

Inferior vena cava size is not associated with shock following injury

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BACKGROUND:	The inferior vena cava (IVC) collapses with shock but may also be collapsed in volume-depleted patients in the absence of shock. The speed and availability of computed tomography (CT) make IVC measurement an attractive diagnostic modality for shock. The purpose of this study was to determine if IVC size following injury is associated with shock.
METHODS:	Retrospective data were collected on 272 trauma patients admitted to an adult trauma center from January 1 to December 31, 2012. Patients who met the highest-level activation criteria and underwent an abdominal CT scan during their initial resuscitation were included. All images were reviewed by two attending radiologists, and concordance was assessed using the Pearson correlation coefficient. The transverse (T) and anteroposterior (AP) diameters of the IVC were measured to calculate a T/AP ratio. Analysis of variance and χ^2 were used to assess for a relationship between this ratio and various indices of shock.
RESULTS:	The mean (SD) age of the study cohort was 50 (21) years, mean (SD) Injury Severity Score (ISS) was 14 (9), 74% were male, and 96% sustained blunt trauma. The overall mean (SD) T/AP ratio was 1.81 (0.68). Patients with a shock index greater than 0.7 were significantly younger (43 [20] years vs. 55 [21] years, $p < 0.0001$), had a significantly lower mean arterial pressure (88 [15] mm Hg vs. 103 [18] mm Hg, $p < 0.0001$), and were more likely to be intubated (56% vs. 24%, $p < 0.0001$). However, IVC T/AP ratio was not significantly different among the cohort. Similarly, there was no association between IVC size and the need for urgent operation, angiography, emergent transfusion, hospital length of stay, or mortality.
CONCLUSION:	The static degree of IVC collapse is not associated with shock following injury. Therefore, measurement of IVC size by CT scan for patients with a T/AP ratio between 1 and 3.5 is not clinically relevant and cannot be used to predict mortality, shock, or impending shock. (<i>J Trauma Acute Care Surg.</i> 2014;77: 34–39. Copyright © 2014 by Lippincott Williams & Wilkins)
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Early detection and resuscitation of hemorrhage is critical to the proper treatment of trauma patients. Hemodynamically unstable patients are rapidly transfused and intervened upon. However, in the absence of Stage III or Stage IV shock, the autoregulatory mechanisms of the body can readily compensate for volume depletion to maintain adequate blood pressure, pulse rate, and mental status. It is well-known that blood pressure is not decreased in states of shock until approximately 30% to 40% of the circulating blood volume has left the intravascular compartment.¹ In addition, the other signs of early shock (tachycardia, pulse rate and pressure, pallor, core temperature) may easily be overlooked or confounded by pain or anxiety, sympathetic surge, pharmaceutical and illicit drugs, and environmental factors in the trauma bay. As such, objective means to diagnose early actual or impending shock following injury are needed.

The inferior vena cava (IVC) collapses with shock because of an absolute or relative hypovolemia.^{2–5} However, it may also be collapsed in chronically volume-depleted patients in the absence of shock. Dynamic ultrasonographic evaluation of the IVC has been used to ascertain the volume status of patients with sepsis who are being mechanically ventilated in the intensive care unit (ICU)⁶ and to help guide fluid therapy in patients with renal failure.⁷ Being that many hemodynamically stable trauma patients will rapidly have a computed tomographic (CT) scan of the abdomen and pelvis, there has been interest in assessing the IVC size by this method to determine the patient's volume status and assess shock and mortality risk. It has previously been reported that the presence of a flat IVC on CT scan can be used as an independent predictor of mortality in trauma patients.³ However, the utility of IVC measurement as an indicator of shock remains uncertain in the acutely injured patient.

The purpose of this study was to determine if IVC size after injury, measured using the patient's initial CT scan, is associated with clinically occult shock defined as a shock index greater than 0.7. Secondary end points included assessment of impending shock, which was defined as the association between IVC size and need for emergent intervention or transfusion, and the relationship between IVC size and hospital mortality and length of stay. We hypothesized that static IVC size cannot

be used to detect clinically occult shock or predict impending shock in injured patients.

PATIENTS AND METHODS

Retrospective data were collected on 276 trauma patients admitted to an adult trauma center from January 1 to December 31st, 2012. Inclusion criteria included trauma patients 18 years or older who met highest-level trauma activation criteria and underwent abdominal CT scan with intravenous contrast during their initial resuscitation. Patients were stratified by age, sex, and mechanism of injury. Injury severity was assessed using the Injury Severity Score (ISS). All vital signs were obtained at admission, and all laboratory studies were obtained within 1 hour after patient arrival. The shock index was derived from the initial set of vital signs, which include a manually obtained blood pressure by the trauma nurse. Shock was defined as a shock index value of greater than 0.7. Only 26% of the cohort had a serum lactate measured on arrival; therefore, this variable was not included in the study. Outcome variables included intubation on arrival, need for transfusion, operative or transcatheter angiographic intervention within the first 24 hours of admission, ICU and hospital lengths of stay, and mortality.

CT scans were obtained during the initial resuscitation at the discretion of the attending trauma surgeon using a 64-slice CT scanner. This is performed typically within 30 minutes of arrival to the trauma bay. Patients who had clinically significant shock unresponsive to initial interventions were excluded from the study because they were taken to the operating room without first obtaining a CT scan. Abdomen and pelvis CT scans were obtained with contiguous 2.5-mm axial sections. Two board-certified attending radiologists, who were blinded to the patient's vital signs and laboratory data, retrospectively reviewed each CT scan for size of the IVC. Each radiologist performed three separate measurements of the transverse (T) and anteroposterior (AP) diameters of the IVC 1 cm below the confluence of the right renal vein and IVC. The averages of the T and AP diameters were then used to calculate the T/AP ratio. A higher ratio equated to a more collapsed IVC.

TABLE 1. Patient Demographics, Results, Physiologic Variables, and Resource Use

Total no. cases	272
Male, n (%)	202 (74)
Female, n (%)	70 (26)
Age, mean (SD), y	50 (21)
ISS, mean (SD)	14 (9)
Blunt injury, n (%)	260 (95.6)
Penetrating injury, n (%)	12 (4.4)
Hemoglobin in trauma bay, mean (SD), g/dL	13.5 (2.0)
Bicarbonate in trauma bay, mean (SD), mmol/L	23.5 (4.4)
Pulse in trauma bay, mean (SD), beats/min	88.6 (21.0)
MAP in trauma bay, mean (SD), mm Hg	97.1 (18.2)
Shock index in trauma bay, mean (SD)	0.67 (0.23)
T/AP ratio, mean (SD)	1.81 (0.68)
Intubated, n (%)	97 (36.5)
Packed red blood cell transfusion in trauma bay, n (%)	13 (4.9)
Operating room within 24 h	54 (21.4)
Interventional radiology within 24 h	13 (5.5)
ICU days, mean (SD)	4.0 (6.1)
Hospital days, mean (SD)	7.3 (9.5)
Died, n (%)	14 (5.2)

The Kolmogorov-Smirnov test and examination of QQ-plots was used to evaluate the normality of the data distributions for shock index, mean arterial pressure (MAP), and ICU and hospital lengths of stay and was significant for all values except MAP. These variables were then log transformed, and a linear correlation against the log-transformed degree of IVC collapse was investigated. However, examination of the scatterplots showed that four outliers had a large influence on these correlations, even after log transformation, and therefore, the outliers were removed from the study cohort. To remove the possible effects of skewed distributions, quartiles of IVC T/AP ratio were created, and the associations between this ordinal variable and continuous variables (such as shock index, MAP, hospital days) were assessed using analysis of variance. To determine whether interrater reliability was adequate for the IVC measurement, Pearson correlation of measurements between raters as well as the interrater scatterplot and a Bland-Altman plot (showing mean score vs. difference between raters) were examined. Two-tailed between-groups *t* tests were used to evaluate associations between continuous variables and binary outcomes (e.g., death). SAS (version 9.2, Cary, NC) was used for all statistical analysis with $p < 0.05$ considered significant, and G-power 3 was used for the power analysis.⁸ A post hoc power analysis ($\beta = 0.8$, $\alpha = 0.05$) found that 240 patients are needed to detect a mean difference of 0.05 in the shock index between each IVC ratio quartile.

The study was approved by the institutional review board at the George Washington University School of Medicine and Health Sciences, Washington, District of Columbia.

RESULTS

After four outliers were removed, our cohort contained 272 patients. The mean (SD) age of the study cohort was

50 (21) years, mean (SD) ISS was 14 (9), 74% were male, and 96% sustained blunt injury (Table 1). Admission, pulse, MAP, shock index, hemoglobin, and serum bicarbonate level were normal in the majority of patients. The overall mean (SD) T/AP ratio was 1.81 (0.68) (Table 1). Interobserver concordance between the two radiologists was $r = 0.85$. The mean (SD) difference between the two evaluators was 0.0035 (0.41) cm, and the correlation between the difference and the mean score was -0.08 ($p = 0.18$), indicating that the two raters had a high level of agreement and that the differences in ratings were distributed randomly.

Table 1 also depicts overall resource use and mortality. Ninety-seven patients (36%) either arrived intubated or were intubated at admission. Within 24 hours of admission, 54 patients (21%) required operative intervention. An additional 13 patients (5.5%) solely required interventional radiologic intervention within 24 hours. The mean (SD) ICU and hospital lengths of stay was 4 (6.1) days and 7.3 (9.5) days, respectively. The overall mortality for the study cohort was 5.2%.

There were 103 patients with a shock index greater than 0.7 in our cohort (Table 2). Patients with a shock index greater than 0.7 were significantly younger (43 [20] years vs. 55 [21] years, $p < 0.0001$), had a significantly lower MAP (88 [15] mm Hg vs. 103 [18] mm Hg, $p < 0.0001$), and were more likely to be intubated (56% vs. 24%, $p < 0.0001$). However, IVC T/AP ratio was not significantly different among the cohort.

We also examined the sensitivity and specificity of patients with a shock index greater than 0.7 in predicting IVC collapse via a cutoff point analysis (Table 3). There was no T/AP cutoff point that produced a clinically useful sensitivity and specificity for predicting a shock index greater than 0.7. The best T/AP IVC diameter ratio for optimizing both positive and negative predictive values was 1.65, at which the positive predictive value was 0.49 and the negative predictive value was 0.51, no different from a chance association. Similarly, the ratio did not allow us to define a cutoff point with sufficient prediction accuracy as to enable its use clinically.

When patients were divided into quartiles based on degree of IVC collapse, age was found to be significantly different ($p = 0.0032$). The mean (SD) age of the least collapsed quartile was

TABLE 2. Shock Index Greater Than 0.7 by Outcomes

Outcome	Shock Index > 0.7 (n = 103)	Shock Index ≤ 0.7 (n = 169)	<i>p</i>
Age, mean (SD), y	42.7 (19.4)	54.9 (20.9)	<0.0001
IVC T/AP ratio, mean (SD)	1.83 (0.7)	1.80 (0.7)	0.71
MAP, mean (SD), mm Hg	87.8 (15.2)	103.0 (17.5)	<0.0001
Hemoglobin, mean (SD), g/dL	13.6 (2.4)	13.4 (1.8)	0.53
Operating room within 24 h, n (%)	26 (26.5)	28 (18.2%)	0.12
Interventional radiology within 24 hours, n (%)	7 (8.1)	6 (4.0)	0.19
Hospital days, mean (SD)	6.9 (7.8)	7.5 (10.4)	0.58
ICU days, mean (SD)	4.3 (6.4)	3.8 (5.9)	0.55
RBC Transfusion, n (%)	8 (7.9)	5 (3.1)	0.09
Intubated, n (%)	57 (55.9)	40 (24.4)	<0.0001
Died, n (%)	6 (5.9)	8 (4.8)	0.69

TABLE 3. Cutoff Point Analysis of Shock Index Greater Than 0.7 Versus IVC Collapse

T/AP Ratio	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Prediction Accuracy	95% Confidence Interval
1	0.39	1.00	1.00	0.01	0.40	
1.1	0.39	0.56	0.96	0.03	0.39	0.21–3.00
1.2	0.39	0.64	0.90	0.12	0.42	0.51–2.63
1.3	0.40	0.65	0.83	0.20	0.44	0.62–2.30
1.4	0.40	0.65	0.74	0.31	0.47	0.71–2.19
1.5	0.39	0.62	0.62	0.40	0.48	0.63–1.77
1.6	0.40	0.62	0.55	0.47	0.50	0.65–1.79
1.65	0.39	0.62	0.49	0.51	0.51	0.62–1.71
1.7	0.38	0.61	0.41	0.57	0.51	0.56–1.56
1.8	0.40	0.62	0.37	0.65	0.54	0.65–1.85
1.9	0.39	0.61	0.30	0.71	0.55	0.60–1.80
2	0.41	0.62	0.26	0.76	0.56	0.62–1.97
2.1	0.41	0.62	0.24	0.78	0.57	0.61–2.00
2.2	0.40	0.61	0.19	0.81	0.57	0.55–1.98
2.3	0.38	0.61	0.16	0.83	0.57	0.49–1.90
2.4	0.38	0.61	0.13	0.87	0.58	0.46–2.04
2.5	0.38	0.61	0.12	0.87	0.58	0.44–2.01
2.6	0.41	0.62	0.12	0.89	0.59	0.51–2.48
2.7	0.42	0.62	0.11	0.90	0.60	0.52–2.67
2.8	0.44	0.62	0.11	0.91	0.60	0.55–2.92
2.9	0.41	0.61	0.09	0.92	0.60	0.45–2.68
3.0	0.40	0.61	0.08	0.92	0.60	0.42–2.68
3.1	0.39	0.61	0.07	0.93	0.60	0.38–2.68
3.2	0.38	0.61	0.06	0.94	0.60	0.33–2.68
3.3	0.36	0.61	0.05	0.94	0.60	0.28–2.67
3.4	0.31	0.61	0.04	0.94	0.59	0.21–2.30
3.5	0.36	0.61	0.04	0.96	0.60	0.26–3.14

There is no T/AP cutoff point that produces acceptable sensitivity and specificity.

At the best cutoff point for optimizing both positive and negative predictive values (1.65), both are near chance prediction (0.49 and 0.51, for positive and negative predictive value, respectively).

46.2 (21.3) years, whereas the mean (SD) age of the most collapsed quartile was 57.4 (20.4) years (Table 4). No significant differences were found among the other patient characteristics, such as mean shock index, MAP, and admission hemoglobin levels between the quartiles. Similarly, no significant differences

were identified in the study cohort regarding overall resource use (intubation on admission, blood transfusion, operative intervention and interventional radiology procedures within 24 hours of admission, and hospital and ICU lengths of stay) and mortality based on degree of IVC collapse.

TABLE 4. Shock, Resource Use, and Mortality as a Function of Degree of IVC Collapse

Outcome	Mean IVC Ratio of Transverse to Anteroposterior Diameter				<i>p</i>
	Least Collapsed < 1.365 (n = 68)	Slight Narrowing 1.365 to <1.635 (n = 68)	Moderate Narrowing 1.635 to <1.99 (n = 68)	Fully Collapsed ≥ 1.99 (n = 68)	
Age, mean (SD)	46.2 (21.3)	45.8 (20.8)	51.7 (20.5)	57.4 (20.4)	0.0032
Shock index, mean (SD)	0.64 (0.19)	0.67 (0.19)	0.67 (0.21)	0.69 (0.29)	0.67
MAP, mean (SD), mm Hg	98.4 (17.0)	98.0 (20.9)	98.0 (16.7)	94.2 (18.1)	0.50
Hemoglobin, mean (SD)	13.3 (2.0)	13.9 (2.1)	13.4 (1.5)	13.3 (2.4)	0.27
Operating room within 24 h, n (%)	13 (21.0), n = 62	15 (24.2), n = 62	11 (16.9), n = 65	15 (23.8), n = 63	0.73
Interventional radiology within 24 h, n (%)	2 (3.4), n = 59	2 (3.5), n = 58	2 (3.3), n = 60	7 (11.9), n = 59	0.11
Hospital days, mean (SD)	5.9 (7.4)	7.4 (10.5)	8.0 (10.5)	7.8 (9.3)	0.56
ICU days, mean (SD)	3.1 (4.9)	3.9 (6.5)	4.8 (6.5)	4.2 (6.4)	0.52
Red blood cell transfusion, n (%)	5 (7.7), n = 65	1 (1.5), n = 65	3 (4.5), n = 67	4 (6.0), n = 67	0.42
Intubated, n (%)	29 (43.9), n = 66	30 (44.8), n = 67	21 (31.3), n = 67	17 (25.8), n = 66	0.055
Died, n (%)	2 (2.9), n = 68	2 (3.0), n = 67	5 (7.5), n = 68	5 (7.4), n = 68	0.44

Four outliers (two with extreme values on hospital days, one on shock index, and one on MAP) were removed.

DISCUSSION

Detection of occult shock and impending shock in patients who arrive with normal vital signs following injury remains difficult. Identification of such patients is important because undertriage in this cohort can delay vital interventions such as massive transfusion protocol activation and mobilization of operative or interventional radiology based on personnel and resources. Conversely, overtriage or unnecessary mobilization of such resources can lead to excessive cost and personnel fatigue. Although scoring systems, such as the ABC⁹ or TASH scores,¹⁰ seek to predict the need for massive transfusion, calculating a score requires specific information, familiarity with the scoring system, and time. Given that the majority of trauma patients with stable or transient vital signs undergo CT scanning, we sought to determine if the static IVC size on CT scan is associated with shock, the need for emergency blood transfusion, invasive procedure, or death. Anecdotally, we had found numerous instances where the IVC was noted to be flat in hemodynamically stable patients following injury and questioned previous studies showing that a flat IVC is associated with shock or death in this cohort.

The presence of shock was assessed using the shock index. Because of the known lack of sensitivity of blood pressure as a predictor of shock, we opted to examine the relationship between the IVC ratio and the shock index. A shock index greater than or equal to 0.7 is associated with a 20% need for massive transfusion, and an increasing shock index has been shown to be directly proportional to a worsening base deficit, ISS, and mortality risk.^{11,12} We also attempted to define an association between IVC size and interventions such as need for emergent operation, angiography, and transfusion as potential harbingers of impending shock.

The study found no association between IVC size and the previously noted end points. We did find that the IVC T/AP ratio is higher (i.e., a more collapsed IVC) in older patients (age > 52 years); however, this finding was not associated with shock based on the shock index. At no time did we observe an association between the IVC T/AP ratio and shock. There was an association between a higher shock index and younger age, intubated patients, and lower MAP; however, IVC T/AP ratio did not differ among the groups. The finding that the T/AP ratio is higher in the elderly is corroborated by a recent study conducted by Milia et al.¹³ where they similarly found that IVC diameter did not correlate with clinical shock for any IVC ratio in a cohort of patients 55 years and older. Their study did find a higher mortality rate in patients with a T/AP ratio of 4; however, this is an extremely exaggerated ratio, which was not evaluated in our study because none of our patients had a T/AP ratio greater than 3.5. Given the findings of both our study and that of Milia et al., we postulate that older patients have a more collapsed IVC at baseline presumably from a more chronic state of dehydration. The higher T/AP ratio found in elderly patients is not associated with increased shock, need for transfusion, intubation status, operative or interventional radiologic procedures, ICU length of stay, or hospital length of stay and thus is of little or no clinical benefit.

Initially, this study also found a positive association between IVC size and shock index, MAP, and length of stay,

but this was mainly caused by outliers. We then removed the outliers and grouped the patients into quartiles based on serially increasing T/AP ratios and found that there was no association between IVC size and any end point. Removing of outliers in this manner is justified because their presence negates the generalizability of the study. The outliers that were removed had extreme values for hospital days (two patients), shock index (one patient), and MAP (one patient). This is the first study to evaluate the data in this fashion.

We believe that our study is more applicable than previous trials in that the average patient had normal appearing vital signs despite being severely injured. It is in this cohort that the clinician is often faced with the difficult task of determining whether the patient is at risk for acute deterioration. Given that these are the patients in whom a CT scan is of particular worth to define the nature of the injury and potential for shock, it is disappointing to find that IVC ratio does not correlate with shock or impending shock. There are several potential reasons for this lack of association including chronic volume depletion caused by inadequate oral intake or diuretic use, adequate physiologic compensation, respiratory variation at the time of image capture, and compensatory venoconstriction.

Our study contradicts other published trials on this topic despite having a similar cohort. A recently published trial found a positive correlation between IVC size and mortality following injury but did not control for outliers that may have skewed the data as we found to be the case.³ Another study of 114 patients found that a vena cava T/AP ratio of 4:1 was associated with shock.⁴ Such an exaggerated degree of IVC collapse is less generalizable to most trauma patients where the average IVC ratio is 1.8 as noted in our study. A third study included only 30 patients and found that the association between IVC size and shock could be obviated by intravenous fluid administration alone and therefore did not represent significant shock.⁵

The strengths of this article include reporting the IVC ratio in a clinically relevant fashion by dividing it into four quartiles and examining this relationship with multiple variables and outcomes in severely injured patients. However, the article has several limitations that must be acknowledged. First, it is a retrospective analysis with all of the limitations inherent in this study design. Second, the study was not powered sufficiently to detect a difference in shock ratio less than 0.05, but such a small difference is not likely to be clinically relevant. Third, the study cohort mostly consisted of only blunt injury, and the results may not be applicable following penetrating trauma. The study also did not assess dynamic changes in IVC size, and it is possible that the degree of IVC collapse may be a more reliable marker for impending shock compared with IVC size alone. In addition, the IVC was only measured in one location, and the study did not include measures such as base deficit or lactate as indicators of shock. Although base deficit has been shown to be associated with shock, most patients do not have an arterial blood gas measured routinely on arrival to the trauma bay, thereby making this end point less clinically useful. Furthermore, lactate clearance rather than initial lactate level is associated with shock and mortality following injury, thereby making this end point also less relevant in the initial assessment of severity of injury. In our study, we show a

21% need for operative intervention within 24 hours. This figure assumes that all operations performed within 24 hours are emergent in nature and includes all operations. It is not possible in a retrospective fashion to determine which operative interventions were associated with impending shock and which were not. Lastly, we did not control for intravenous fluid given in the trauma bay before CT scan because of lack of consistently exact documentation.

CONCLUSION

The static degree of IVC collapse is not associated with shock following injury. Therefore, measurement of IVC size by CT scan for patients with a T/AP ratio between 1 and 3.5 is not clinically relevant and cannot be used to predict mortality, shock, or impending shock.

AUTHORSHIP

R.Ag., S.K., J.M., D.S., N.K., and K.B. contributed to data collection. R.Am., M.R., J.D., and B.S. participated in the data analysis, writing/editing of the manuscript, and critical revisions of the manuscript.

DISCLOSURE

The authors declare no conflicts of interest.

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EDITORIAL CRITIQUE

The purpose of the present study was to determine if inferior vena cava (IVC) size on initial computed tomographic (CT) scan is associated with early shock in injured patients.

Vital signs alone can be an inaccurate measurement of shock (*J Trauma Acute Care Surg*. 2012;73:674–678). Infusing crystalloid in excess, even in patients who are bleeding, has been shown to be deleterious (*Am Surg*. 2012;78:962–968; *J Trauma Acute Care Surg*. 2012;73:674–678). Finding a way to predict a lack of perfusion in the early phase of resuscitation is an important question yet to be answered.

In our experience, IVC diameter and ventricular end-diastolic volume are dynamic parameters. To use IVC diameter change as a surrogate for fluid responsiveness, one is required to evaluate the collapsibility of the vessel during the respiratory cycle (*Am Surg*. 2012;78:468–470; *J Trauma*. 2011;70:56–62; *Intensive Care Med*. 2004;30:1834–1837). In addition, these parameters can change rapidly, depending on the administration of fluid or blood or the physiologic state of the patient. CT scan provides a “snap shot” that may not accurately reflect the overall volume status. In this study, the authors conclude that CT scan estimation of IVC size does not correlate with shock.

Previous authors have attempted to evaluate the utility of IVC diameter using CT scan, resulting in findings inconsistent with the present study (*J Emerg Med*. 2013;45:872–878; *J Trauma*. 2011;70:1358–1361). Both of the previous articles and the present one have the limitation of being retrospective in nature, and none of them report during which phase of respiration these IVC measurements were taken.

Moreover, to diagnose occult shock, one must identify decreased tissue oxygenation before it becomes obvious, causing end-organ damage. Lack of oxygen delivery or extraction in some instances can be independent of volume status, even while in the trauma bay (*Emerg Med Australas*. 2012;24:127–35). We have learned to use IVC and cardiac imaging to guide therapy when the diagnosis of shock has been made clinically. While most of these hypotensive patients show echocardiographic evidence of hypovolemia, some patients can present with other sources for their oxygen debt (*J Trauma Acute Care Surg*. 2014;76:31–7).

Nonetheless, I congratulate the authors for their work and for attempting to find answers to a difficult clinical question.

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