DIAGNOSTIC ACCURACY OF LEFT VENTRICULAR FUNCTION FOR IDENTIFYING SEPSIS AMONG EMERGENCY DEPARTMENT PATIENTS WITH NONTRAUMATIC SYMPTOMATIC UNDIFFERENTIATED HYPOTENSION

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ABSTRACT—The hypothesis of this study states that in emergency department (ED) patients with nontraumatic symptomatic hypotension, the presence of hyperdynamic left ventricular function (LVF) is specific for sepsis as the etiology of shock. We performed a secondary analysis of patients with nontraumatic symptomatic hypotension enrolled in a randomized, clinical diagnostic trial. The study was done in an urban tertiary ED with a census over 100,000 visits per year. Inclusion criteria were nontrauma ED patients aged >17 years, initial vital signs consistent with shock (systolic blood pressure <100 mm Hg or shock index >1.0), and agreement of two independent observers for one sign and symptom of circulatory shock. All patients underwent focused ED echocardiography (echo) during initial resuscitation. Echos were reviewed post-hoc by a blinded physician and categorized by qualitative LVF as hyperdynamic (ejection fraction [EF] >55%), normal to moderate impairment (EF 30%–55%), and severe impairment (EF <30%). Main outcome was the criterion standard diagnosis of septic shock. Analyses include the diagnostic performance of LVF, Cohen’s k for interobserver agreement of LVF, and logistic regression for independent predictors of sepsis. There were 103 echos that were adequate for analysis. The mean age was 57 ± 16.7 years, 59% were male, and the mean initial systolic blood pressure was 83 ± 11.3 mm Hg. A final diagnosis of septic shock was made in 38% (39/103) of patients. Seventeen of 103 (17%) patients had hyperdynamic LVF with an interobserver agreement of k = 0.8. The sensitivity and specificity of hyperdynamic LVF for predicting sepsis were 33% (95% CI 19%–50%) and 94% (85%–98%), respectively. Hyperdynamic LVF had a positive likelihood ratio of 5.3 for the diagnosis of sepsis and was a strong independent predictor of sepsis as the final diagnosis with an odds ratio of 5.5 (95% CI 1.1–45). Among ED patients with nontraumatic undifferentiated symptomatic hypotension, the presence of hyperdynamic LVF on focused echo is highly specific for sepsis as the etiology of shock.

KEYWORDS—Sensitivity, specificity, shock, sepsis, ultrasound, hypotension

INTRODUCTION

The diagnosis of circulatory shock remains one of the most complex clinical scenarios that physicians face. Patients often present with a clinical constellation consistent with circulatory shock (e.g., ill appearance, low blood pressure, high heart rate) but without an obvious or apparent etiology. This undifferentiated clinical picture of shock is most problematic early in the clinical course, when treatment initiatives have the greatest impact. Three previous studies have reported high mortality rates, 16%–25%, among emergency department (ED) patients with nontraumatic undifferentiated shock (1–3). These poor outcomes underscore the importance of utilizing a systematic approach to determining the etiology of shock (1).

Sepsis represents an especially important etiology of shock, causing 215,000 deaths per year in the United States (4), and is a major cause of undifferentiated shock in the ED (1). The importance of early identification of patients with severe sepsis is highlighted by recent investigations that show a substantial improvement in mortality rates when the therapeutic interventions of appropriate antibiotic administration (5) and goal-directed resuscitation (6) are implemented immediately after disease recognition. However, little prior research related to the diagnosis of sepsis has focused on the problem of early detection of sepsis in patients with symptomatic hypotension of unknown etiology (7–12). The hypothesis of the present study states that in a heterogeneous ED population with undifferentiated symptomatic persistent hypotension, the presence of hyperdynamic left ventricular function (LVF) on focused echocardiogram will be specific for the diagnosis of septic shock.

MATERIALS AND METHODS

Patient selection

This study was a preplanned secondary analysis of 184 patients enrolled in a randomized clinical trial investigating the role of an ultrasound protocol in evaluating the etiology of undifferentiated hypotension in the emergency department (1). Subjects were enrolled from July 2002 through September 2003 in the ED at Carolinas Medical Center, an 800-bed teaching hospital with more than 100,000 patient visits per year. This study protocol was reviewed and approved by the institutional review board for the conduct of human research before enrollment of patients. Written informed consent was obtained from all patients.

The explicit inclusion criteria for enrollment in the study included age >17 years, absence of trauma in the previous 24 h, vital signs consistent with shock (systolic blood pressure <100 mm Hg or shock index >1.0 for two consecutive measurements at least 10 min apart) present on initial measurement in the ED, agreement of two independent physician observers on the presence of at least one sign and one symptom of widespread inadequate tissue perfusion, and no immediate identifiable cause of the hypotension. Exclusions included the following: (a) either observer found no symptom and/or no sign of inadequate tissue perfusion; (b) history of “low blood pressure” reported by the patient or discovered from chart review; (c) cardiopulmonary resuscitation, defibrillation, or advanced cardiac life support medications before enrollment; (d) history of significant trauma to the chest or...
abdomen in the previous 24 h; (c) a 12-lead electrocardiogram diagnostic of acute myocardial infarction; (f) presence of an obvious cause of shock that would mandate immediate specific treatment (active gastrointestinal bleeding, known drug overdose, external hemorrhage); (g) referral from another hospital with a known diagnosis; (h) development of signs and symptoms of shock in the ED after the results of diagnostic testing (radiographic imaging and laboratory results) was known to the treating physician; (i) any systolic blood pressure of >120 mm Hg prior to enrollment.

**Study protocol**

The study design specified that clinicians proceed with a standardized evaluation that included a history and physical examination, intravenous access, supplemental oxygen, continuous cardiac monitoring, electrocardiography, anterior–posterior chest radiography, and a point-of-care venous whole-blood assay that measured serum potassium, sodium, blood urea nitrogen, glucose, lactate, hemoglobin, pH, \(P_{O_2}\), \(P_{CO_2}\), and base deficit. In addition, within 30 min of identification and concurrent with initial resuscitation, all patients received an emergency physician–performed goal-directed ultrasound protocol, which was recorded on a VHS tape. Included in this protocol were three cardiac views: (a) subcostal view—the subcostal region of the abdomen was examined in the transverse plane in a sweeping motion to include all four chambers of the heart and the pericardium; (b) Parasternal long cardiac view—the left parasternal chest was examined in a sagittal plane for visualization of the left ventricle, left atrium, right ventricle, aortic valve, and mitral valve; (c) apical four-chamber cardiac view—the apex of the heart was examined in the transthoracic plane for visualization of all four heart chambers and relative ventricular size. All ultrasounds were performed in B-mode gray scale using a Shimadzu SDU-400 ultrasound system with a 3.5-MHz (moldal frequency range 2–4), small footprint, tightly curvilinear array electronic transducer (Shimadzu Medical Systems, Torrance, CA). All clinical and diagnostic data were collected on standardized forms and entered into a database (Excel, Microsoft, Redmond, WA) for later analysis.

All echocardiograms were reviewed post hoc by an emergency physician with focused training in emergency echocardiography who was blinded to subject identity and outcome (13). In light of the lack of published criteria to define a technically adequate echocardiographic study, for study purposes, we defined adequate echocardiographic images as at least two of three views (subcostal, parasternal long axis, apical four-chamber) that were recorded on video that an independent emergency physician trained in emergency echocardiography deemed to contain sufficient visual clarity to determine qualitative left ventricular function. The examiner then graded echocardiograms for qualitative LVF: (a) hyperdynamic (estimated ejection fraction [EF] >55%); (b) normal to moderate impairment (estimated EF 30%–55%); or (c) severe impairment (estimated EF <30%). Left ventricular function was judged by visual inspection of gross wall contraction and wall thickening during systole and relaxation during diastole (3, 13).

**Definition of criterion standard**

The main outcome was the criterion standard final diagnosis of septic shock. The diagnosis of septic shock was established using a predefined, structured method of chart review and explicit consensus criteria published by the American College of Chest Physicians/Society of Critical Care Medicine (14). These criteria require all of the following: (a) at least two of four systemic inflammatory response syndrome (SIRS) criteria—(i) temperature >38°C or <36°C; (ii) heart rate >90 beats/min; (iii) respiratory rate >20 breaths/min or \(P_{CO_2} <32\) mm Hg; (iv) white blood cell count >12 or <4 cell/mm\(^3\) or body temperature >38°C or <36°C) versus the results of the criterion standard diagnosis of septic shock. Odds ratios (ORs) were calculated to determine independent predictors of septic shock as the etiology of nontraumatic shock (n = 103) from logistic regression with bootstrap correction of 95% confidence intervals (16). The candidate independent variables that were entered into the regression analysis were presence of hyperdynamic LVF, WBC >12 or <4 cell/mm\(^3\), body temperature >38°C or <36°C, age >60 years, and the presence of at least one of five predefined preexisting conditions (chronic obstructive pulmonary disease, dialysis-dependent end-stage renal disease, acquired immunodeficiency disease, active malignancy, or paraplegia/quadriplegia).

**RESULTS**

One hundred three of 184 (56%) had visually adequate echocardiograms and were included in this analysis. The criterion standard diagnosis of septic shock was made in 39/103 (38%, 95% CI 28%–50%) of patients. Figure 1 shows the bacteriology and site of infection of the 39 patients with septic shock. The overall in-hospital mortality rate was 20/103 (19%, 95% CI 12%–28%). Hyperdynamic LVF was present in 17/103 (17%, 95% CI 10%–25%). Interobserver agreement of echocardiographic evaluation of qualitative left ventricular function was \(\kappa = 0.80\). We observed no differences in mean age, pulse, respiratory rate, oxygen saturation, white blood cell count (unpaired t test, \(P > 0.05\)), and no difference in the proportions of race, gender, and diagnosis rate of septic shock between the 103 patients included in this study and those excluded (n = 81) for inadequate echocardiograms. Patients included in the analysis had a significantly lower initial systolic blood pressure (83 mm Hg) than those excluded for inadequate echoes (87 mm Hg, \(P = 0.004\), unpaired t test). Table 1 shows the patient demographics and initial ED clinical characteristics. The most common final diagnoses in all 184 patients were septic shock 43%, hypovolemia (dehydration, occult hemorrhage) 33%, cardiovascular (cardiomyopathy, acute coronary syndrome, pulmonary embolism, aortic aneurysm rupture) 15%, and toxicological (calcium antagonist and \(\beta\)-blocker toxicity) 7%.

Table 2–4 show the two-by-two tables constructed to calculate the diagnostic assignments of hyperdynamic LVF, WBC >12 or <4 cell/mm\(^3\), and body temperature >38°C or <36°C for the diagnosis of septic shock. Hyperdynamic LVF had a low sensitivity; however, it had the highest specificity of 94% (95% CI 85%–98%) among the three variables examined. We interpret this finding to indicate that the presence of hyperdynamic LVF on an echocardiogram in the setting of undifferentiated symptomatic hypotension is highly suggestive of sepsis as the etiology of shock. The likelihood ratio (LR) of a positive finding of hyperdynamic LVF was 5.3 (95% CI 2.0–14.7), which is higher than the LR (+) of either WBC >12 or <4 cell/mm\(^3\) (2.0; 95% CI 1.3–3.2) or body temperature >38°C.
or <36°C (2.8; 95% CI 1.7–4.8). The combination of WBC >12 or <4 cell/mm³ and body temperature >38°C or <36°C for the diagnosis of septic shock resulted in worse diagnostic performance than individual tests, with a sensitivity of 38% and a specificity of 50%. The details of the four false-positive echocardiographic examinations that found hyperdynamic LVF are shown in Table 5.

To examine the relative importance of ED clinical variables as predictors of septic shock, multivariate logistic regression analysis was performed on five variables, and the results are shown in Table 6. The logistic regression data indicate that the strongest independent predictors of the presence of septic shock were body temperature >38°C or <36°C (OR 5.8, 95% CI 1.7–21) and hyperdynamic LVF (OR 5.5, 95% CI 1.1–45).

**DISCUSSION**

This study tested the hypothesis that in the setting of undifferentiated symptomatic hypotension, the presence of hyperdynamic LVF on focused ED echocardiography would be a specific finding for sepsis as the etiology of shock. We found the lower limit of the 95% confidence intervals for the specificity of hyperdynamic function to be higher than the point estimate of specificity for the other parameters classically associated with severe infections such as an abnormal WBC count or abnormal body temperature. In addition,

![Fig. 1](https://example.com/figure1.png)

**FIG. 1.** (A) Bacteriology of 39 patients in the study group with the final diagnosis of septic shock. (B) Site of infection as determined by either positive culture or suspected infection as evidence by a high-risk diagnosis for infection as defined in text.
Hyperdynamic LVF had the highest positive likelihood ratio of 5.3 and remained a significant independent predictor of sepsis as the etiology of shock in the five-variate logistic regression model. We interpret these results to demonstrate the positive diagnostic potential of hyperdynamic ventricular function in the setting of undifferentiated symptomatic hypotension for implicating sepsis as the potential etiology of shock.

The presence of hyperdynamic ventricular function in patients with septic shock is a well recognized compensatory mechanism to vasodilatation and relative reduction in ventricular filling. Previous investigations have examined the cardiovascular patterns of septic patients in relation to prognosis or outcome. Septic patients with hyperdynamic function are thought to be in a “distributive phase” of shock manifested by a high cardiac output and low systemic vascular resistance. If present early in the clinical course, this hemodynamic pattern often persists and is associated with nonsurvival (17). This is in distinction to survivors of sepsis who have either an initially normal cardiac contraction or who are initially hyperdynamic and rapidly exhibit reversion to a normal or hypodynamic left ventricular contractile state (18). We were unable to identify previous reports investigating the diagnostic ability of various left ventricular contractile patterns in patients with undifferentiated shock for identifying sepsis.

The importance of establishing the diagnosis of septic shock is evidenced by the high mortality rate, between 30%–50%, in most studies (4, 6, 19). Once the diagnosis is established, many new therapeutic interventions have been shown to improve the outcomes of these patients, including activated protein C (19), early appropriate antibiotic administration (5), and goal-directed resuscitation (6). Clinical and laboratory parameters that are classically associated with severe infection including leukocytosis, leukopenia, hypothermia, and hyperthermia have been previously shown to be limited by their lack of sensitivity and specificity for severe infection (8, 11, 20). In the present study we compare these classic findings to echocardiographic findings in a heterogeneous population of ED patients with shock of uncertain origin. Our findings agree with previous studies in confirming the marginal to poor performance of WBC count or body temperature for identifying sepsis. In addition, to our knowledge, this is the first report to identify hyperdynamic cardiac function as a potential clue to the identifying sepsis as the etiology of shock of unknown origin.

Although we found hyperdynamic LVF to be a specific finding for septic shock, we do not suggest that hyperdynamic function excludes other etiologies of shock. Our patient population was selected based on explicit inclusion and exclusion criteria to identify patients who had no obvious or overt cause of their shock after an initial history, physical examination, and pertinent bedside laboratory testing. Thus, applying our findings to all patients in shock may result in a lower specificity than we have reported. Patients with an
obvious cause of shock such as large volume losses, impaired oxygen-carrying capacity (severe anemia or toxins), or endocrine dysfunction (thyroid storm) may have hyperdynamic LVF but not sepsis. A hypothetical patient with any of these conditions could be harmed by misdiagnosis as having septic shock. Thus, we emphasize that hyperdynamic function, as with any diagnostic test, must be interpreted in the context of all available clinical data in the setting of undifferentiated symptomatic hypotension.

This report has several limitations that warrant discussion. First, we provide no physiological measurement to prove the presence of circulatory insufficiency in our patients. We submit that it would be implausible to measure oxygen delivery and consumption on all ED patients with clinical suspicion for shock. Instead, we incorporated the surrogate marker of independent physician observers to identify patients with clinical characteristics and vital signs consistent with circulatory insufficiency. Also, for this investigation, all echocardiograms were graded post hoc. It is possible that, if the echocardiograms had been interpreted in real time, they would have performed with different diagnostic accuracies. Echocardiograms were also interpreted by emergency physicians with focused training. Had they been interpreted by Level 3 echocardiographers it is possible our results would be altered. Only 56% of patients had technically adequate echocardiograms for analysis, which raises the concern of selection bias. However, analysis of demographics, clinical characteristics, and diagnoses revealed no significant differences between the included and excluded groups other than a 4-mm Hg difference in the initial systolic blood pressure, which we submit is likely not of clinical significance. Another limitation of our study is the size of the sample studied. It is possible that a larger sample would have resulted in different estimation of the diagnostic performance of hyperdynamic left ventricular function. This was a single-center study with relatively specific inclusion criteria (nontrauma adult hypotensive patients), both of which limit the generalizability of the results to other centers and patient populations (i.e., trauma patients and nonhypotensive patients).

**CONCLUSION**

In conclusion, among ED patients with nontraumatic undifferentiated symptomatic hypotension, the presence of hyperdynamic left ventricular function on focused echocardiogram is highly specific for sepsis as the etiology of shock. Future studies should prospectively confirm these findings before their widespread acceptance into clinical practice.

**REFERENCES**


