.4-4.6]; pooled specificity, 76%), but a CVP greater than the threshold made fluid responsiveness less likely (negative LR, 0.50 [95% CI, 0.39-0.65]; pooled sensitivity, 62%). Respiratory variation in vena cava diameter measured by ultrasound (distensibility index >15%) predicted fluid responsiveness in a subgroup of patients without spontaneous respiratory efforts (positive LR, 5.3 [95% CI, 1.1-27]; pooled specificity, 85%). Patients with less vena cava distensibility were not as likely to be fluid responsive (negative LR, 0.27 [95% CI, 0.08-0.87]; pooled sensitivity, 77%). Augmentation of cardiac output or related parameters following passive leg raising predicted fluid responsiveness (positive LR, 11 [95% CI, 7.6-17]; pooled specificity, 92%). Conversely, the lack of an increase in cardiac output with passive leg raising identified patients unlikely to be fluid responsive (negative LR, 0.13 [95% CI, 0.07-0.22]; pooled sensitivity, 88%).

CONCLUSIONS AND RELEVANCE Passive leg raising followed by measurement of cardiac output or related parameters may be the most useful test for predicting fluid responsiveness in hemodynamically unstable adults. The usefulness of respiratory variation in the vena cava requires confirmatory studies.

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Clinical Scenario

A 66-year-old woman with a body mass index of 31 (calculated as weight in kilograms divided by height in meters squared) is admitted to the intensive care unit (ICU) with suspected sepsis of pulmonary origin. Following intubation, she was resuscitated with 3 L of Ringer lactate and her systolic blood pressure stabilized at 105 mm Hg. Now, she has been in the ICU for 6 hours. A central venous line and an arterial line have been placed, and she has received another 3 L of Ringer lactate and 0.5 L of 5% albumin. She is lightly sedated and receiving norepinephrine, 0.2 µg/kg/min, to maintain the target mean arterial pressure of 65 mm Hg. Auscultatory examination reveals a few crackles at the posterior bases, and heart sounds are normal. She is receiving pressure support ventilation with an inspiratory fraction of oxygen of 0.5. Arterial hemoglobin oxygen saturation is 90%. Heart rate is 105/min and regular. Her serum lactate is 3.2 mEq/L. Central venous pressure is 8 mm Hg. Her urine output is 0.3 mL/kg/h and creatinine has increased from 1.0 to 1.6 mg/dL since admission. One minute following a passive leg-raising maneuver, her pulse pressure has increased by 7%, and her cardiac output, measured by echocardiography, increases minimally (by <10%). Will she respond to additional fluid administration?

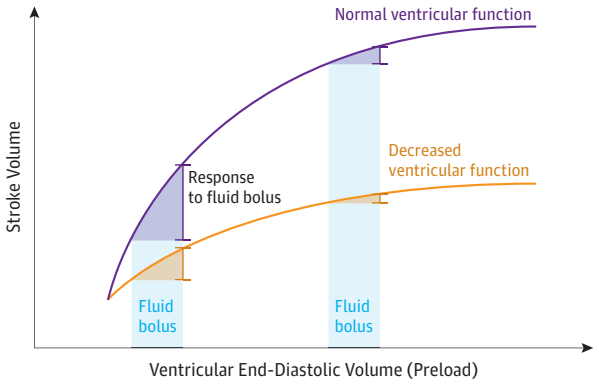
Why Is This Question Important?

Intravenous crystalloids and colloids are given to hemodynamically unstable patients to increase cardiac output and improve tissue perfusion.[1] However, excessive intravenous fluid therapy may create pulmonary and peripheral edema and abdominal and other compartment syndromes and impair oxygen diffusion.[2-8] A primary clinical challenge in every hemodynamically unstable patient is to distinguish accurately between those who will respond to continued fluid administration with increased cardiac output vs those who will not respond, thereby avoiding adverse events from unnecessary intravenous fluid administration. Sepsis is a common cause of hypotension in the critical care unit and associated with high mortality; moreover, the response to fluid resuscitation may also provide prognostic information.[9-11]

Cardiac Output in the Critically Ill

Cardiac output, the product of stroke volume and heart rate, is an important determinant of oxygen delivery. Stroke volume depends on ventricular end-diastolic volume (preload). The relationship between stroke volume and preload is described by the hyperbolic Frank-Starling curve (**Figure 1**).[12] When the heart is operating on the steep portion of the curve, stroke volume increases substantially when preload increases with intravenous fluids, which means administration of fluids improves cardiac output and oxygen delivery. In contrast, when the heart is operating on the flat portion of the curve, further increasing preload with intravenous fluids will not substantially increase stroke volume. The shape of the Frank-Starling curve is dependent on the individual patient's cardiac contractility and afterload.

Figure 1. Effect of Increase in Preload on Stroke Volume of Ventricles With Normal and Decreased Contractility



Frank-Starling curves illustrate that the effect of a given increase in preload on stroke volume is dependent both on ventricular contractility and on baseline preload.

The clinical challenge is to determine whether an individual patient's heart is operating on the steep or flat portion of the Frank-Starling curve.[13,14]

At presentation, hemodynamically unstable patients are commonly hypovolemic and will often respond to intravenous fluids with an increase in cardiac output.[15] If signs of hypoperfusion and hypotension do not resolve after the initial fluid resuscitation, the clinician must decide whether further intravenous fluid will augment cardiac output or if other measures (such as vasopressors or inotropes) should be used to stabilize the patient. One approach often used in clinical practice is not to predict responsiveness but instead to empirically administer a fluid bolus to all patients and evaluate the effect on cardiac output or other parameters reflecting perfusion.[16] This approach is indiscriminate and suboptimal because not all patients will respond to a fluid bolus, and repeated fluid challenges may result in considerable fluid administration without benefit.[17]

How to Elicit Symptoms and Signs of Fluid Responsiveness

Appropriate history taking and physical examination of the cardiovascular system have been described in detail in previous articles.[18,19] A prior review, describing clinical assessment of the central venous pressure (CVP), evaluated the jugular venous pulse to estimate CVP.[20]

Methods and measures to predict fluid responsiveness can be divided into static and dynamic tests. Static measurements are estimates of preload by the bedside clinician following placement of intravenous catheters and include the direct measurement of CVP and pulmonary capillary wedge pressure (although pulmonary artery catheters for volume assessments are used less frequently than CVP measurement).[21,22] Dynamic measurements analyze changes in cardiac output or related parameters, in response to bedside maneuvers that reversibly and

Figure 2. Performance of a Passive Leg-Raising Test

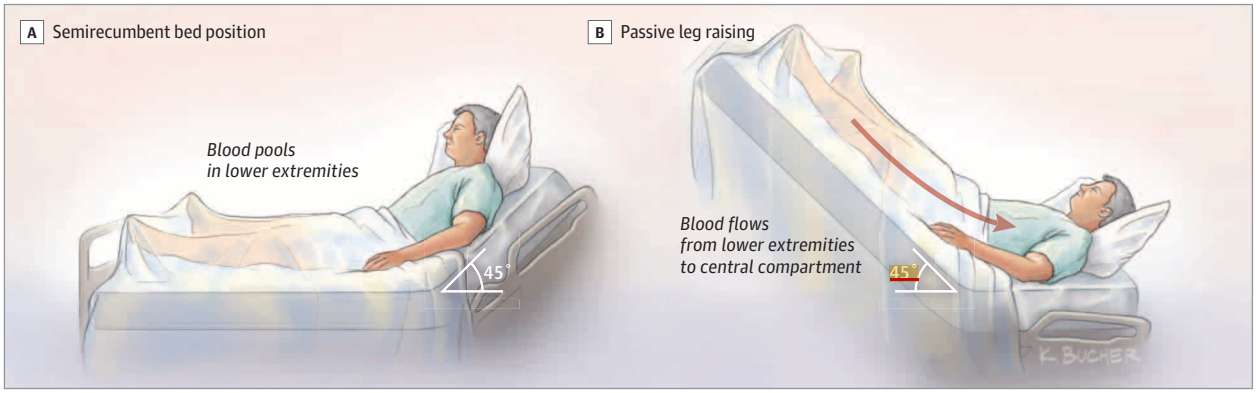
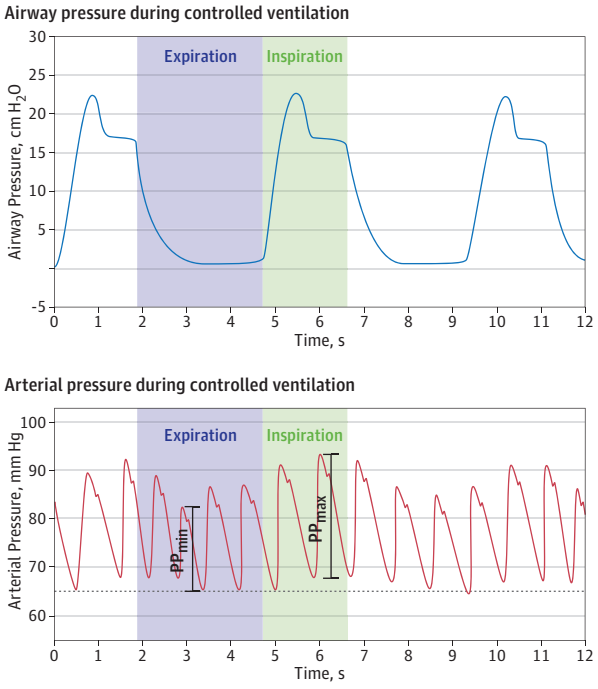


Figure 3. Airway Pressure and Arterial Pressure During Controlled Ventilation



Airway pressure and blood pressure tracings illustrating variations in pulse pressure (PP) during pulse pressure variation (PPV).
PPV = $(PP_{max}-PP_{min}/[(PP_{max}+PP_{min})/2])*100$.[75]

transiently change preload. The 2 most common maneuvers are passive leg raising and positive pressure breaths during mechanical ventilation.

Leg Raising

Passive leg raising increases preload by transferring blood pooled in the lower extremities to the central compartment.[23] In order to maximize the change in preload induced by leg raising, the patient is commonly semirecumbent at baseline rather than horizontal. Passive leg raising is then performed by adjusting the bed to an obtuse angle with the upper section in a flat position and the lower section inclined to 45° (**Figure 2**). Maximal change in cardiac output or related parameters occur within 60 seconds,[24] and an increase suggests that the patient will respond to a fluid bolus.

Respiratory Variation

Positive pressure breaths in mechanically ventilated patients transiently squeeze blood into the left heart from the pulmonary circulation. If the patient is on the steep portion of the Frank-Starling curve, there should be a corresponding increase in left ventricular stroke volume and cardiac output, resulting in increased systemic blood pressure and pulse pressure (the difference between systolic and diastolic pressure that reflects the product of stroke volume and peripheral vascular resistance; **Figure 3**).

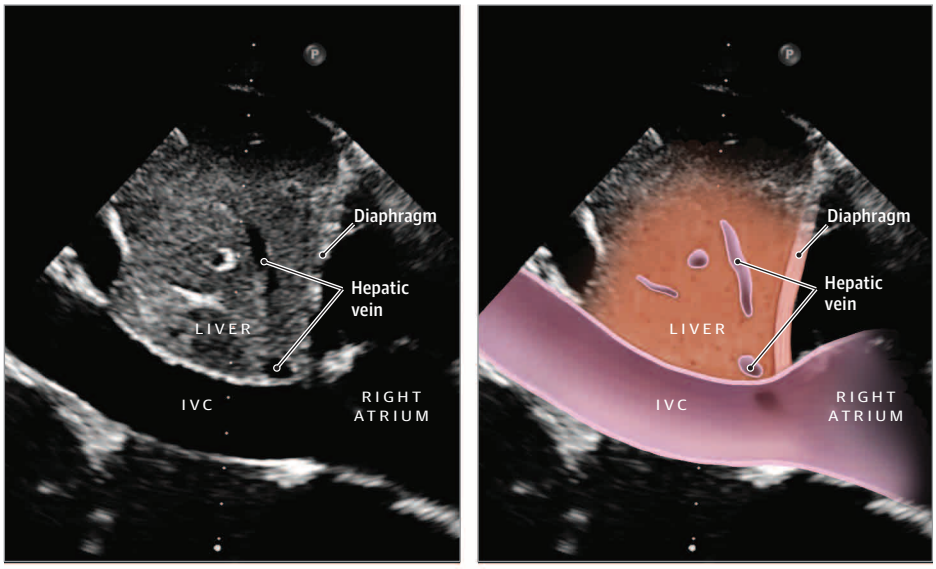
However, positive pressure inspirations also decrease venous return to the right side of the heart, which reduces right ventricular preload and output, ultimately causing a delayed reduction in left ventricular filling and preload. Depending on the individual's location on the Frank-Starling curve, this reduction in preload may reduce left ventricular stroke volume, systemic blood pressure, and pulse pressure at the end of inspiration or during exhalation (Figure 3). Patients who are likely to respond to fluid administration will show larger variations in pulse pressure or stroke volume during the respiratory cycle than patients who are less likely to be fluid responsive.

Pulse pressure variation during the respiratory cycle can be calculated manually and derived from monitoring intra-arterial blood pressure, although some hemodynamic monitors display the result calculated from built-in algorithms (Figure 3). Real-time stroke volume variation, an indicator of cardiac output, can be derived from pulse contour analysis that is displayed on cardiac output monitors.[25,26]

Respiration also induces cyclical changes in right atrial and central venous pressures due to transmission of pressure changes from the pleural space. Depending on the compliance of the vessel, these cyclical changes can also result in changes in the dimensions of the vena cava. Diameter of the inferior vena cava can effectively be measured close to the entrance into the right atrium by using bedside ultrasound (**Figure 4**).[27,28] Positive pressure breaths in mechanically ventilated patients increase the size of the inferior vena cava, while spontaneous negative pressure breaths reduce the size of the inferior vena cava. When the vena cava is underfilled, the compliance is greatest so large respiratory variations in vena cava dimensions suggest reduced intravenous volume and predict fluid responsiveness.

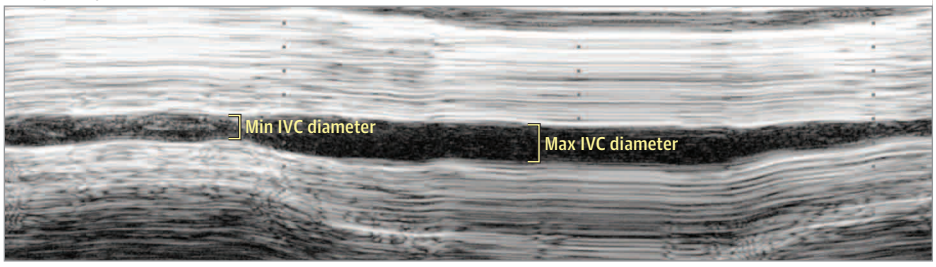
Figure 4. Inferior Vena Cava (IVC) Ultrasonography

A Longitudinal subcostal ultrasound of IVC (left) with illustration of anatomical structures in view (right)



B M-mode ultrasound of IVC in spontaneously breathing patient

Collapsibility index of IVC = [(max IVC diameter - min IVC diameter)/max IVC diameter] x 100



This figure demonstrates measurement of IVC variation in a hemodynamically unstable patient to assess for potential fluid responsiveness.

A, Two-dimensional view of the IVC, hepatic vein, and right atrium in subcostal view. The dotted line (vertical white dots) indicates where M-mode is recorded.

B, Respiratory variation in the IVC in M-mode in a spontaneously breathing patient. Diameter decreases with inspiration and increases with expiration. Image shows the most commonly used formula to calculate variation in spontaneously breathing patients. In patients receiving positive pressure ventilation, variation in IVC diameter is usually expressed as a distensibility index with the denominator being the minimum or mean IVC diameter.

See **Interactive**.-

The objective of this review is to systematically review the literature and provide summary estimates of the accuracy of the various symptoms, signs, and measurements used to predict fluid responsiveness in patients with refractory hypotension, signs of organ hypoperfusion, or both.

Methods

Search Strategy and Study Selection

Two of the authors (P.B. and N.T.A) conducted a computerized search of MEDLINE and EMBASE (from 1966 to June 15, 2016) to identify English-language studies about the diagnostic accuracy of components of the clinical examination or physiological parameters that discriminate fluid-responsive from fluid-nonresponsive hemodynamically unstable patients (eAppendix 1 in the Supplement).

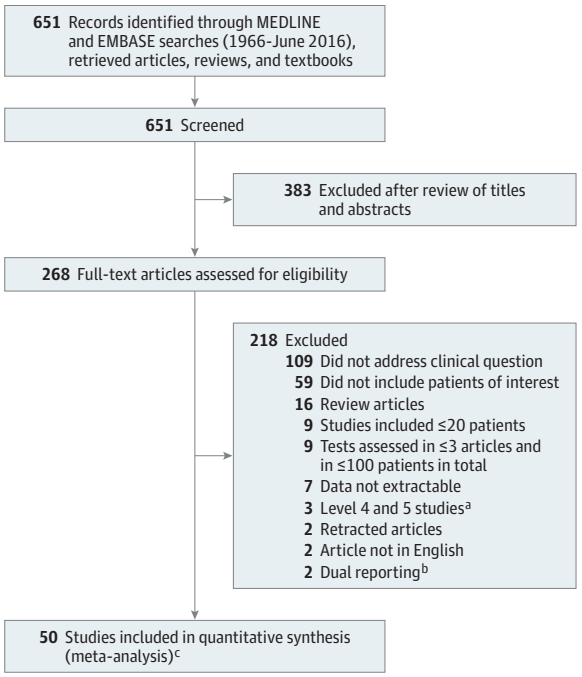
Only studies that evaluated the diagnostic accuracy of some element of the physical examination or physiological or ultrasound parameters for fluid responsiveness were included. Studies were limited to those of adult patients presenting to the emergency department or ICU with hemodynamic instability. Unpublished data were not included. No restraints were placed on type or volume of resuscitation fluids prior to study inclusion. The reference standard for fluid responsiveness was an objective increase in cardiac output (measured noninvasively or invasively; eTable 1 in the Supplement) following fluid administration. Data had to be presented so that 2 × 2 contingency tables could be constructed. If there were insufficient data to calculate likelihood ratios (LRs), the study was not included in the analysis, and authors were not contacted to obtain original data.

Studies with 20 or fewer participants were excluded. This threshold was chosen because the CIs with these small sample sizes would be large, the weighted contribution to a meta-analysis would be small, and because these small studies would have high risk of biased enrollment. Studies were excluded if the majority of patients had total irreversible loss of all brain function or were admitted following thoracic or cardiac surgery because these were felt to represent separate patient populations.

Assessment of Study Quality

Independently and in duplicate, the quality of the included studies were graded as described for *The Rational Clinical Examination*,[29] in which level 1 indicates the highest quality and level 5 indicates the lowest. Quality of the included studies was also assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool

Figure 5. Screening Process for Studies of Fluid Responsiveness in Hemodynamically Unstable Adults



[a] Level 4 and 5 studies refers to grading according to The Rational Clinical Examination (see Assessment of Study Quality). Level 4 is defined as a nonindependent comparison of signs and symptoms with a criterion standard among "grab" samples of patients who obviously have the target condition plus, perhaps, normal individuals. Level 5 is defined as nonindependent comparisons of signs and symptoms with a standard of uncertain validity (which may even incorporate the sign or symptom result in its definition) among grab samples of patients plus, perhaps, normal individuals.

[b] Dual reporting indicates that the same patients' data were used in more than 1 article.

[c] The 50 studies included in the meta-analysis comprised 2260 patients.

adapted for studies of fluid responsiveness (eAppendix 2 in the Supplement).[30] We excluded studies with level 4 or 5 evidence.

Statistical Methods

Two authors (P.B., K.M, or N.T.A.) independently extracted data from each article to construct 2 × 2 contingency tables for each clinical finding and calculated the sensitivity, specificity, and LRs. For each study, the exact 95% CIs were calculated. Data analysis was facilitated using Stata 10.0 (StataCorp). For meta-analyses of findings for fluid responsiveness, only those findings that were evaluated in more than 3 studies and with more than a total of 100 patients were summarized because of the belief that otherwise, the data would be insufficient to draw meaningful conclusions.

A bivariate mixed-effects regression model was used to pool the sensitivities and specificities across studies using the *midas* command in STATA. When a bivariate model failed to converge, a univariate random-effects regression model was used to pool the sensitivities and specificities across studies using the *metan* command in STATA. Effect measure modification of CVP thresholds on the pooled sensitivities and specificities was assessed. Using the *midas* command in STATA, univariable meta-regression to model CVP cutoffs (as a continuous variable) on the pooled sensitivities and specificities was done.

In addition, pooled LRs and diagnostic odds ratios (ORs) were calculated. A diagnostic OR is a measurement of the performance of a diagnostic test (ratio of the odds of test positivity if the patient has the disease divided by the odds of test positivity if the patient does not have the disease). The between-study heterogeneity for the pooled LRs for a diagnostic test was quantified using the I^2 statistic[31] (degree of heterogeneity: 25%, low; 50%, moderate; or 75%, high). Because of the importance of pleural pressure changes on the dynamic parameters, subgroup effects by type of ventilation (spontaneous vs controlled) and tidal volumes (median or mean; ≥7 mL/kg vs <7 mL/kg) were examined.

Publication bias was assessed using the Deeks test.[32] The Deeks test (a plot of the lnOR against 1/effective sample size) was developed especially for meta-analyses of diagnostic test accuracy. Publication bias was examined when there were 10 or more studies for a diagnostic test.[33]

Results

A total of 651 articles were found. We retained 13 quality level 2 studies and 37 quality level 3 studies with a total of 2260 patients (**Figure 5** and eTable 1 in the Supplement). In all studies, indices were measured prior to assessment of fluid responsiveness. The QUADAS criterion that describes whether the patients were consecutively enrolled was the most frequent missing criterion (eAppendix 2 and eTable 2 in the Supplement).

Prevalence of Fluid Responsiveness

The patient characteristics most commonly used to identify patients for inclusion were hypotension (76% of studies), oliguria (60%), skin mottling (48%), tachycardia (48%) and the physician's overall clinical impression of hypovolemia (34%). The most common criteria for excluding patients were presence of arrhythmias (60% of studies), cardiogenic pulmonary edema (24%), significant valvular disease (20%), low ratio of fraction of inspired oxygen to arterial oxygen partial pressure (20%), and right ventricular or left ventricular failure (18%). Fluid responsiveness was defined as an increase in cardiac output of at least 15% in 78% (39 of 50) of the studies and an increase of at least 10% to 12% in 22% (11 of 50) of the studies. The summary prevalence of fluid responsiveness was 50% (95% CI, 42%-56%).

Patient Characteristics

Physical examination findings that were present at inclusion were reported in 10 studies (402 patients).[34-43] The most common findings were oliguria (median, 49% [interquartile range {IQR}, 27%-66%]), hypotension (median, 30% [IQR, 9.1%-53%]), and tachycardia (median, 22% [IQR, 0%-35%]). The most commonly reported cause of hemodynamic instability was sepsis (median, 71% [IQR, 60%-94%]), which was followed by nonseptic systemic inflammatory response syndrome (eg, in the setting of pancreatitis, trauma, or major surgery) (median, 23% [IQR, 12%-34%]). The approximate median of patients who were treated with vasopressors at inclusion was 66% (IQR, 50%-85%). All studies were

performed in an ICU setting. In 86% of the studies it was either clearly stated or it could be concluded from demographic data or study methodology that the patients had been fluid resuscitated prior to inclusion. Data regarding specific indication for fluid are missing in most of the studies (n = 31).

Accuracy of Physical Examination

Two studies investigated the accuracy of physical examination in predicting fluid responsiveness. One study investigated the diagnostic accuracy of dry mucous membranes, dry axilla, decreased tissue turgor, capillary refill time greater than 2 seconds, tachycardia, and low jugular venous pressure.[44] The LR and respective 95% CIs for all of these findings crossed 1.0. A second study investigated the diagnostic accuracy of a systematic clinical assessment of skin turgor, capillary refill time, jugular vein distension, appearance of mucus membranes, pulmonary auscultation and presence or absence of leg edema, ascites, and pleural effusions[45] and found that this approach was a poor predictor of fluid responsiveness with the 95% CIs of the LRs crossing 1.0 (positive LR, 0.93 [95% CI, 0.55-5.2] and negative LR, 1.2 [95% CI, 0.28-5.2]).

Accuracy of Static Measurements

Invasively measured CVP was the only static measure that was included in the analysis (**Table** and eTable 3 in the Supplement). In these studies, the mean CVP used for the threshold to identify fluid responsiveness was 8 mm Hg (11 cm water; range, from 6-9 mm Hg, equivalent, 8-12 cm water). Patients with CVP below the threshold used in each study had a modestly increased likelihood of fluid responsiveness (summary specificity, 76%; positive LR, 2.6 [95% CI, 1.4-4.6]) while patients with a CVP above the threshold had about half the likelihood of fluid responsiveness (summary sensitivity, 62%; negative LR, 0.50 [95% CI, 0.39-0.65]). At a pretest probability of 50% of fluid responsiveness, these results confer a positive predictive value of 72% and a negative predictive value of 33%. Meta-regression of the CVP cutoff (as a continuous variable) did not demonstrate any effect-measure modification on either the pooled sensitivity (P = .66) or the pooled specificity (P = .78).

Accuracy of Pulse Pressure Variation and Stroke Volume Variation

Pulse Pressure Variation in Ventilated Patients

Because the accuracy of pulse pressure variation in response to positive pressure ventilation might depend on tidal volume,[46] studies using low (<7 mL/kg) and high (≥7 mL/kg) mean or median tidal volumes were analyzed separately (Table). The mean threshold for pulse pressure variation was 8% (range, 5%-12%) in low tidal volumes studies and 11% (range, 4%-15%) in high tidal volumes studies. For this analysis, only studies that included mechanically ventilated patients without spontaneous respiratory efforts and without arrhythmias were included.

A pulse pressure variation that was greater than the respective threshold was useful to predict fluid responsiveness for low tidal volumes (summary specificity, 91%; positive LR, 7.9 [95% CI, 4.1-16]) and also for high tidal volumes (summary specificity, 84%; positive LR, 5.3 [95% CI, 3.5-8.1]). A pulse pressure variation that was less than the thresholds predicted lack of fluid responsiveness for patients with low tidal volume (summary sensitivity, 72%; negative LR, 0.30 [95% CI, 0.21-0.44]) and also for patients with high tidal volume (summary sensitivity, 84%; negative LR, 0.19 [95% CI, 0.12-0.30]).

Stroke Volume Variation in Ventilated Patients

Studies investigating the accuracy of stroke volume variation during positive pressure ventilation had a mean cutoff of 13% (range, 10%-20%). Stroke volume variation above respective study cutoff had a summary specificity of 84% with a positive LR of 4.9 (95% CI, 2.8-8.5; Table).

Pulse Pressure Variation and Stroke Volume Variation in Spontaneously Breathing Patients

The accuracies of pulse pressure variation and stroke volume variation in spontaneously breathing patients is uncertain because they were evaluated in only 2 small studies for each parameter (eTable 3 in the Supplement).[47-49] The positive LR range was 1.0 to 2.3 and negative LR range was 0.05 to 0.98.

Of note, studies investigating stroke volume variation or pulse pressure variation that included a mixture of mechanically ventilated and spontaneously breathing patients, and studies in which it was unclear if mean tidal volume was greater than or less than the 7 mL/kg threshold, were not included in the meta-analysis but are presented in eTable 1, eTable 2, and eTable 3 in the Supplement. There was evidence of publication bias with respect to the pulse pressure variation in patients with a tidal volume of at least 7 cc/kg (P = .01, Deeks test) as smaller studies tended to have better accuracy.

Accuracy of Changes in Inferior Vena Cava Diameter

Ventilated Patients

In ventilated patients without spontaneous respiratory efforts, the mean inferior vena cava distensibility index threshold was 15% (range, 12%-21%; Table and eTable 3 in the Supplement). An elevated caval distensibility index had summary specificity for fluid responsiveness of 85% (positive LR, 5.3 [95% CI, 1.1-27]) among ventilated patients, while those with a caval distensibility index that was lower than the threshold were less likely to be fluid responsive (summary sensitivity, 77%; negative LR, 0.27 [95% CI, 0.08-0.87]).All studies used tidal volumes that were greater than 8 mL/kg. At a pretest probability of 50% of patients being fluid responsive, these results confer a positive predictive value of 84% and a negative predictive value of 21%. The interobserver variation of the caval distensibility index was reported in 2 studies and was 6% and 9% (eTable 4 in the Supplement).[50,51]

Spontaneously Breathing Patients

Two studies evaluated collapsibility of the inferior vena cava in spontaneously breathing patients (Figure 3).[52,53] At a threshold of inferior vena cava collapsibility of 41% (range, 40%-42%), the positive LRs were 3.5 (95% CI, 1.1-15) and 9.3 (95% CI, 0.88-51). The negative LRs were 0.38 (95% CI, 0.13-0.93) and 0.71 (95% CI, 0.49-1.0) (eTable 3 in the Supplement).

Accuracy of Measurements Dependent on Changes in Preload Induced by Passive Leg Raising

Cardiac Output

Studies investigating the accuracy of passive leg raising on cardiac output or related parameters were pooled because the underlying

Table. Summary of Diagnostic Accuracy for Hypovolemia Responsive to Fluids[a]

Measures and Included Studies	No. of Studies	No. of Patients	Cutoff for Measures, Mean (Range)[b]	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR (95% CI)	I^2, %	Negative LR (95% CI)	I^2, %	Diagnostic OR (95% CI)
Static Measure										
Central venous pressure[44,47,49,71-74]	7	356	8 mm Hg (6-9)	62 (54-69)	76 (60-87)	2.6 (1.4-4.6)	0	0.50 (0.39-0.65)	58	5 (2-11)
Dynamic Measures										
Pulse pressure variation										
Controlled ventilation, V_t≥7.0 mL/kg[36,37,40,66,75-83,92,96,97]	17	768	11 (4-15)[c]	84 (75-90)	84 (77-90)	5.3 (3.5-8.1)	52	0.19 (0.12-0.30)	50	28 (13-57)
Controlled ventilation, V_t<7.0 mL/kg[37,84-87]	5	219	8 (5-12)[c]	72 (61-81)	91 (83-95)	7.9 (4.1-16)	22	0.30 (0.21-0.44)	0	26 (11-61)
Stroke volume variation										
Controlled ventilation[34,36,77,78,80,81,88-90]	9	343	13 (10-20)	79 (67-87)	84 (74-90)	4.9 (2.8-8.5)	45	0.25 (0.15-0.43)	20	19 (7-53)
Spontaneous breathing[48,49]	2	53	10-12[d]	57-100[d]	44-57[d]	1.0-2.3[d,e]		0.05-0.98[d,e]		1-43[d]
Inferior vena cava variation										
Controlled ventilation[28,50,51,90]	4	137	15 (12-21)	77 (44-94)	85 (49-97)	5.3 (1.1-27)	76	0.27 (0.08-0.87)	71	20 (2-222)
Spontaneous breathing[52,53]	2	99	40-42[d]	31-70[d]	80-97[d]	3.5-9.3[d]		0.38-0.71[d]		9-13[d]
Response to passive leg raising										
Change in cardiac output[24,35,38,39,41,43,45,48,53,60,91-97]	17	788	11 (7-15)	88 (80-93)	92 (89-95)	11 (7.6-17)	60	0.13 (0.07-0.22)	0	88 (39-199)
Change in pulse pressure[24,38,41,43,48]	5	278	10 (9-12)	62 (54-70)	83 (76-88)	3.6 (2.5-5.4)	0	0.45 (0.36-0.57)	0	8 (5-14)
Change in cardiac output following passive leg raising										
Controlled ventilation[38,41,92,93,96,97]	6	294	10 (7-12)	92 (82-97)	92 (86-96)	11 (6.3-21)	41	0.08 (0.03-0.21)	0	139 (41-474)
Spontaneous breathing[35,39,43,53,94]	5	181	12 (10-13)	88 (80-94)	88 (80-94)	7.0 (3.8-13.1)	60	0.22 (0.09-0.54)	0	54 (15-195)

Abbreviations: LR, likelihood ratio; OR, odds ratio; V_t, tidal volume.

[a] For results from individual studies, see eTable 3 in the Supplement.

[b] Mean cutoff ranges for all dynamic measures are reported as percent values.

[c] Only studies that included mechanically ventilated patients without spontaneous respiratory efforts and without arrhythmias were included.

[d] Reported values are between-study ranges.

[e] Accuracies of pulse pressure variation and stroke volume variation in spontaneously breathing patients is uncertain because they were evaluated in only 2 small studies for each parameter (eTable 3 in the Supplement).

physiology was considered to be similar. Transpulmonary thermodilution was most commonly used to assess response to leg raising in ventilated patients and transthoracic echocardiography was most common in spontaneously breathing patients. The mean threshold in the studies was a 11% increase (range, 7%-15%) in the hemodynamic parameters. Patients with an increased cardiac output above the threshold after leg raising were much more likely to increase cardiac output with fluid administration (summary specificity, 92%; positive LR, 11 [95% CI, 7.6-17]) than patients who did not change cardiac output after leg raising (summary sensitivity, 88%; negative LR, 0.13 [95% CI, 0.07-0.22]) (Table). The change in cardiac output of at least 10% after passive leg raising had the highest predictive value of 92% (assuming a baseline prevalence of 50%). When the cardiac output changes were less than the threshold after passive leg raising, the negative predictive value of 11% was the lowest of all tests studied.

The results are similar during controlled ventilation (positive LR, 11 [95% CI, 6.3-21]) or spontaneous breathing (positive LR, 7.0 [95% CI, 3.8-13.1]) (Table). Negative LRs are similar during controlled ventilation (negative LR, 0.08 [95% CI, 0.03-0.21]) or spontaneous breathing (negative LR, 0.22 [95% CI, 0.09-0.54]).

Pulse Pressure

Studies using change in pulse pressure following passive leg raising to predict fluid responsiveness had a mean threshold of 10% (range, 9%-12%). An increase in pulse pressure of at least 10% increased the likelihood of fluid responsiveness (summary specificity, 83%; positive LR, 3.6 [95% CI, 2.5-5.4]) and patients with a smaller increase had a lower likelihood of fluid responsiveness (summary sensitivity, 62%; negative LR, 0.45 [95% CI, 0.36-0.57]). At a pretest probability of 50%, these results confer a positive predictive value of 78% and a negative predictive value of 31%.

Limitations

The reference standard for measuring cardiac output is normally considered to be transcardiac thermodilution via a pulmonary artery catheter.[54] However, this method is invasive, and not surprisingly, the use of pulmonary catheters has decreased dramatically in recent years.[55] Many of the studies included in this analysis therefore used other methods as reference tests to evaluate response to a fluid challenge. Most of these methods demonstrated good agreement with transcardiac thermodilution,[56-58] but some are not as well validated.[59,60] In all but 6 studies, the reference standard or methods with good agreement with reference standard was used.

Many studies excluded patients in whom withholding fluid resuscitation would be considered unethical (eg, ongoing bleeding, unresuscitated shock). Also, patients in whom fluid resuscitation was considered to be potentially dangerous (eg, low ratio of fraction of inspired oxygen to arterial oxygen pressure and/or other signs of pulmonary edema) were excluded in some studies. Therefore, the included patients represent a subset of critically ill patients and the accuracy of the included tests and optimal threshold values may be different in general medical patients who are less ill.

The volume of fluid used to identify responders was similar or greater than the recommended amount.[61] However, the possibility cannot be excluded that the volume may have been too small in certain patients to increase preload and cardiac output sufficiently, thereby underestimating the fraction of patients needing fluids. We would surmise that this could especially be the case in patients who are extremely hypovolemic and who could be labeled as fluid nonresponders even though they require fluids.

In addition, many of the studies were small (mean, 45 patients per study) with different inclusion and exclusion criteria.

Discussion

In at least 43 of the 50 included studies, patients received fluid resuscitation prior to enrollment in the study. Approximately 50% of these hemodynamically unstable patients were fluid responsive. Traditional physical examination findings do not differentiate responders from nonresponders, and measurement of CVP is inadequate. Thus, the clinical evaluation for fluid responsiveness requires a different set of skills in which the physician integrates observations with bedside ultrasound, real-time hemodynamic monitoring, or echocardiography to assess cardiac output. In particular, changes in cardiac output or related parameters following passive leg raising are useful in a wide range of patients, and variation in pulse pressure or inferior vena cava diameter with positive pressure ventilation have reasonable accuracy in selected subgroups of patients.

The result that CVP is a poor predictor of fluid responsiveness is consistent with results presented in previous meta-analyses.[62,63] Ventilator settings (especially positive end-expiratory pressure), and variations in the ratio of chest wall/lung compliance may compromise the accuracy of CVP as a predictor of fluid responsiveness. Accounting for these variables in an individual patient might improve the predictive value of CVP but needs evaluation.

Spontaneous breathing efforts in intubated or unintubated patients result in variable changes in intrathoracic pressure and preload for each breath and may influence the accuracy of ventilation-induced changes in preload to predict fluid responsiveness. Arrhythmias will cause beat-to-beat changes in preload, which are independent of ventilation. Therefore, the majority of studies using respiratory changes in hemodynamic parameters to predict fluid responsiveness excluded patients with irregular cardiac rhythms and spontaneous respiratory efforts.

It should also be recognized that pulse pressure variation and stroke volume variation reflect fluid responsiveness of the left ventricle, which means that the accuracy of these measurements is likely to be lower in patients with a failing right ventricle (ie, fluid administration may not increase preload of the left ventricle).[64] It should be noted that patients with right ventricular failure may benefit from a reduction of preload such as accomplished with diuretics. For example, a patient in shock from a massive pulmonary embolism might improve cardiac output with fluid removal because of improved left ventricular filling secondary to a reduction of right ventricular volume. In addition, pulse pressure variation is decreased at high respiratory rates (30-40/min) independent of volume status.[65] Decreases in chest wall and lung compliance could influence pulse pressure variation independent of volume status, which would alter threshold values and compromise accuracy.[66,67] We conclude that the use of stroke volume

variation and pulse pressure variation to assess fluid responsiveness is only validated in patients without spontaneous respiratory efforts and arrhythmias, and that high respiratory rates, right heart failure, or decreased chest wall and lung compliance may compromise test accuracy.

Based on the same reasoning as previously described, all but 2 studies[52,53] investigating the accuracy of respiratory variation in inferior vena cava diameter included only patients without spontaneous respiratory efforts and without arrhythmias. Despite this attempt to standardize patient populations, the 95% CI for LRs are wide and I^2 values indicate a high degree of heterogeneity. Therefore, the accuracy of the test may differ depending on the patient population as well as other factors related to the measurement. Despite the fact that the pooled LRs indicate relatively good accuracy, the test should be interpreted with some caution.

Although the passive leg-raising test was the most broadly applicable, there are conditions in which it is of limited utility. If preload is not sufficiently increased by passive leg raising, accuracy may be compromised. The importance of a sufficient increase in preload during passive leg raising is supported by the finding that accuracy is higher in patients with an increase in CVP of at least 2 mm Hg (indicative of increased preload) following passive leg raising.[68] Such conditions include the use of compression stockings and intra-abdominal hypertension.[69] The presence of intra-abdominal hypertension should be considered especially in patients with abdominal pathologies such as ascites and after surgery; measurement of urinary catheter pressures is useful in detecting increased abdominal pressures.[70]

Critically ill patients can have complex hemodynamic presentations. Therefore, relying on a single measurement to make clinical decisions could lead to poor outcomes. The wide 95% CIs for many predictors suggest that the decision to administer fluid at bedside should not be based solely on a test result but also on risks and benefits of fluid administration in the clinical context. For example, in the spontaneously breathing patient, excessive fluid administration may induce respiratory failure, resulting in intubation, and one might be more cautious in such a patient.

In addition, administration of vasopressors may increase preload while inotropes may shift the Starling curve, thereby potentially changing fluid responsiveness. Fluid responsiveness is thus a dynamic property of the patient who needs to be reassessed frequently, especially if there are changes in vasoactive drugs or other changes in status.

Another way to assess these various tests is to classify them into 3 groups: observation of the patient at a single time point (physical examination or static parameters), dynamic changes due to small changes in the system (respiratory changes in physiological parameters), and dynamic changes due to a larger perturbation of the system (passive leg raising). Other factors such as costs, training, and time burden may also affect the usefulness of these tests in the clinical context.

Scenario Resolution

This patient exhibits several signs that could be explained by inadequate tissue perfusion, and it is reasonable to consider fluid administration. An increase in pulse pressure by 7% following passive leg raising is below the mean threshold of 10% used to identify fluid responsiveness. Assuming a 50% pretest probability for fluid responsiveness, this finding only reduces the probability to 30% that this patient will respond to fluid administration. To further evaluate if the patient is fluid responsive, additional measurements should be considered. Given that the patient is triggering her own breaths and only receives pressure support via the ventilator, none of the measurements based on respiratory variation are useful. However, changes in cardiac output following passive leg raising have excellent diagnostic accuracy. The lack of substantial increase in cardiac output (below mean threshold of 10% in the included studies) has a LR of 0.12 and decreases the probability of fluid responsiveness to 10%. The patient is unlikely to respond to fluid, and other interventions to improve cardiac output should be considered.

Clinical Bottom Line

Approximately 50% of hemodynamically unstable patients remain fluid responsive after the initial resuscitation. For intubated patients without spontaneous respiratory efforts, respiratory variation in pulse pressure appears to be useful to predict fluid responsiveness. Respiratory variation in the vena cava is less useful and requires further confirmatory studies. The change in cardiac output following passive leg raising appears to be the most accurate predictor of fluid responsiveness and can be used independent of ventilation mode. The generalizability of the results to less ill patients is uncertain.

ARTICLE INFORMATION

Author Contributions: Drs Ayas and Bentzer had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of all the data analysis.
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Acquisition, analysis, or interpretation of data: Bentzer, Griesdale, MacLean, Sirounis, Ayas.
Drafting of the manuscript: Bentzer, Boyd, Sirounis, Ayas.
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