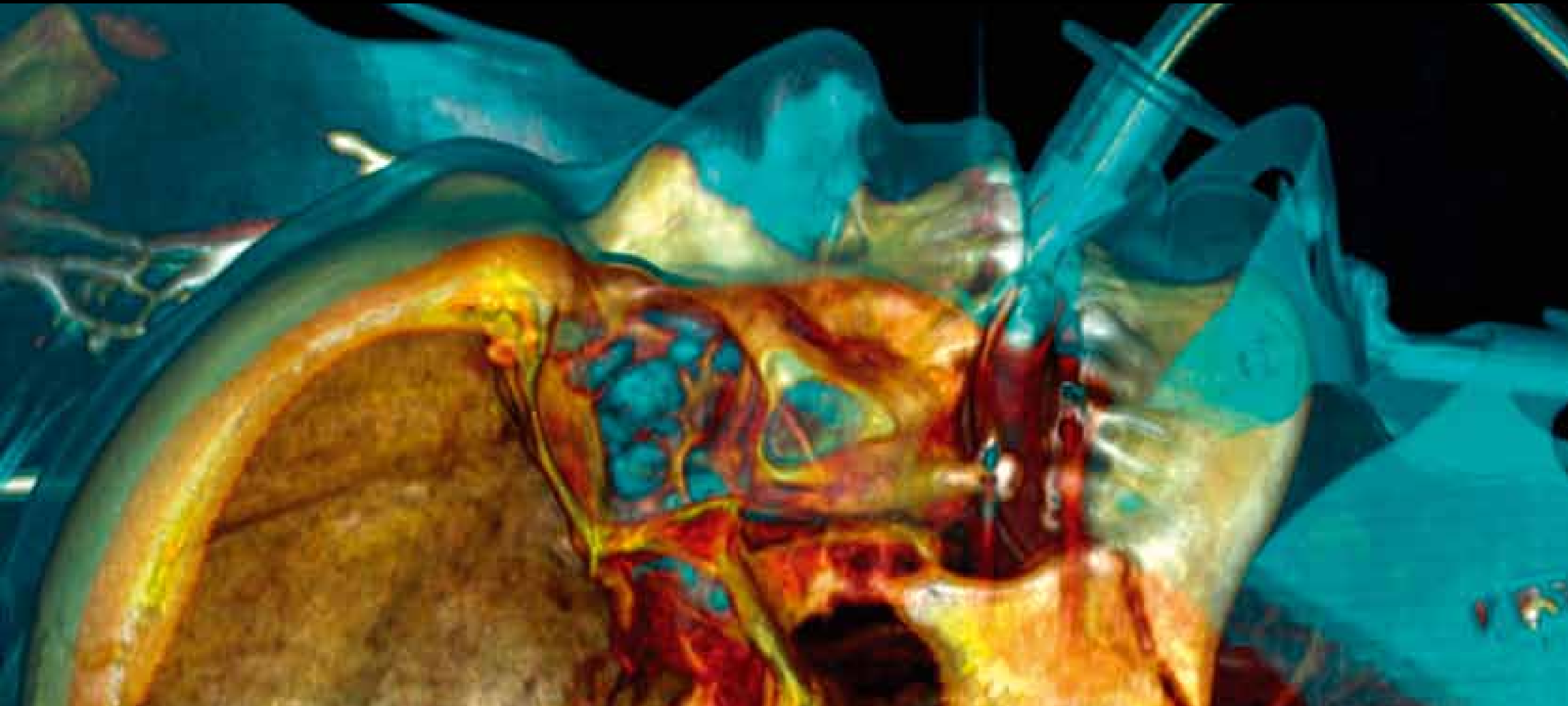
Critical Care Research and Practice

Ultrasound Applications in Critical Care Medicine

Guest Editors: Dimitrios Karakitsos, Michael Blaivas, Apostolos Papalois, and Michael B. Stone



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Editorial Board

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Editorial

Ultrasound Applications in Critical Care Medicine

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The use of ultrasound has expanded enormously over the last two decades in critical care research and practice. Despite the fact that the method has several inherent limitations and is largely operator dependent, it enables clinicians for rapid, by-the-bed, and relatively inexpensive diagnostic evaluation of unstable patients. Point-of-care ultrasound applications such as lung ultrasound are gradually replacing traditional imaging modalities (i.e., chest X-rays), while the use of ultrasound for procedure guidance has been shown to reduce complications and thus to increase patients' safety [1–3].

In this issue, various papers illustrated the important role of ultrasound in the intensive care unit (ICU). K. Stefanidis et al. applied echogenic technology during ultrasound-guided cannulation of the internal jugular vein (IJV) and of the subclavian vein (SCV), respectively. Both case-control studies included intubated critical care patients and were performed under controlled ICU conditions. Ultrasound-guided cannulation of the IJV was attempted on the transverse axis and cannulation of the SCV on the longitudinal axis via an infraclavicular approach. In both studies, the use of echogenic technology significantly improved cannula visibility and decreased access time and technical complexity optimizing thus real-time ultrasound-guided central venous cannulation irrespective of the technique used.

Current trends promote the optimization of two-dimensional ultrasound imaging by applying various technologies. Advances in ultrasound software can reduce artifacts and "noise" such as speckle arising from coherent wave interference or clutter arising from beamforming artifacts, reverberations, and other acoustic phenomena, while infusion of contrast agents during imaging facilitates interpretation of various pathologies [4, 5]. In that sense, the application of echogenic material could optimize procedural ultrasound applications. This may be of importance as ultrasound scanning is oftentimes performed under suboptimal conditions in the ICU, while the presence of mechanical ventilation, air and/or edema, may affect the clarity of images [6]. The clinical notion that IJV cannulation in patients at risk for intracranial hypertension could impair cerebral venous return was explored by D. Vailati et al. in a prospective study. They used two-dimensional and Doppler techniques to evaluate IJV cross-sectional diameter and flow patterns before and after ultrasound-guided cannulation in neurosurgical patients placed in a supine or a head-up position at 30 degrees. No significant alterations in IJV flow rates following cannulation were recorded; however, the study was focused only on the venous system and no data about the arterial flow were presented. Future studies exploring changes in both vascular circuits are clearly required to clarify further possible changes in cerebral hemodynamics that might be attributed to the cannulation procedure itself and/or to the relevant body position acquired. In an interesting vascular study, M. Blaivas et al. studied retrospectively 320 critical care patients receiving a SCV or IJV central venous catheter (CVC) to evaluate the rate of upper extremity deep venous thrombosis (UEDVT) and the sonographic appearance of thrombi. In this series, 2.7% of patients died and 5.5% had pulmonary embolism, while approximately 11% had UEDVT. Risk factors associated with UEDVT were presence of CVC (odds ratio (OR) 2.716, $P = 0.007$), malignancy (OR 1.483, $P = 0.036$), total parenteral nutrition (OR 1.399, $P = 0.035$), hypercoagulable state (OR 1.284, $P = 0.045$), and obesity (OR 1.191, $P = 0.049$). Eight thrombi were chronic, and 28 were acute. Notably, the authors presented a new sonographic sign which characterized acute thrombosis: a double hyperechoic line at the interface between the thrombus and the venous wall. They concluded that the presence of CVC was a strong predictor for the development of UEDVT, while the actual rate of subsequent PE was low. Surely, contrast venography remains a standard diagnostic technique in the evaluation of UEDVT; however, ultrasound has a clear established diagnostic role, while imaging with gadolinium contrast-enhanced magnetic resonance imaging is routinely used but has not been properly validated yet. Moreover, the recognition of gadolinium as a cause of nephrogenic systemic fibrosis has increased interest in noncontrast magnetic resonance venography [7].

Apart from vascular ultrasound studies discussed above, P. Myrianthefs et al. evaluated whether routine ultrasound examination may illustrate gallbladder abnormalities, including acute acalculous cholecystitis (AAC) in a cohort of critical care patients. The authors evaluated major (gallbladder wall thickening and edema, sonographic Murphy's sign, pericholecystic fluid) and minor (gallbladder distention and sludge) ultrasound criteria. Notably 47.2% of patients showed at least one abnormal imaging finding; however, only 5.7% of cases were identified as AAC. They conclude that diagnosis of AAC requires high levels of clinical suspicion. Nevertheless, this series was small and future larger studies are clearly required to investigate the potential screening role of ultrasound in detecting gallbladder disorders in the ICU.

Reading further on, three interesting papers focus on echocardiography emerge. T. Bagger et al. compared conventional and automated speckle tracking echocardiography to determine whether left ventricular (LV) systolic function could be estimated from one single imaging plane. They found a bias of 0.6 (95% CI −2.2–3.3) for global peak systolic strain comparing the automated and the conventional method. Notably, global peak systolic strain of apical 4-chamber cine-loops versus averaged global peak strain obtained from apical 4, 2, and long axis cine loops showed a bias of 0.1 (95% CI −3.9–4.0), and agreement between 4-chamber subcostal and apical global peak systolic strain was 4.4 (95% CI −3.7–12.5). Hence, they found good agreement between conventional and automated methods; moreover, speckle tracking ultrasound applied to single apical 4-chamber cine loops showed excellent agreement with overall averaged global peak systolic strain. In contrast, subcostal 4-chamber cine loops were rather unsuitable for the automated method. Technical issues related to the subjective evaluation of LV function may be solved by the application of advanced echocardiographic methods. Implementing the latter in routine practice remains debatable but represents an option that should be discussed awaiting the validation of currently applied basic echocardiography training programs for noncardiologists. Despite the fact that only basic elements of echocardiography are currently integrated in point-of-care ultrasound training programs, the method represents a "hot spot" of debate in critical care research and practice. J. C. Mandeville and C. L. Colebourn discussed whether transthoracic echocardiography can predict fluid responsiveness in the critically ill following a thorough literature search. They concluded that inferior vena cava analysis and transaortic Doppler signal changes with the respiratory cycle in mechanically ventilated patients were predictors of fluid responsiveness. Fluid responsiveness in the critically ill is a subject of ongoing research. Oftentimes various pathologies which may affect volume status coexist, while the clinical picture can be easily blurred in ICU patients. Recently, suggestions of noninvasive hemodynamic models comprising of lung and cardiovascular ultrasound emerged [8]. Development of advanced noninvasive hemodynamic monitoring models based on current ultrasound techniques remains to be explored in future studies. Surely, the role of echocardiography in hemodynamic monitoring remains pivotal. Also, clinical entities such as LV diastolic dysfunction become increasingly recognized in ICU patients. In their expert analysis, L. A. Eisen et al. illustrated that heart failure with a normal or nearly normal LV ejection fraction (HFNEF) may represent more than 50% of heart failure cases. However, there is a relative lack of information regarding LV diastolic dysfunction incidence and prognostic implications in critical care patients. In the ICU, many factors related to patient's history, or applied therapies, may induce or aggravate LV diastolic dysfunction, while the latter was linked as well to weaning failure. This may impact on patients' morbidity and mortality. Finally, in this issue, K. Stefanidis et al. evaluated prospectively the utility of lung ultrasound in detecting and localizing alveolar-interstitial syndrome in respective pulmonary lobes as compared to computed tomography scans in ICU patients. The authors designated lobar reflections along intercostal spaces and surface lines by means of sonoanatomy in an effort to accurately localize lung pathology, while the presence of diffuse comet-tail artifacts was considered a sign of alveolar-interstitial syndrome. They found that lung ultrasound showed high sensitivity and specificity values (ranging from over 80% for the lower lung fields up to over 90% for the upper lung fields) and considerable consistency in the diagnosis and localization of alveolar-interstitial syndrome. The diagnostic role of lung ultrasound is well established in the ICU. As the method grows and technology advances, lung ultrasound may represent an alternative to computed tomography in the monitoring of pulmonary disorders, although further studies are clearly required to validate this notion.

Surely, applying point-of-care ultrasound in the ICU requires formal training. Critical care fellowships offered by European and US residency programs are currently taking on the burden of such responsibility [9]. Notably, several US-based institutions are integrating ultrasound teaching programs in medical schools' curricula as this would aid all graduates to obtain basic ultrasound skills [10, 11]. Such skills should not be used as a replacement to standard physical examination and/or to clinical judgment, but as an adjunctive tool that could facilitate patients' diagnosis and treatment. Changing practices by implementing ultrasound technology in the ICU is a cost-efficient and robust strategy which signals an era of pure "visual" medicine.

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Clinical Study

An Ultrasound Study of Cerebral Venous Drainage after Internal Jugular Vein Catheterization

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Objectives. it has been advocated that internal jugular vein (IJV) cannulation in patients at risk for intracranial hypertension could impair cerebral venous return. Aim of this study was to demonstrate that ultrasound-guided IJV cannulation in elective neurosurgical patients is safe and does not impair cerebral venous return. *Methods*. IJV cross-sectional diameter and flow were measured using two-dimensional ultrasound and Doppler function bilaterally before and after IJV cannulation with the head supine and elevated at 30°. *Results*. Fifty patients with intracranial lesions at risk for intracranial hypertension were enrolled in this observational prospective study. IJV diameters before and after ultrasound-guided cannulation were not statistically different during supine or head-up position and the absolute variation of the venous flow revealed an average reduction of the venous flow after cannulation without a significant reduction of the venous flow rate after cannulation. *Conclusions*. Ultrasound-guided IJV cannulation in neurosurgical patients at risk for intracranial hypertension does not impair significantly jugular venous flow and indirectly cerebral venous return.

1. Introduction

Patients with head injury, cerebral haemorrhage, brain tumors, and hydrocephalus have a hemodynamic that could be easily impaired. In these patients, internal jugular vein (IJV) represents the main cerebral venous output and any reduction in its flow could create an increase in cerebral blood volume and intracranial pressure (ICP) [1–3].

It has been advocated for decades that internal jugular vein cannulation should have to be avoided in any kind of neurosurgical patients in order to avoid intracranial hypertension (HICP) and subclavian vein cannulation was advised as the best choice even if this procedure could be associated with major and life-threatening complications.

Furthermore, some authors demonstrated that the positioning of a central venous catheter (CVC) in the internal jugular vein may cause a lesion of the valve of the IJV [4] and a jugular vein incompetence [5] and there are some other manoeuvres that can cause this impairment till to the transient global amnesia [6, 7], with the appearance that a retrograde jugular flow is the cause of cardiovascular and neurological problems [8].

Several publications supported these assertions [9–12], while only two works stated the opposite. Goetting et al. [13] analyzed a population of 37 children with elevated ICP; after a central venous line placement in the IJV, variation of ICP was measured and this study demonstrated that IJV cannulation did not increase ICP. Woda et al. [14] took into consideration 11 adult patients, stating that the ICP increase after the positioning of CVC in IJV was not significant. These two studies did not evaluate the physiopathological compensatory mechanism that avoided cerebral venous output impairment.

When cerebral veins are suddenly blocked, the brain begins to undergo an engorgement process. By increasing the cerebral venous volume, the cerebrospinal fluid is reabsorbed and/or moved towards the subarachnoid space causing a reduction of the ventricles size. In order to restore normal values of pressure and volume of the cerebral venous blood, it causes a considerable effort in channeling the blood through the collateral vessels [15].

This response is definitely less valid in case of occlusion or acute obstruction of the main cerebral venous output, while it is more effective both in cases where thrombosis occurs slowly (e.g., invasion of the sagittal sinus by meningiomas) and in those where the obstruction is extracranial, using forms of cardio circulatory compensation. When major cerebral venous occlusion occurs, the brain is congested and interstitial oedema and haemorrhage could appear. Internal jugular vein cannulation may have a double effect on intracranial pressure.

First, cerebral venous blood moves through the cerebral venous sinus, reaching the sigmoidal sinus, which drains in the jugular bulb and then in the internal jugular vein [1]. An occlusion, even if partial, of the IJV, which represents the main cerebral venous draining system, could cause an engorgement of the venous sinus system with a consequent increase of ICP [2]. The second mechanism results in the inability of the cerebrospinal fluid to leave the skull through the arachnoid granulations.

The cerebral venous pressure is generally around 5 mm Hg, while the cerebrospinal fluid has pressure values between 5 and 20 mm Hg [16]. If the venous pressure increases due to the obstruction of the draining system, cerebrospinal fluid could not be removed, as what normally happens from the arachnoid villi. This series of events can cause an increase of ICP due to an increased amount of cerebrospinal fluid.

Ultrasound-guided cannulation has been suggested to be safe and effective by meta-analyses and guidelines [17–20]. For this reason this procedure should be preferred to subclavian cannulation in order to avoid post procedural major complications but with avoiding cerebral damage. Our primary endpoint was to measure, by means of ultrasound, if IJV cross-sectional diameter and flow in elective neurosurgical patients at risk for intracranial hypertension were different before and after IJV cannulation. Our secondary endpoint was to measure IJV before and after its cannulation when the head was placed in supine position and the head tilted up at 30°, a commonly used position for treatment of intracranial hypertension.

2. Materials and Methods

National Neurological Institute “C. Besta” Ethics Committee was informed according to Italian Guidelines for clinical observational studies and approved this study. Between November 2010 and May 2011, fifty patients affected by intracranial lesions, with neurological and radiological findings of intracranial hypertension (presence of two or more of the following signs: midline shift >1 cm, cerebral oedema, reduction of mesencephalic cisterns, obstructive hydrocephalus), were recruited. Inclusion criteria were patients scheduled for major neurosurgical procedures, ASA-physical status I and II, GCS 12–15 requiring a central venous line for perioperative hemodynamic management after informed written consent.

Exclusion criteria were emergency surgery, ASA physical status 3 or more, any condition causing elevated right-sided pressures, GCS ≤ 10, any alteration of bleeding according to British Society of Haematology [18], previous neck surgery (thyroidectomy, tracheostomy, radical neck dissection), IJV thrombosis detected by compressive ultrasound [21], and patients with an accidental carotid artery puncture and/or a multiple vein puncture.

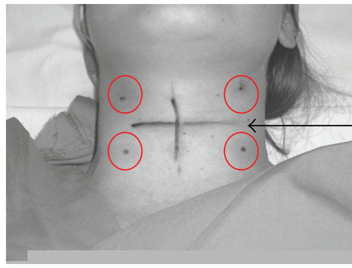

Figure 1: Landmarks used for measurements (in circle) and cricoid cartilage (arrow).

Study Design. Five anaesthesiologists experts in ultrasound-guided cannulation and with advanced ultrasound skills performed the study. During the study, the same ultrasound machine (MicroMaxx, Sonosite Inc. Bothell, WA, USA) with a 13–6 MHz broadband linear probe (L25e, Sonosite Inc. Bothell, WA, USA) and Doppler function was used.Central venous cannulation of the IJV was performed using a double-lumen catheter (Arrow International, Reading, USA) avoiding occupying more than 1/3 of the IJV sectional diameter with the catheter (e.g., a 5 mm cross-sectional IJV diameter was occupied with a catheter no more than 5 F). All IJV catheterizations were done using a real-time US-guided technique with short-axis visualization of the vein an out-of-plane puncture.In all cases there were two anaesthesiologists performing the study. The first one was in charge of positioning the probe on the skin landmarks and of cannulating IJV; the second one was responsible for measuring sizes and flows of the jugular veins before and after CVC placement. All cannulation procedures were carried when patients were on general anaesthesia, mechanically ventilated, and in supine position. IJV measurements were performed at two points for each jugular vein at end expiration (Figure 1) [22]. Having identified the cricoid cartilage, two points were marked bilaterally: the first one located 2 cm up of the cricoid in correspondence with the IJV and the second one located 2 cm down of the cricoid in correspondence with the IJV. At this point bilateral IJV cross-sectional diameters, IJV cross-sectional area, velocimetry, and valve continence (by mean of Color-Doppler function) were measured. The same measurements were therefore carried out with patient’s head in supine position (0 degree) and head tilted up at 30°. The head elevation was obtained and measured by protractor. With a sterile technique (neck skin disinfection and probe isolation with sterile cover) and under ultrasound guidance, IJV ultrasound-guided cannulation was then performed at a point between the two landmarks labelled. An out-of-plane technique was used for vein puncture. The choice for cannulating right or left IJV was taken after measuring IJV cross-sectional diameters and flows and according to surgical requirements. The larger IJV (dominant) was usually cannulated. After central venous line placement, the same measurements were repeated at same points previously marked, on both sides and with the head in supine position and tilted up at 30°.

Data Collection. Patient's demographic data, ASA-physical status, body-mass index, location, and type of intracranial lesions were recorded in a special data collection sheet. Ultrasound measurements were performed collecting major IJV cross-sectional transverse diameter, IJV cross-sectional area, and IJV Doppler velocimetry in the four-labelled landmarks points. IJV flow was calculated as result of the sum of the values at the top or at the bottom of the IJV (e.g., IJV top flow 0° = IJV right side flow 0°+ IJV left side flow 0°). All these measurements were repeated before and five minutes after IJV cannulation. Cerebral venous flow was calculated according to the formula:

$$\text{Flow (mL/min)} = \text{IJV cross-sectional area } (\text{cm}^2) \times \text{Doppler Velocimetry (cm/sec)} \times 60. \quad (1)$$

Mean IJV flow variation rate was calculated according to the formula:

$$\text{IJV Variation rate} = (\text{IJV flow after cannulation} - \text{IJV flow before cannulation}) \times 100/\text{IJV flow before cannulation}. \quad (2)$$

In order to assess if IJV cannulation impaired cerebral venous output, the anaesthesiologist that performed the cannulation asked the neurosurgeon before dura mater opening to grade the rate of intracranial hypertension with a clinical subjective score (1-normal appearance of the dura mater, 2 thin dura mater, 3-brain swelling after dura mater opening).

Statistical Analysis. In order to calculate patients' sample size we hypothesised to detect an increase of mean IJV cross-sectional of 30% from 1.3 to 1.7 mm (SD 0.5) ($\alpha = 0.05$; $\beta = 0.1$). For this purpose, we enrolled 50 patients. All data are presented as means and their standard deviations. A t-test for paired data was used. The mean diameters before and after central venous cannulation were compared using a t-test for paired data. The normality of flows and diameters distributions was evaluated using the Kolmogorov-Smirnov test. A P-value < 0.05 was considered as significant.

3. Results and Discussion

Fifty patients were included in the study; four patients were excluded after IJV cannulation because of repeated vein puncture ($n = 3$) and one after multiple jugular puncture with concomitant accidental carotid puncture ($n = 1$; right and left IJVs were posterior to carotid artery). These major complications could probably be avoided if in-plane real-time ultrasound needle guidance would be used for IJV cannulation. Forty-six patients were successfully included in the analysis. Demographics' characteristics are depicted in Table 1.

Table 1: Demographic characteristics. [a]Values are expressed as mean ± SD.

	Total (n = 46)
Sex (M/F)	22/24
Age[a] (years)	51.73 ± 14.30
BMI[a]	26.07 ± 5.24
ASA physical status (I/II)	21/25
IJV cannulation side (right/left)	32/14

Diameters of the jugular veins measured in each landmark are expressed as mean ± standard deviation (Table 2). There was no significant difference between IJV cross-sectional diameters before and after cannulation, both at 0° and at 30° degree of head elevation.

Flow of the jugular vein measured at each landmark is expressed as mean ± standard deviation (Table 3). Ipsilateral and contra lateral IJV flows were not significantly different after cannulation. For this reason, we calculated IJV global flow and IJV global flow variation rate. A reduction of the absolute variation of IJV flows was observed at each landmark point, but with significant value only at the bottom point of the IJV when the head was at 0° (IJV 0° bottom: −68.2 ($P = 0.01$)). However, IJV flow variation rate resulted to be not significant in any of the four landmark points.

At each measuring point, there was also a reduction of the mean values of the IJV flow when the head was tilted up from 0° to 30° both in the cannulated and the non cannulated vein.

Data obtained by Color-Doppler analysis of the IJV valve after IJV cannulation did not reveal any valve incontinence after central venous line placement. No intra operative clinical signs of intracranial hypertension (grade 2 or 3: thin dura, brain swelling) were recorded in these patients.

Our study demonstrated that IJV cannulation in elective neurosurgical patients at risk for intracranial hypertension does not impair cerebral venous return. In these patients, IJV diameters and venous flow were studied before and after central venous cannulation and with patients lying in supine position and with head tilted up to 30°. Our results demonstrate that, in supine position, mean IJV cross-sectional diameters at the top of the IJV were reduced after cannulation while they were increased at the bottom of the vein after cannulation. On the contrary, when the head was tilted up to 30°, IJV diameters increased at all points of examination after vein cannulation. Despite all these differences were not significant before and after cannulation, these differences suggest how the elasticity of the vein wall allows reestablishing a balance in the vein flow increasing IJV diameter and maintaining the same cerebral venous output. The mechanism of compensation should be an opening of the IJV valves that do allow impairing cerebral venous return.

IJV flow variation rates demonstrate a light reduction of the cerebral venous drainage after IJV cannulation. This, in part, could justify why all our patients did not have any intraoperative clinical signs of cerebral oedema.

Table 2: Analysis of IJV cross-sectional diameters for each landmark point, with head in supine and head elevation at 30° (mean ± SD).

		Top			Bottom		
		IJV diameter before cannulation	IJV diameter after cannulation	P-value	IJV diameter before cannulation	IJV diameter after cannulation	P-value
Head 0°	R	1.29 ± 0, 38	1.23 ± 0.34	0.36	1.50 ± 0.57	1.55 ± 0.50	0.41
	L	1.03 ± 0.33	1.13 ± 0.43	0.09	1.21 ± 0.44	1.26 ± 0.46	0.29
Head 30°	R	0, 95 ± 0, 41	0, 99 ± 0, 30	0.47	1, 14 ± 0, 49	1, 22 ± 0, 48	0.14
	L	0, 80 ± 0, 27	0, 85 ± 0, 29	0.18	0, 96 ± 0, 40	0, 97 ± 0, 42	0.72

Table 3: Flows analysis results.

		IJV flow before cannulation	IJV flow after cannulation	Absolute variation		IJV flow variation rate	
		Mean ± SD	Mean ± SD	Mean	P-value*	Mean	P-value**
IJV 0°	Apex	891.4 ± 440.9	854.5 ± 396.1	−36.9	0.14	−1.8%	0.44
	Base	833.7 ± 384.3	765.5 ± 376.8	−68.2	0.01	−5.5%	0.14
IJV 30°	Apex	540.8 ± 375.1	515.7 ± 347.4	−25.1	0.12	−2.7%	0.31
	Base	481.8 ± 315.5	465.4 ± 293.5	−26.4	0.18	−0.4%	0.90

There are no previous data regarding IJV flow measurements in patients with intracranial hypertension or at risk for it because of intracranial masses. It has been suggested that a 30° tilting of the head could reduce cerebral blood volume by increasing cerebral venous drainage.

Given our results it seems that this is not justified because after positioning the head at 30° there was a reduction of the IJV global flow both when IJV was free from catheter and when IJV was cannulated. We have no clear explanation for these data but one main concern could be that in our study we measured IJV flow only five minutes after tilting the head and after positioning the catheter. One more explanation could be that cerebral blood volume after head elevation is altered not only in terms of output (venous drainage) but also in input (arterial flow). Our measurements were done probably too early after head elevation and this could not be enough to allow a balance for the cerebral hemodynamic.

Further studies are required in order to determine the cause of mean IJV flow reduction when the head is elevated at 30° by measuring both components of the cerebral blood volume and to evaluate if a longer time of head elevation allows cerebral flows to obtain a balance and a reduction of ICP.

Our study has some limits due to the small sample size and because intracranial pressure was not measured during IJV measurements by assessing it with a simple clinical score. Further research should be focused on a large population of patients with intracranial hypertension in order to determine if the dimensions of the central venous catheters impact on cerebral venous return.

Ultrasound-guided cannulation of the IJV is a safe procedure and, when using ultrasound, a study of IJV diameters and flows in neurosurgical patients could avoid cannulating the vein with the wrong central venous catheter worsening cerebral damage.

4. Conclusions

Central venous catheter placement in the IJV determines not significant changes in the cerebral venous return increasing mean IJV diameters and a reduction in mean IJV global flow in the internal jugular veins. Our results confirm that cerebral venous output has a good compensation system. IJV central venous cannulation is safe because it does not create any significant reduction in cerebral venous flow drainage in patients with risk for cerebral hypertension. The increase of IJV diameters demonstrates that there are some changes after central vein cannulation and an ultrasound evaluation of these diameters and IJV flow should be performed after IJV cannulation in every patient with intracranial hypertension or when bilateral cannulation of the internal jugular vein has to be performed (e.g., for jugular bulb oxygen saturation monitoring).

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Review Article

Left Ventricular Diastolic Dysfunction in the Intensive Care Unit: Trends and Perspectives

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Heart failure with a normal or nearly normal left ventricular (LV) ejection fraction (HFNEF) may represent more than 50% of heart failure cases. Although HFNEF is being increasingly recognized, there is a relative lack of information regarding its incidence and prognostic implications in intensive care unit (ICU) patients. In the ICU, many factors related to patient's history, or applied therapies, may induce or aggravate LV diastolic dysfunction. This may impact on patients' morbidity and mortality. This paper discusses methods for assessing LV diastolic function and the feasibility of their implementation for diagnosing HFNEF in the ICU.

1. Introduction

Diastolic heart failure (DHF) has been described since 1998 [1]. At that time, it was thought to be less frequent than systolic heart failure (SHF) and have a better prognosis [2]. Nowadays, DHF is known to account for more than 50% of all heart failure patients, with a similar prognosis to SHF [3–5]. Diastolic left ventricular (LV) dysfunction is associated with slow LV relaxation and increased LV stiffness [6]. Many factors can result in DHF such as ventricular hypertrophy, myocardial fibrosis, infiltrative disease, pericardial constrictive disorders, right ventricular (RV) alterations due to a variety of causes, advanced age, hypoxia, and acidosis, but most commonly coronary artery disease (CAD) [3, 4]. Therefore, DHF may coexist with SHF, leading to the formulation of a "single syndrome" hypothesis, which postulates that diastolic LV dysfunction is actually a precursor of SHF and is due to increased interstitial deposition of collagen and modified matricellular proteins [3]. For this reason, experts propose the term heart failure with normal ejection fraction (HFNEF) instead of DHF, to indicate that HFNEF could be a precursor to heart failure with reduced LVEF [3, 4].

Diagnosis of HFNEF requires the presence of heart failure symptoms and signs, with normal or mildly abnormal LVEF, (LVEF >50% and LV end-diastolic volume index <97 mL/m^2), and evidence of LV diastolic dysfunction [3, 4]. The latter is associated with slow LV relaxation, increased LV stiffness, reduced ventricular compliance, and increased LV filling pressure. Thus, it can be diagnosed invasively by means of right heart catheterization (LV end-diastolic pressure >16 mmHg or mean pulmonary capillary wedge pressure >12 mmHg). Alternatively, echocardiography may be used for noninvasive assessment of diastolic dysfunction. Newer echocardiographic techniques like tissue Doppler (TD) have provided indices of LV diastolic dysfunction like the TD derived $E/E' > 15$ (early transmitral flow velocity/early TD diastolic lengthening velocity). If this ratio is inconclusive, ($15 > E/E' > 8$), then additional echocardiographic information relevant to LV diastolic dysfunction can be derived by Doppler interrogation of mitral valve or pulmonary veins or left atrial volume index. Finally, elevated levels of plasma natriuretic peptides may aid in the diagnosis of DHF [3, 4, 7].

Nagueh et al. provide a simple recommendation for grading LV diastolic dysfunction by using pulsed Doppler at the mitral valve and at the mitral annulus [7]. This is briefly reviewed here but can be seen in full detail in the original paper [7]. In all forms of diastolic dysfunction left atrial volume should be greater than 34 mL/m^2. In mild (Grade I) diastolic dysfunction, the mitral E/A ratio is <0.8, and the deceleration time of the E wave (DT) is >200 ms. In moderate (Grade II) diastolic dysfunction, the mitral E/A ratio is 0.8–1.5 and DT is 160–200 ms. In severe (Grade III) diastolic dysfunction, the mitral E/A ratio is ≥2 and DT<160 ms. The severity of diastolic dysfunction predicts mortality in longitudinal followup of outpatients [8].

While useful, there are several problems with this classification. A reduced mitral E/A ratio may be seen in hypovolemia. The majority of people >60 years old have E/A ratios <1 and DT >200 ms and in the absence of other indications of cardiac disease should be considered normal [7]. Trained athletes may have enlarged left atrial volumes. Doppler measurements can show individual variability and can vary with changes in preload, afterload, and sympathetic tone. As long as the operator is aware of these factors, the grading system can be very helpful for clinical practice as it is a simple method of communicating important information. Additionally, it can be valuable for research trials as it can be used to compare different populations in a standardized fashion.

2. LV Diastolic Dysfunction in the Intensive Care Unit (ICU)

In the ICU, there are many scenarios where factors influencing LV relaxation, diastolic distensibility, and filling pressures coexist. These factors may be linked to underlying disorders (CAD, arrhythmia, valvular dysfunction, pericardial disease, sepsis, and hypoxia), to patients' history (age, hypertension, diabetes mellitus, and chronic renal failure), or to applied therapies (volume resuscitation and positive end-expiratory pressure (PEEP)). Despite the fact that HFNEF has been increasingly identified, its incidence and impact on prognosis in critically ill patients in the ICU remain uncertain. The ICU-specific literature is reviewed below, but due to its sparse nature, extrapolations sometimes have to be made from the non-ICU cardiology literature. This is not only due to lack of extensive research in this setting, but also due to practical differences in patient populations. The clinical signs and symptoms of HF required for the diagnosis of HFNEF may be difficult to recognize in the ICU patient [3]. The presence of normal or mildly abnormal systolic LV function, which constitutes the second criterion for the diagnosis of HFNEF, is easily identified by echocardiography with the generally accepted definition of normal or mildly abnormal LVEF being >50% [3, 4]. Additionally, normal or mildly abnormal LVEF depends on the time elapsed between the clinical heart failure episode and the echocardiographic examination. Thus, it is recommended that information on LV systolic function be obtained within 72 h following the heart failure episode. In ICU patients, echocardiographic examination should be done promptly, once signs of possible heart failure are present.

The typical patient seen in the MICU or surgical ICU differs from a CCU patient. In the CCU, diastolic dysfunction is often seen in the context of coronary artery disease, valvular disease, or arrhythmias. While these may be present in the MICU or SICU patient, there will be a higher percentage of sepsis, renal failure, and hypoxemia. In the MICU or SICU patient there will be a higher incidence of noncardiac comorbidity; so differentiating cardiac from noncardiac causes of dyspnea is of great importance. Finally, there will be a higher percentage of applied therapies that may affect diastolic heart function such as fluid resuscitation and positive pressure ventilation.

Importantly the methods used to assess LV relaxation, diastolic distensibility, stiffness, and filling pressure suffer from many drawbacks in the ICU setting. Hence, even invasive measurements may produce inconclusive results, and finding a clinically hypovolemic patient with "normal" pulmonary artery catheter wedge pressure (PCWP) or a normovolemic patient with an elevated PCWP is not uncommon. Doppler indices of diastolic dysfunction only moderately correlate with invasive parameters [9, 10]. Also, echocardiography, which has been widely applied for providing diagnostic and monitoring solutions in patients with HFNEF, carries well-known flaws [3, 4, 7], and some of the newer echocardiographic techniques (i.e., strain, strain rate, etc.) may be difficult to conduct in the ICU.

While critical care ultrasound is a growing field, the nature of ICU practice leads to several limitations to ultrasound use. Many ICU patients are receiving mechanical ventilation which may impede imaging of the heart. ICU patients sometimes cannot be positioned adequately for all cardiac views. Surgical wounds, dressings, subcutaneous emphysema, tubes, and foreign devices may obstruct views [11]. The (at least partial) failure rate of TTE in the ICU setting has been reported to be between 30 and 40% in older studies [12, 13]. Contrast echocardiography or harmonic imaging can help in some cases [14]. Also, many of these limitations can be overcome with the use of TEE when clinically indicated. With proper training, noncardiologist intensivists can perform adequate TEE examinations [15, 16].

The presence of concentric LV remodeling may have important implications for the diagnosis of HFNEF, and an increased LV wall mass index may provide sufficient evidence for the diagnosis of HFNEF when TD yields nonconclusive results or when plasma levels of natriuretic peptides are elevated [3]. The latter, (Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP)) are produced by atrial and ventricular myocardial cells in response to an increase of atrial or ventricular diastolic stretch and mediate natriuresis, vasodilation, and improved LV relaxation. Their diagnostic accuracy for HF has been established, and combination with TD-derived E/E' ratio may prove an extremely valuable tool in the ICU setting for diagnosis of HFNEF [3, 4]. Finally, left atrial enlargement and/or evidence of atrial fibrillation are considered adjunctive evidence for the diagnosis of HFNEF [3, 4].

Recent studies have linked the presence of diastolic dysfunction to weaning failure in the critically ill [17–19]. Papanikolaou et al. have studied a small series of critical care patients with preserved LV systolic function and reported that weaning failure was related not only to grade III but also to grade I diastolic dysfunction [17], while Caille et al.

reported similar results in 117 unselected patients; however diastolic dysfunction was often associated with systolic dysfunction in the latter series [18]. Lamia et al. discovered that an increase in LV filling pressures related to spontaneous breathing trials (SBTs) was predictive of weaning failure in a highly selected population (patients with two preceding failed SBTs, and approximately 20% of them had a decreased LVEF) [19]. In outpatients, relaxation impairment of the LV can be unmasked by performing Doppler echocardiography during exercise [20]. In the ICU, weaning trials can be considered as exercise due to increments in respiratory and cardiovascular load and in oxygen demand [17–21]. Hence, weaning may reveal subtle diastolic dysfunction in the ICU.

Another issue associated with LV diastolic dysfunction, which is largely unstudied, is its possible relation to acute loading and unloading conditions of the LV commonly observed in the ICU. An LV with diastolic dysfunction is considered in cardiodynamic terms volume sensitive hence exploring those echocardiographic indices as aids to guide fluid loading or unloading is of great clinical interest. Tissue Doppler indices might be extremely useful in this regard, as E' can be conceptualized as the amount of blood entering the LV during early filling, whereas E represents the gradient necessary to make this blood enter the LV. Therefore, a high E/E' represents a high gradient for a low shift in volume [3]. Additionally, echocardiography may be used with adjunctive lung ultrasound examination, as the latter may identify alveolar-interstitial syndrome by evaluating lung-rocket artifacts (B-lines) that may provide additional information about lung water [22, 23].

The concept of isolated diastolic dysfunction is becoming a new trend in cardiodynamic analysis; however, as previously mentioned, cases which have been characterized as isolated diastolic dysfunction may well exhibit "subtle" systolic dysfunction [3, 4]. This energy interaction between systole and diastole will surely produce further pathophysiologic debate and might also lead towards new concepts in the development of ventricular assist devices [24]. In theory, alterations in LV stiffness that relate to diastolic dysfunction might be linked as well to changes in the three-dimensional (3D) systolic twisting and diastolic untwisting of the LV. However, the effects of load and inotropic state on LV systolic twist and diastolic untwist in human subjects remain to be studied [25]. The interaction of altered 3D ventricular geometry with the formatting vortices observed in the LV by modern magnetic resonance imaging techniques and complex fluid-structure numerical models may hold the key to the pathophysiologic development of diastolic dysfunction [26, 27]. Yet again the latter may represent another example of phenotypic plasticity, the capacity of a genotype to exhibit a range of phenotypes in response to environmental variations [28], reflecting a physiologic adaptation of the ventricle to altered myocardial cell structure and disturbed flow patterns in states of cardiovascular disease [29, 30].

Furthermore, LV tolerance to fluid loading might be better monitored by ultrasound in common scenarios such as the resuscitation of septic shock. In the latter, experimental models and clinical studies have previously reported that apart from systolic dysfunction, alterations in LV stiffness and various grades of diastolic dysfunction may exist [31–37]. In such patients, diastolic dysfunction seems to be an independent predictor of mortality [31].

Consideration should be given to the issue of training of intensivists in echocardiographic analyses of patients with diastolic dysfunction. In the United States, only 55% of critical care fellowship programs provide training in echocardiography [38]. How many of these provide training in analysis of diastolic dysfunction is unknown as this is not recommended by recent guidelines [39, 40]. In our experience, the extra training time required to perform basic analysis of diastolic dysfunction is not excessive. However, depending on the skill of the examiner and the clinical scenario, advanced consultation from expert-level echocardiographers may be required.

Despite the fact that we have still much to learn about many of the above-mentioned mechanisms, by integrating sophisticated "functional cardiac imaging" techniques with current research our clinical understanding of the specificities encountered in critical care patients who may present with LV diastolic dysfunction will be improved. Knowledge of diastolic dysfunction should not be considered a sophisticated approach designated only for cardiologists but should be familiar to all intensivists.

3. Conclusion

Although HFNEF is being increasingly recognized, there is a relative lack of information regarding its incidence and prognostic implications in the critically ill. There may be difficulties in the implementation of criteria for the diagnosis of HFNEF in the ICU. However combination of simple echocardiographic indices of LV diastolic dysfunction like TD-derived E/E' with other simply derived echocardiographic parameters like left atrial size, or presence of left ventricular hypertrophy with natriuretic peptides, may prove invaluable tools for studying the role of diastolic LV dysfunction in such patients.

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Research Article

Sonographic and Clinical Features of Upper Extremity Deep Venous Thrombosis in Critical Care Patients

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Background-Aim. Upper extremity deep vein thrombosis (UEDVT) is an increasingly recognized problem in the critically ill. We sought to identify the prevalence of and risk factors for UEDVT, and to characterize sonographically detected thrombi in the critical care setting. *Patients and Methods*. Three hundred and twenty patients receiving a subclavian or internal jugular central venous catheter (CVC) were included. When an UEDVT was detected, therapeutic anticoagulation was started. Additionally, a standardized ultrasound scan was performed to detect the extent of the thrombus. Images were interpreted offline by two independent readers. *Results*. Thirty-six (11.25%) patients had UEDVT and a complete scan was performed. One (2.7%) of these patients died, and 2 had pulmonary embolism (5.5%). Risk factors associated with UEDVT were presence of CVC [(odds ratio (OR) 2.716, $P = 0.007$)], malignancy (OR 1.483, $P = 0.036$), total parenteral nutrition (OR 1.399, $P = 0.035$), hypercoagulable state (OR 1.284, $P = 0.045$), and obesity (OR 1.191, $P = 0.049$). Eight thrombi were chronic, and 28 were acute. We describe a new sonographic sign which characterized acute thrombosis: a double hyperechoic line at the interface between the thrombus and the venous wall; but its clinical significance remains to be defined. *Conclusion*. Presence of CVC was a strong predictor for the development of UEDVT in a cohort of critical care patients; however, the rate of subsequent PE and related mortality was low.

1. Introduction

Upper extremity deep venous thrombosis (UEDVT) may be underdiagnosed as imaging of these vessels is not a routine part of pulmonary embolism (PE) investigation [1]. Moreover, PE is thought to occur at low rates (7 to 9%) in patients with UEDVT [1–3]. The clinical significance of UEDVT remains uncertain and much variability in reported treatment [4]. Nevertheless, current guidelines recommend that UEDVT should be treated similarly to lower extremity deep venous thrombosis [5]. In various series, 35 to 75% of patients who have upper extremity, neck, or torso central venous catheters (CVCs) develops thrombosis, with 75% being asymptomatic [6–10]. CVCs have been increasingly used in the intensive care unit (ICU) hence there is rationale to further investigated UEDVT [11–15]. CVC-associated UEDVT may be related to the material the catheter is made of and its diameter [11–17]. Other commonly reported risk factors for development of UEDVT are malignancy and thrombophilia. Less frequently reported risk factors include an obstructing tumor, pregnancy, and estrogen use [1, 18–21]. However, it is difficult to find extensive data on the incidence and clinical characteristics of UEDVT in the ICU [9, 10, 12].

The situation is further complicated by the use of different imaging techniques to diagnose UEDVT such as radionuclide scanning, ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), and contrast venography. Venography remains the reference standard but cannot be used readily in the critically ill and has a small incidence of complications [10, 22]. Ultrasonography is considered the initial imaging test of choice as it can exclude deep venous thrombosis and identify proximal venous obstruction [1, 3, 8–11, 21, 23]. The advantages of this test include its noninvasiveness, portability, lack of ionizing radiation, and high sensitivity and specificity [23].

In this study, we aimed to clarify the clinical uncertainties and risk factors associated with the diagnosis and significance of UEDVT by retrospectively analyzing ultrasound data derived from a cohort of critical care patients. Moreover, we analyzed the sonographic features of detected thromboses in order to assess thrombus age.

2. Materials and Methods

We extracted data from the archives of previously registered trials, which were conducted by our team and concerned subclavian (SCV) and internal jugular vein (IJV) ultrasound-guided cannulation (ISRCTN-61258470) [24, 25]. The present study was approved by the General State Hospital of Athens ethical committee. Three hundred and twenty critical care patients, who were hospitalized in a multipur-pose intensive care unit (ICU) from 2006 to 2012, and in whom complete sonographic records were available for retrieval, were enrolled. All patients were sedated and mechanically ventilated (Servo-I ventilator, Maquet Inc., Bridgewater, NJ, USA). All patients were routinely scanned before, during and after ultrasound-guided IJV and SCV cannulation by means of a portable HD11 XE ultrasound machine (Philips, Andover, MA, USA) equipped with a high-resolution 7.5–12 MHz transducer, as described in detail elsewhere [1, 2]. When an UEDVT was identified, a complete scanning protocol was initiated [23, 26]. In brief, the IJV was examined from the level of the mandible to the point at which it traveled under the clavicle. The junction of the SCV and IJV originating at the innominate vein is difficult to visualize, therefore Doppler was utilized to provide indirect information regarding the patency of the veins in this area. Next, the SCV was followed in the direction of the clavicle distally until it anatomically changed to the axillary vein, which in turn was followed in the direction of the upper arm where the brachial vein was identified. The latter was followed distally until the junction of the radial and ulnar veins, which in turn were followed until the region of the wrist. Thus, a complete assessment of the deep veins of the upper extremity and torso was completed. Ultrasound scanning included utilization of two-dimensional (2D) scanning with compression testing and Color-Doppler modes. Venous thromboses were identified according to American College of Radiology criteria [23].

All ultrasound data were stored in a computerized off-line system. Sonographic images were reviewed retrospectively by one independent radiologist and one intensivist trained in vascular ultrasound, both of whom were blinded to the subjects' clinical characteristics. When a visible intraluminal thrombus was identified, several of its characteristics were evaluated to determine its relative age. Sonographic features suggesting chronic thrombosis were a contracted venous segment, thrombus adherence to the venous wall, hyperechoic and heterogeneous appearance of the clot, partial recanalization of the vessel, and presence of venous collaterals. Features suggestive of acute thrombosis were venous distention, a partially compressible or noncompressible lumen, hypoechoic, homogeneous appearance of clots, and presence of free floating thrombi [26–35]. UEDVT was characterized either as spontaneous if no intravascular catheters were related to the thrombus or as CVC associated [1, 8, 9, 21, 24]. The segmental location of thrombosis was analyzed according to the affected veins (IJV, SCV, innominate, axillary and brachial veins). All ultrasound images were analytically reviewed to investigate whether any other sonographic findings related to thrombosis age existed.

Clinical parameters included: patient age, diagnosis upon admission, days of hospitalization, CVC insertion location, type of CVC (triple lumen, double-lumen catheter used for hemodialysis), other indwelling vascular devices (i.e., pacemakers), administration of total parenteral nutrition (TPN), known anatomic vascular anomaly and hypercoagulable disorder, untreated coagulopathy, increased ($\geq 35\,\text{kg/m}^2$) body mass index (BMI), and known malignancy [1, 2, 8, 12, 14–21]. Use of prophylactic treatment with low molecular weight heparin (LMWH) and subsequent incidence of PE and ICU death was investigated [1–3]. Moreover, we analyzed the sonographic features of recorded thrombosis in an effort to assess the relative age of the thrombus.

3. Statistical Analysis

Continuous data were expressed as mean ± standard deviation (SD). The student's t-test or Fisher's exact test was used as appropriate to compare group means for patient data. A two-sided P value of <0.05 was considered significant. Agreement between the two observers in the evaluation of sonographic data was evaluated by Cohen's weighted κ, with 2.5th and 97.5th percentiles of 5,000 bootstrap replicates estimated, using 95% confidence intervals [13]. Multivariate logistical regression in determining potential risk factors facilitating the development of UEDVT, as well as all other statistical analyses, was performed using the R2.10.1 statistical package (R Development Core Team, 2009. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

4. Results

Demographic and clinical characteristics of the total study population are presented in Table 1. Thirty-six cases of UEDVT were recorded out of 320 patients reviewed (11.25%). The vast majority of patients in this cohort were trauma victims. All patients had CVC inserted and received prophylactic treatment with LMWH (Table 1).

Clinical and sonographic characteristics of the 36 cases identified with UEDVT are shown in Table 2. UEDVT was most commonly observed in the SCV and IJV sites, while the number of veins involved was usually 1 to 3. The vast majority of UEDVTs recorded were CVC-associated

Table 1: Baseline characteristics of the study population.

Characteristics	Patients $n = 320$
Age (years)	51 ± 15.5
Gender (male/female ratio)	0.52 ± 0.4
APACHE II score	20.2 ± 3.1
Diagnosis upon admission	
Trauma	205 (64%)
Burn	12 (3.75%)
ARDS	26 (8.12%)
Sepsis	48 (15%)
Postsurgical complications	29 (9.13%)
Body mass index (kg/m^2)	27.2 ± 10.3
Anatomic vascular abnormality (%)	6 (1.87%)
Untreated coagulopathy (%)	0 (0%)
Prophylactic treatment with LMWH (%)	320 (100%)
Hypercoagulable state (%)	16 (5%)
Malignancy (%)	23 (7.18%)
Total number of UEDVT (%)	36 (11.25%)
Central venous catheters	177 (55.3%)
Other intravascular devices	16 (5%)
Days of hospitalization	59 ± 26

Abbreviations are: APACHE II: acute physiology and chronic health evaluation score; ARDS: acute respiratory distress syndrome; LMWH: low molecular weight heparin; UEDVT: upper extremity deep venous thrombosis.

Table 2: Characteristics of the 36 cases with upper extremity deep venous thrombosis (UEDVT).

Characteristics	Number (percent)
Location of UEVT	
Internal jugular vein	25
Subclavian vein	27
Innominate vein	9
Axillary vein	11
Brachial	6
Number of venous segments involved	
Single segment	14
Two segments	12
Three segments	10
Four segments	4
Five segments	2
Clinical characteristics	
Spontaneous thrombosis	3 (8.3%)
Catheter-associated thrombosis	33 (91.7%)*
Triple-lumen catheter	14 (38.8%)
Hemodialysis (double-lumen catheter)	19 (52.7%)
Malignancy	14 (38.8%)
Hypercoagulable state	8 (22.2%)
Total parenteral nutrition	9 (25%)
Body mass index ≥35 kg/m^2	8 (22.2%)
Asymptomatic thrombosis	16 (44.4%)
Symptomatic thrombosis	20 (55.6%)
Subsequent pulmonary embolism	2 (5.5%)
ICU deaths	1 (2.7%)
Therapeutic anticoagulation	36 (100%)
General sonographic characteristics	
Acute thrombosis	28 (77.8%)**
Chronic thrombosis	8 (12.2%)

*Catheter-associated versus spontaneous thrombosis and
**acute versus chronic thrombosis (both $P < 0.01$; Fisher's test).

thromboses (91.7%). Acute thromboses (77.8%) were more commonly observed compared to chronic ones (Table 2) (Figures 1 and 2). UEDVT was mainly symptomatic (55.6%) presenting with edema (20/20) and erythema (5/20) of the affected extremity; however, some asymptomatic cases were noted (Table 2). Other factors that also predisposed to thromboses such as obesity, TPN, and malignancy; these parameters are presented in Table 2. Six of the 9 thromboses associated with TPN were catheter associated. Eight cases of thrombophilia were recorded in patients with UEDVT, which were attributed to mutations of factor V and prothrombin gene (6 cases) and to protein C and S deficiency (2 cases), following laboratory investigation. Notably, only two cases of subsequent PE (5.5%) and one death were recorded in patients with UEDVT (Table 2). All critical care patients with UEDVT received full anticoagulation treatment (unfractionated or LMWH) with no side effects noted.

Table 3 presents the typical sonographic features of UEDVT as registered by the two independent observers. Clot adherence to the venous wall, partial recanalization of the lumen, and presence of venous collaterals was associated with chronic thrombosis; while free-floating thrombi with echolucent and homogeneous appearance, lack of compressibility and distended veins were observed in acute thrombosis (Figures 1 and 2). Notably, in 20 out of 28 cases of acute thrombosis a double hyperechoic line along the thrombus and wall interface was identified (Table 3, Figure 3). The overall agreement between the two observers who reviewed the sonographic findings was significant ($\kappa = 0.88$, 95% confidence intervals by bootstrap analysis = 0.85–0.93, $P < 0.02$).

Multivariate logistic regression analysis (Table 4) identified that insertion of CVC (both triple lumen and double-lumen catheters for hemodialysis), administration of TPN; presence of malignancy, presence of thrombophilia as well as body mass index ≥35 kg/m^2 were all significantly correlated with the occurrence of UEDVT (all $P < 0.05$). Notably, insertion of CVC was the factor with the strongest effect upon the incidence of UEDVT (odds ratio = 2.716, 95% confidence intervals = 2.312–2.911; $P = 0.007$).

5. Discussion

A rate of 11.25% of UEDVT in patients being examined for CVC placement was detected in this study, consistent with previously published series [1, 2, 9, 20, 21, 36]. Ultrasound

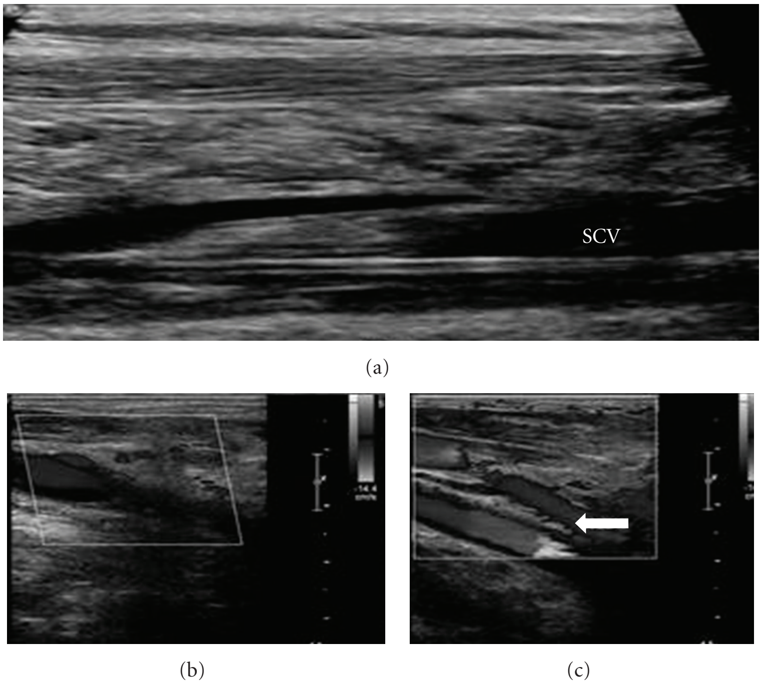


Figure 1: Left subclavian vein catheter-associated chronic thrombosis with partial recanalization (a); proximal right internal jugular vein (b) and ipsilateral subclavian vein (c) with associated collateral flow (arrow) in a patient with chronic spontaneous thrombosis. SCV: Subclavian Vein.

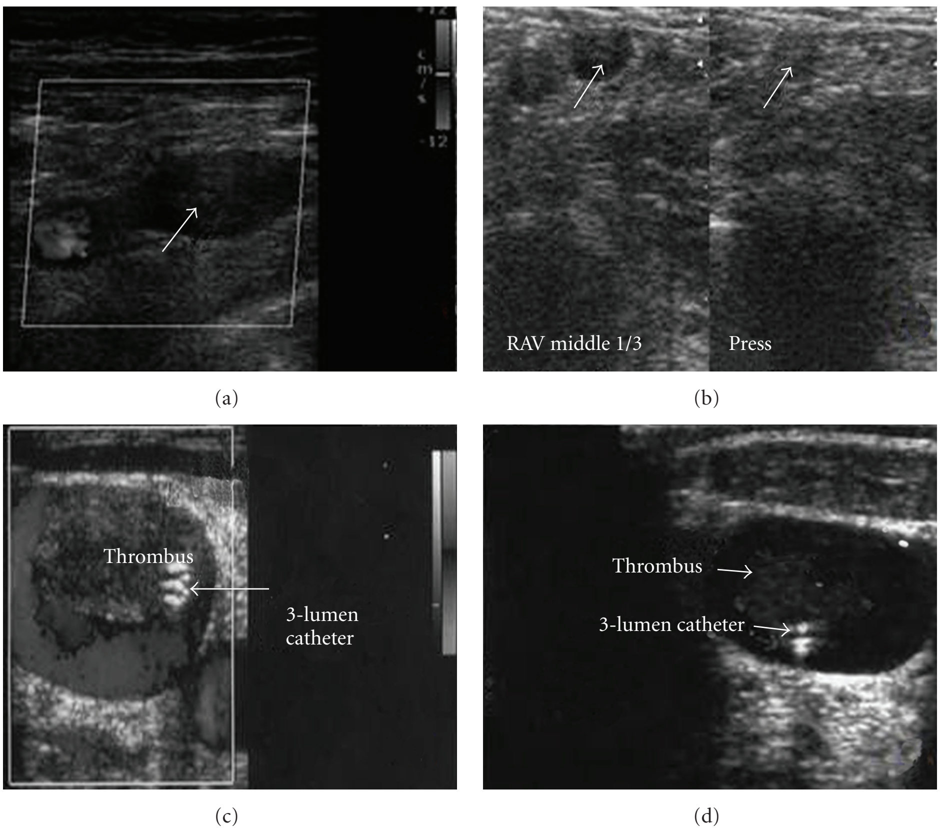
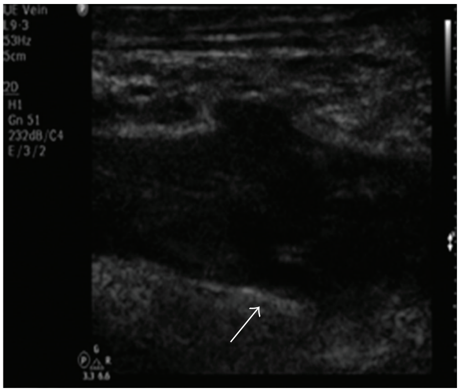
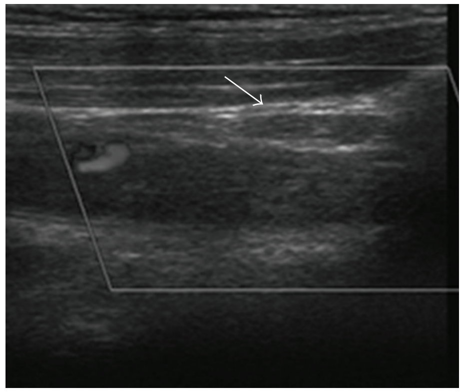


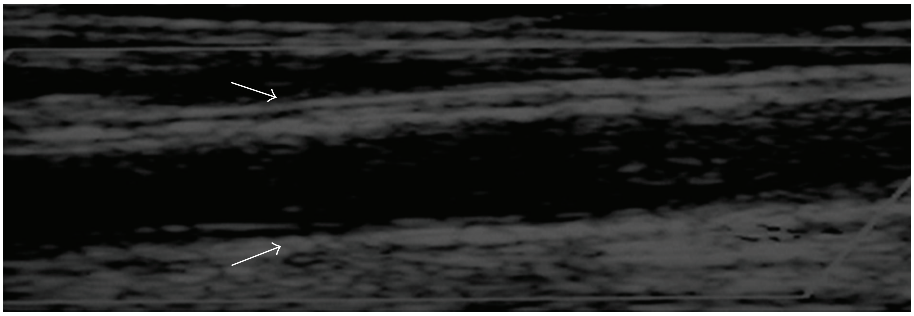
Figure 2: Incompressible proximal right and medial left axillary veins (arrows) in two cases of spontaneous acute thrombosis, respectively ((a), (b)); two cases of catheter-associated thrombosis of the right internal jugular vein with fresh clots obstructing almost totally the venous lumen (c); one of the three lumens of the catheter (in this case delivering total parenteral nutrition, (d)).



(a)



(b)



(c)

Figure 3: Double hyperechoic line along fresh thrombus/wall interface (arrows) in limited segments of the subclavian vein ((a), (b)) and in extended segments of the left brachial vein (panoramic view with zoom, (c)).

Table 3: Estimating the relative age of venous thrombus by ultrasound.

Characteristics	Number/total cases
Chronic thrombosis ($n = 8$)	
Contracted venous segment	6/8
Clot adherence	8/8
Free-floating thrombi	1/8
Hyperechoic thrombi	4/8
Homogeneous thrombi	1/8
Partial recanalization	7/8
Venous collaterals	7/8
Acute thrombosis ($n = 28$)	
Venous distention	22/28
Lumen partially and/or noncompressible	26/28
Hypoechoic thrombi	18/28
Homogeneous thrombi	22/28
Free-floating thrombi	20/28
Double hyperechoic line along the thrombus/wall interface	20/28

was able to diagnose UEDVT and a high agreement was registered between the two independent observers as previously suggested [8, 11, 22, 23, 26, 28–30, 32, 36]. The sensitivity of Doppler sonography in the diagnosis for UEDVT has been reported to range from 78% to 100% and its specificity from 82% to 100% in various series [8–11, 22, 23, 32, 36]. Our results add to the prior literature on detection of UEDVT in ICU patients.

The subsequent rate of PE was on the low end of previously published data [1–4, 12, 20, 21, 36, 37]. The reasons for this are not entirely clear; however, we note that in this study, all patients with UEDVT were fully anticoagulated as per recommended guidelines [5]. Notably, in the study of Mustafa et al., all patients with symptomatic UEDVT received anticoagulant therapy and none developed PE [9]. However, despite guideline recommendations, prescribing full anticoagulation for UEDVT remains controversial [1–3].

The highest risk for UEDVT was having a CVC. Of note, these were all critically ill patients who were being examined for CVC insertion. Risk factors have been established for catheter-related DVT which include catheter material, diameter, and position of the catheter. Clinical and in vitro studies have demonstrated that both polyurethane and silicone catheters are associated with a lower rate of catheter-related DVT as compared with polyethylene or Teflon-coated catheters [16, 17]. In our study all CVCs were polyurethane.

The pathogenesis of thrombosis is multifactorial and ICU patients may have a higher incidence of risk factors than the general population. We confirmed previously published data which suggested that obesity, malignancy, a hypercoagulable state, and administration of TPN are potential risk factors for UEDVT [9, 12, 14, 15, 37, 38]. Obesity may

Table 4: Multivariate logistical regression correlating various parameters with the incidence of upper extremity deep venous thrombosis.

Effect	Odds ratio estimates		
	Point estimate	95% confidence limits	P
Central venous catheter	2.716	2.312–2.911	0.007
Triple lumen catheter	1.515	1.108–2.166	0.035
Hemodialysis (double-lumen) catheter	1.823	1.245–2.344	0.024
Malignancy	1.483	1.107–1.746	0.036
Total parenteral nutrition	1.399	1.066–1.699	0.042
Hypercoagulable state	1.284	1.108–1.382	0.045
Body mass index $\geq$35 kg/m^2	1.191	1.079–1.402	0.049

predispose to DVT via several mechanisms, including the physical effects of body fat inhibiting venous return as well as endocrine changes and changes in signaling molecules. Obesity is a proinflammatory, prothrombotic, and hypofibrinolytic state with increased concentrations of coagulation factors and plasminogen activator inhibitor-1 [39]. Out of the 9 patients who had thromboses associated with TPN, 6 were catheter associated. Infusion of TPN may be irritating to veins causing vascular injury and inflammation that is prothrombotic [40].

It is increasingly noted that venous thrombosis is associated with an inflammatory response which plays an essential role in both formation and resolution. This could explain why ICU patients are at higher risk of thrombosis. Thrombus generation is dependent on adhesion molecules such as the selectin family. These molecules are critical for recruitment and attachment of inflammatory cells and fibrin deposition within the thrombus. The mechanism of delivery of the components necessary for thrombus formation is via microparticles shed from the plasma membrane of various cells. Leukocytes and cytokines associated with inflammation are also essential to angiogenesis and fibrinolysis of thrombus resolution. Outlining the inflammatory mechanisms involved in the genesis and resolution response may lead to potential treatments for venous thromboembolism. Current anticoagulation therapies primarily that prevent thrombus propagation are associated with bleeding risk, and do not directly modulate the associated inflammation [41–46].

We also found that the most common location of UEDVT was in the IJV and SCV sites as observed by others [1, 2, 7, 9, 10, 12, 18, 20, 36, 37] and that UEDVT may involve several venous segments [1, 2, 9, 10, 12, 37]. Since femoral catheters were not placed in this study, our data do not challenge prior evidence that femoral CVCs have the highest thrombotic risk [47].

In addition to detecting thromboses, ultrasound facilitated the estimation of the relative age of clots in this cohort. Cases of acute thrombosis were more commonly observed than cases of chronic thrombosis. Clot adherence to the venous wall, partial recanalization of the lumen, and presence of venous collaterals were commonly observed in chronic thrombosis; while free-floating thrombi with echolucent and homogeneous appearance as well as noncompressible, distended veins were observed in acute thrombosis, respectively [26–30].

We also described a new sonographic sign in 2D images that was present in 20 out of 28 cases of acute thrombosis: a double hyperechoic line at the interface between the thrombus and the venous wall. Histology studies show that a smooth coat of fibrin lines the external surface of an acute thrombus [48]. The latter are three-dimensional networks of fibrin fibers stabilized by factor XIIIa. Fibrin fibers are long, thin fibers that easily bend rather than stretch; however, fibrin itself is very dense and stiff thus exhibiting high acoustic impedance [26–30]. We speculate that this double hyperechoic line might represent fibrin fibers coating acute clots. If confirmed in other studies, this finding may assist in determining thrombus age. Recently, Rubin et al. suggested that sonographic elasticity imaging, a technique measuring tissue hardness, can discriminate between acute and chronic thrombi [49, 50].

There were several limitations in this study. First, the study was performed retrospectively solely in patients receiving a CVC and may not be extrapolated to all critically ill patients. Second, ultrasound is an operator-dependent technique, and the amount of training required to become facile at upper extremity DVT examination is unknown. Third, there were a small number of cases of UEDVT, confirming previously reported studies. The small numbers precluded subgroup analyses. However, despite the small numbers we were able to find various parameters that were significantly related to thrombosis. Fourth, our cohort consisted of a high percentage of trauma patients which may affect the generalizability of our findings. Further prospective studies would be required to confirm that a strategy of universal anticoagulation is correct for all ICU patients with this problem.

6. Conclusions

The present study characterized the incidence of UEDVT in a mixed ICU population. We confirmed risk factors associated with UEDVT including presence of a CVC, BMI > 35, a hypercoagulable state, malignancy, and use of TPN. We have fully characterized the locations, extent, and ultrasound findings of UEDVTs in an ICU population. In this study, a clinical strategy of universal anticoagulation led to favorable outcomes. We also describe a new ultrasound finding of acute thrombosis: a double hyperechoic line at the interface between the thrombus and the venous wall. Further studies are required to document the utility of this sign as well as the best methods to diagnose and treat UEDVT in ICU patients.

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Research Article

Echogenic Technology Improves Cannula Visibility during Ultrasound-Guided Internal Jugular Vein Catheterization via a Transverse Approach

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Objective. Echogenic technology has recently enhanced the ability of cannulas to be visualized during ultrasound-guided vascular access. We studied whether the use of an EC could improve visualization if compared with a nonechogenic vascular cannula (NEC) during real-time ultrasound-guided internal jugular vein (IJV) cannulation in the intensive care unit (ICU). *Material and Methods.* We prospectively enrolled 80 mechanically ventilated patients who required central venous access in a randomized study that was conducted in two medical-surgical ICUs. Forty patients underwent EC and 40 patients were randomized to NEC. The procedure was ultrasound-guided IJV cannulation via a transverse approach. *Results.* The EC group exhibited increased visibility as compared to the NEC group (88% $\pm$ 8% versus 20% $\pm$ 15%, resp. $P < 0.01$). There was strong agreement between the procedure operators and independent observers ($k = 0.9$; 95% confidence intervals assessed by bootstrap analysis = 0.87–0.95; $P < 0.01$). Access time (5.2 s $\pm$ 2.5 versus 10.6 s $\pm$ 5.7) and mechanical complications were both decreased in the EC group compared to the NEC group ($P < 0.05$). *Conclusion.* Echogenic technology significantly improved cannula visibility and decreased access time and mechanical complications during real-time ultrasound-guided IJV cannulation via a transverse approach.

1. Introduction

Real-time ultrasound-guided central venous cannulation has been associated with higher success rates, faster access times, and a reduction in mechanical complications when compared to landmark techniques, especially for the cannulation of the internal jugular vein (IJV) [1–6]. The ultrasound-guided method via a longitudinal approach has been favored since it offered another view to visualize the needle tip in the lumen and the back wall of the vein [6]. However, the transverse axis approach has been the standard monoplanar ultrasound view since the introduction of the above technique [7], but it was rather problematic in visualizing the cannula and thus controlling its depth without arterial puncture or transfixion of the vein [8, 9]. This may be particularly relevant to the intensive care unit (ICU) setting as the clarity of two-dimensional (2D) ultrasound images is oftentimes affected in critical care patients by the presence of various factors such as obesity, subcutaneous air and/or edema, trauma and mechanical ventilation, while complications may occur even under ultrasound guidance [6–12]. Cannula visualization is fundamental to the safety and efficacy of all ultrasound-guided methods, but no single technology meant to improve cannula echogenicity has been widely adopted or studied in the ICU setting [13–20]. Recently, a vascular cannula (VascularSono, Pajunk, GmbH, Medizintechnologie, Geisingen, Germany) incorporating "Cornerstone" reflectors on the distal 2 cm, to increase echogenicity, was developed based on technology previously used in regional anesthesia cannulas [16]. We hypothesized that the use of an echogenic vascular cannula (EC) would improve visualization when compared with a nonechogenic vascular cannula (NEC) (Arrow Howes, PA, USA) during real-time ultrasound-guided internal jugular vein (IJV) cannulation via a transverse approach.

2. Materials and Methods

During 2011, eighty patients who required central venous access were prospectively enrolled in this randomized study that was conducted in two medical-surgical ICUs. Forty patients underwent EC and 40 patients were randomized to NEC. The procedure was ultrasound-guided IJV cannulation via a transverse approach. All patients were sedated and mechanically ventilated. Randomization was performed by means of a computer-generated random-number table and patients were stratified with regard to age, gender, and body mass index (BMI). Block randomization was used to ensure equal numbers of patients in the above groups [6]. All physicians who performed the procedures had at least five years of experience in central venous catheter placement. The study was approved by the Institutional Ethics Committee, and appropriate informed consent was obtained. Chest radiography was used to assess catheter placement after the procedure. Mechanical complications were defined as arterial puncture, hematoma, hemothorax, pneumothorax, and catheter misplacement [6].

2.1. Real-Time Ultrasound-Guided IJV Cannulation. All patients were placed in Trendelenburg position and were cannulated as described in detail by Karakitsos et al. [6]. Triple-lumen catheters were used in all cases and all procedures were performed under controlled, nonemergent conditions in the ICU. Standard sterile precautions were utilized. The EC and NEC were both 18-gauge cannulas specifically intended for use in vascular access. Ultrasonography was performed with an HD11 XE ultrasound machine (Philips, Andover, MA, USA) equipped with a high-resolution 7.5–12 MHz transducer, which was covered with sterile ultrasonic gel and wrapped in a sterile sheath (Microtec medical intraoperative probe cover, 12 cm × 244 cm). Vessels were cannulated using the Seldinger technique under real-time ultrasound guidance.

2.2. Data Acquisition, Study Protocol, and Outcome Measures. The cannulation was performed by a single operator and was observed by a second physician. The operators and observers were blinded to the cannula used. Following each procedure, the operator and the observer were asked to score the percentage of time they were able to continuously visualize the cannula; a 10-point scale was used (ranging from 1 = 0%–10%, to 10 = 90%–100%). The observer measured access time, number of attempts, and complications. Access time was defined as the time between penetration of skin and aspiration of venous blood. Data was collected using a standardized form and was entered in a database. We documented baseline patient characteristics, side of catheterization, the presence of risk factors for difficult venous cannulation, previous difficulties during cannulation, previous mechanical complications, known vascular abnormalities, and untreated coagulopathy (international normalization ratio > 2; activated partial thromboplastin time > 1.5; platelets < 50 × 109 litre − 1) [6].

3. Statistical Analysis

Data were expressed as mean ± standard deviation (SD). The Student's t-test for independent mean, χ^2 analysis, or Fisher's exact test where appropriate were used to identify differences between the two groups. A P value (two-sided in all tests) of <0.05 was considered significant. Study power was based on data from a previous cannula visibility study, which were adjusted for our intervention [19]. Assuming data to be nonparametric, power sample analysis gave a minimum sample size of 40 cannulations. Wilcoxon rank sum test was used to compare cannula visibility data for the 2 groups. The agreement between the operator and observer cannula visibility results was evaluated by Cohen's weighted kappa, while 2.5th, and 97.5th percentiles of 5,000 bootstrap replicates estimated 95% confidence intervals. The bootstrap is a resampling method used for estimating a distribution, from which various measures of interest can be calculated [21]. Statistical analysis was performed using SPSS, version 11.0 (SPSS Inc. Chicago, IL, USA).

4. Results

Baseline characteristics of the study population are presented in Table 1. There were no significant differences in age, gender, body mass index (BMI), and presence of risk factors for difficult venous cannulation between the NEC and the EC groups; moreover no cases of preexisting thrombosis were identified.

Results of cannula visibility are presented on Figure 1. Operators reported improved cannula visualization in the EC group when compared to the NEC group (88% ± 8% versus 20% ± 15%, resp.; $P < 0.01$). Also, operators reported that when using the NEC via the transverse approach they might have visualized it, but surely have noticed its acoustic shadow (Figure 2). In contrast, the echogenic vascular cannula could be clearly identified, even if the insonation angle was slightly modified (Figure 2). Finally, the agreement between the operators and observers was statistically significant (kappa = 0.9; 95% confidence intervals assessed by bootstrap analysis = 0.87–0.95; $P < 0.01$).

Table 1: Baseline characteristics of the study population; values are presented either in percentages or as mean ± SD.

Characteristics	EC group (n = 40)	NEC group (n = 40)
Age (years)	45 ± 9.5	46 ± 10.9
Gender (male/female ratio)	0.49 ± 0.4	0.5 ± 0.5
APACHE II score	20.6 ± 2.1	20.8 ± 2.4
Diagnosis upon admission		
Trauma without brain injury	15 (37.5%)	15 (37.5%)
Trauma with brain injury	15 (37.5%)	15 (37.5%)
Burn	1 (2.5%)	0 (0%)
ARDS	2 (5%)	2 (5%)
Sepsis	5 (12.5%)	7 (17.5%)
Postsurgical complications	2 (5%)	1 (2.5%)
Side of catheterization (left/right)	14/26	12/28
Body mass index (kg/m^2)	21.1 ± 3.6	21.8 ± 3.9
Prior catheterization	7 (17.5%)	5 (12.5%)
Limited sites for access attempts	5 (12.5%)	5 (12.5%)
Previous difficulties during Catheterization	9 (22.5%)	7 (17.5%)
Previous mechanical complications	6 (15%)	4 (10%)
Known vascular abnormality	1 (2.5%)	1 (2.5%)
Untreated coagulopathy	1 (2.5%)	1 (2.5%)
Skeletal deformity	1 (2.5%)	1 (2.5%)

APACHE II score: acute physiology and chronic health evaluation score II; ARDS: acute respiratory distress syndrome; NEC: nonechogenic cannula, EC: echogenic cannula.

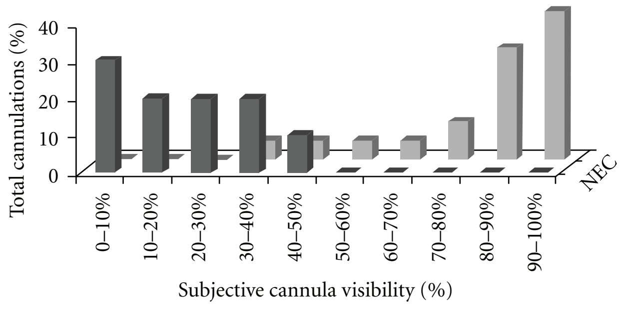

Figure 1: Subjective cannula visibility assessments (echogenic cannula, EC: gray; nonechogenic cannula, NEC: black).

Table 2: Secondary outcome measures in the EC group versus the NEC group.

Outcome measures	EC group (n = 40)	NEC group (n = 40)
Access time (sec)	5.2 ± 2.5 (4.5–12.4)*	10.6 ± 5.7 (8.1–17.3)
Success rate (%)	40 (100%)	40 (100%)
Average number of attempts	1 ± 0.2 (1–1.3)	1.1 ± 0.4 (1–1.7)
Artery puncture	0 (0%)	1 (2.5%)
Hematoma	0 (0%)*	4 (10%)
Pneumothorax	0 (0%)	0 (0%)
Hemothorax	0 (0%)	0 (0%)

EC: echogenic cannula, NEC: nonechogenic cannula; Comparisons between the NEC and the EC group of patients; $P < 0.05$*; Access time and average number of attempts are expressed as mean ± SD (95% confidence intervals).

Results of the secondary outcomes are presented in Table 2. Access time (5.2 s ± 2.5 versus 10.6 s ± 5.7) and mechanical complications, notably hematomas (0% versus 10%), were both decreased in the EC group compared to the NEC group ($P < 0.05$).

5. Discussion

Our study demonstrated improved cannula visibility with the use of EC during ultrasound-guided IJV cannulation via a transverse approach. The latter has been the standard monoplanar 2D view since the introduction of the ultrasound technique [7]. Intrinsically, cannulation of a vessel using the transverse approach often limits cannula visibility; hence controlling the trajectory of the cannula may be problematic, especially when the 2D image is of low quality due to various factors (i.e., subcutaneous air and/or edema, trauma, etc.) [1–12].

Nevertheless, we found that the use of EC statistically increased the likelihood of continued successful cannula visualization. This could be attributed to the fact that the EC is brightly echogenic as it incorporates "Cornerstone" reflectors mainly arranged at the distal 2 cm of the needle. These reflectors guarantee the visibility of the cannula shaft, independent of the puncture angle according to the manufacturer. The principle is the same as that used in bicycle reflectors, where light is reflected back to its source regardless of the angle at which it approaches [16–19]. The present results demonstrated that using the EC resulted in significantly reduced access times and mechanical complications. Notably, once IJV cannulation is pursued via a transverse approach, the adjacent carotid artery may be a potential "target" for the cannula, especially if the operator cannot fully control its trajectory [3–9].

The present methodology was designed to test EC in actual clinical practice in the ICU, where image acquisition is affected or limited by the presence of various factors such as obesity, subcutaneous air, edema, trauma, and mechanical ventilation [1–12]. The use of EC may improve image acquisition and success rates in technically challenging cases of vascular access. Moreover, we should underline that the transverse approach is less technically demanding compared to the longitudinal one under ultrasound guidance, and thus can be easily applied by inexperienced operators [1–12]. This technical "advantage" can be further enhanced by the implementation of echogenic cannulas, and hence resulting in a simpler ultrasound-guided method but with optimal cannula visibility results. There is no definitive method for objective assessment of cannula visibility. Previous studies used scoring systems with skilled observers rating static images [14–19]. We aimed to examine cannula visibility

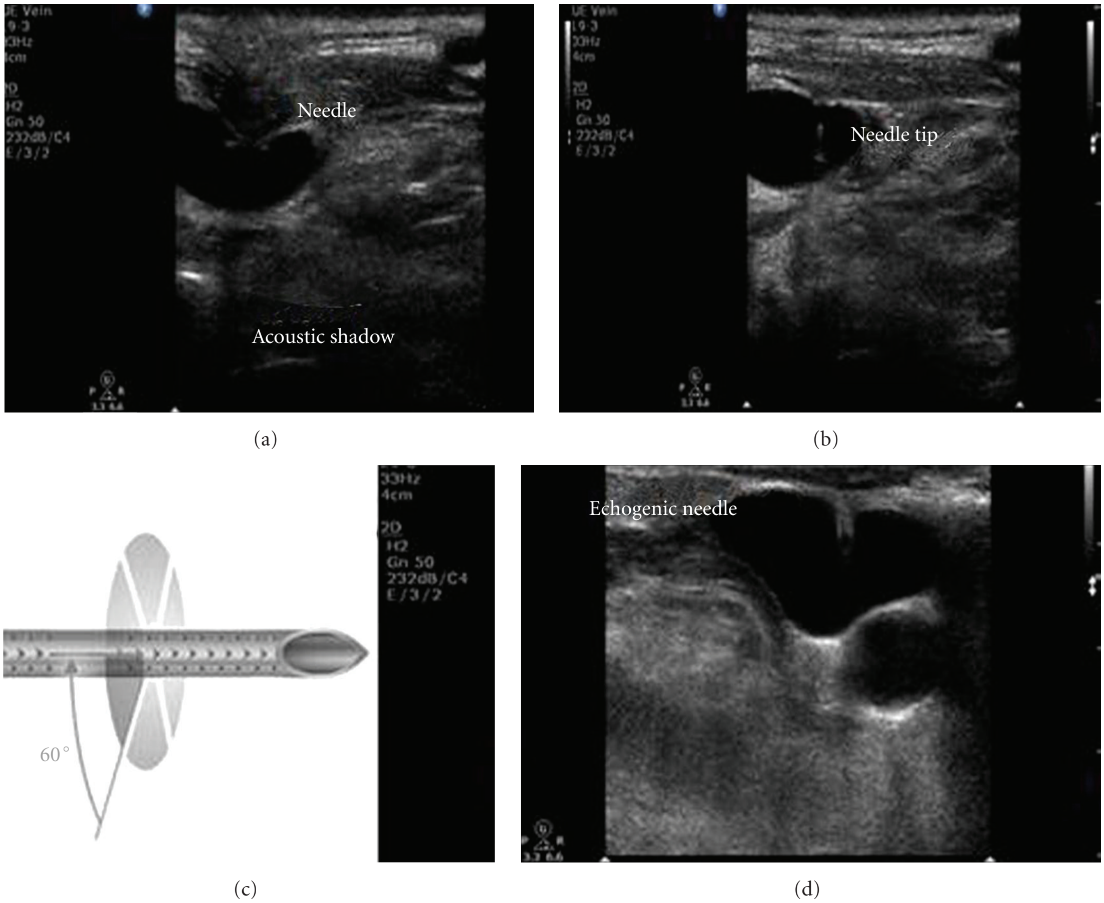

Figure 2: Nonechogenic cannula entering the anterior wall (a) and depicted within the lumen of the internal jugular vein, on the transverse axis (b); please observe that the echogenic cannula incorporates "cornerstone" reflectors arranged at its distal 2 cm (c), which increases dramatically its visibility (d).

during IJV cannulation, under real-time clinical conditions. Although interpretation of dynamic 2D ultrasound images remains subjective, we used an analytical 10-point scale along with a dual evaluation model of operators and observers. We demonstrated that high operator and observer agreement existed between the subjective estimations of cannula visibility rates. The study has several limitations. Despite the fact that the operators were blinded at the initiation of the procedure, the two vascular cannulas inherently exhibited different ultrasonographic appearance, and could possibly be differentiated. Although we demonstrated a significant reduction in hematoma formation, we failed to find a significant reduction of major mechanical complications. This may be due to the fact that our baseline mechanical complication rate was extremely low (given the fact that our study group is highly skilled in ultrasound-guided vascular access) and that the sample size was rather small. Concluding, the present investigation demonstrated that echogenic technology significantly improved cannula visibility and decreased access time during real-time ultrasound-guided IJV cannulation via a transverse approach. Our data provide clinical rationale to study the evolving field of enhanced echogenic ultrasound technology. Further studies are required to determine if EC is cost-effective and changes overall outcomes in the ICU.

Disclosure

The authors declare that they have no financialor other interest in the echogenic vascular cannula nor do they have any financial or other affiliation with pajunk.

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Research Article

Is Routine Ultrasound Examination of the Gallbladder Justified in Critical Care Patients?

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Objective. We evaluated whether routine ultrasound examination may illustrate gallbladder abnormalities, including acute acalculous cholecystitis (AAC) in the intensive care unit (ICU). *Patients and Methods*. Ultrasound monitoring of the GB was performed by two blinded radiologists in mechanically ventilated patients irrespective of clinical and laboratory findings. We evaluated major (gallbladder wall thickening and edema, sonographic Murphy's sign, pericholecystic fluid) and minor (gallbladder distention and sludge) ultrasound criteria. *Measurements and Results*. We included 53 patients (42 males; mean age 57.6 ± 2.8 years; APACHE II score 21.3 ± 0.9; mean ICU stay 35.9 ± 4.8 days). Twenty-five patients (47.2%) exhibited at least one abnormal imaging finding, while only six out of them had hepatic dysfunction. No correlation existed between liver biochemistry and ultrasound results in the total population. Three male patients (5.7%), on the grounds of unexplained sepsis, were diagnosed with AAC as incited by ultrasound, and surgical intervention was lifesaving. Patients who exhibited ≥2 ultrasound findings (30.2%) were managed successfully under the guidance of evolving ultrasound, clinical, and laboratory findings. *Conclusions*. Ultrasound gallbladder monitoring guided lifesaving surgical treatment in 3 cases of AAC; however, its routine application is questionable and still entails high levels of clinical suspicion.

1. Introduction

Abnormalities of the gallbladder (GB) are frequent in the intensive care unit (ICU) [1, 2]. Critical care patients have many risk factors for acute acalculous cholecystitis (AAC) which is an acute inflammation of the GB in the absence of gallstones and accounts for 2–14% of all cases of acute cholecystitis [3–5]. AAC is an insidious complication that has been increasingly recognized in the critically ill with an incidence ranging from 0.2 to 3% [6–8].

Although the etiology is uncertain, AAC in the ICU has been associated with prolonged enteral fasting, total parenteral nutrition (TPN), duration of mechanical ventilation (MV) and the use of positive end-expiratory pressure (PEEP), activation of factor XII, trauma, sepsis, drugs (opiates, sedatives, and vasopressors), multiple transfusions, dehydration, and shock states [6, 9, 10]. Ultimately these factors may lead to bile stasis and GB hypoperfusion/ischemia resulting in acute inflammation of the GB.

AAC is an emergency condition, and without immediate treatment there may be rapid progression to gangrenous cholecystitis (approximately 50%) or perforation (approximately 10%), with mortality rates as high as 65% [11]. However, with timely diagnosis and intervention, the mortality drops to 7%. The clinical presentation is variable and often depends upon the underlying predisposing conditions.

Hence, we evaluated whether the routine application of standardized GB sonographic examination upon critical care patients, irrespective of their clinical presentation and/or laboratory findings, might aid in identifying the range and the significance of GB abnormalities, including AAC, and consequently affect our decision making.

2. Patients and Methods

2.1. Study Cohort. This prospective study was conducted in a seven-bed ICU based at KAT General Hospital, Athens, Greece, following approval from our institutional ethics committee. All patients who were admitted to the ICU during an 8-month period (1/5/2011–1/12/2011) were enrolled in this study. Right-upper quardant sonography was performed by means of a Vivid 4 portable ultrasound system (GE, Medical System, Waukesha, WI, USA) equipped with a convex 5 to 7 MHz transducer. Sonographic examinations were performed upon admission, while follow-up examinations were performed twice weekly until patients were either discharged from the ICU or expired, in all cases. Upon admission, all patients were sedated using midazolam or propofol and/or remifentanil according to recommended doses and clinical response; moreover, they were mechanically ventilated (Taema HORUS Ventilator, Air Liquide, *Paris Cedex,* France). All sonographic examinations were performed by two independent and experienced radiologists who were blinded to patients' identity.

2.2. Definitions and Outcomes. Abdominal sonographic investigations were focused on the GB as previously described [1–4, 9]. AAC was defined as acute inflammation of the gallbladder in the absence of gallstones [12]. Ultrasound findings that were evaluated included major criteria: gallbladder wall thickening (greater than 3 mm), striated (edematous) gallbladder wall, sonographic Murphy's sign, pericholecystic fluid in the absence of ascites, and hypoalbuminemia and minor criteria: gallbladder distention (hydrops with a long-axis caliper over 100 mm and a short axis (transverse diameter) over 50 mm) and biliary or gallbladder sludge [1, 2, 9, 13, 14]. Hepatic dysfunction was defined as bilirubin >2 mg/dL and/or alkaline phosphatase (ALP) >200 IU/L [15]. Pertinent clinical and laboratory parameters were recorded: demographics, temperature, WBC, MV status, liver function tests, and administration of parenteral nutrition, narcotic analgesics, and vasopressor agents, and predisposing factors which are associated with high incidence AAC.

2.3. Statistics. Continuous data are presented as means ± SD. Categorical data are presented as numbers and percentages. Relationships between categorical variables were tested with chi-square analysis. Tests were two sided, and $P < 0.05$ was considered statistically significant. All data were analyzed using SPSS 17.0 software (SPSS Inc. Chicago, IL, USA).

3. Results

Fifty-three consecutive critical care patients participated in this study. Demographics, admission diagnosis, severity of illness, and mortality rate of the study population are presented on Table 1.

Table 1: Clinical characteristics of the study population.

Total number of patients	$n = 53$
Age (years)	57.6 ± 2.8
Male gender (%)	42 (79.2%)
Admission diagnosis	Trauma-burns: 27 (50.9%) postsurgical complications: 8 (15.1%) SAH: 7 (13.2%) medical: 11 (20.7%)
APACHE II (mean ± SD)	21.3 ± 0.9
SAPS II (mean ± SD)	53.3 ± 2.3
SOFA score (mean ± SD)	10.2 ± 0.2
ICU stay (days) (mean ± SD)	35.9 ± 4.8
Mortality	17/53 (32.1%)

Abbreviations are: SAH: acute subarachnoid hemorrhage; APACHE: acute physiology and chronic health evaluation score; SAPS: simplified acute physiology score; SOFA: sequential organ failure assessment; ICU: intensive care unit.

There were 1680 days of ICU hospitalization and 265 gallbladder/biliary tract ultrasound examinations (median 5.1, mean ± SEM 4.7 ± 2.1 per patient) recorded. Twenty-five patients (47.2%) exhibited at least one abnormal GB finding on ultrasound examination, while 16 patients (30.2%) had two or more concomitant findings. Imaging findings are presented in Table 2. Of the 25 patients who exhibited at least one sonographic finding, only six patients (24%) presented concomitant hepatic dysfunction, while 3 patients (12%) had solely increased γ-glutamyltransferase (γ-GT $\geq$ 150 IU/Lt, 415.3 ± 50.2) and 2 patients (8%) had solely increased alanine transaminase (ALT $\geq$ 150 IU/Lt, 217.5 ± 31.2), respectively. Hence, patients with at least one positive imaging finding and normal liver biochemistry results were significantly more than patients with hepatic dysfunction (χ^2, $P = 0.0005$). In contrast, 23 (82.1%) out of the 28 patients with normal ultrasound findings exhibited transient abnormalities in liver function tests but no hepatic dysfunction. These included increased transaminases, bilirubin, ALP, or γ-GT which were after meticulous investigation attributed to reasons other than AAC (drugs, sepsis, trauma-rhabdomyolysis, etc.).

Notably, 3 male trauma victims (5.7%), during the course of their hospitalization, presented with clinical features of sepsis without definite source of infection (unexplained fever, leucocytosis, hemodynamic instability). The above patients had sonographic findings compatible with AAC and consequently underwent urgent open cholecystectomy as decided by the attending intensivist and the surgeon in charge (Figure 1). All 3 patients exhibited sonographic findings of gallbladder wall thickening (>3.5 mm), marginally increased GB dimensions, and pericholecystic fluid. All of them were under MV, vasopressors, midazolam and remifentaniyl, and TPN. Only one out of these three patients with AAC showed evidence of hepatic dysfunction as defined [15]. Day of surgery was the 14th, 22nd, and 42nd of ICU stay, respectively, leading to clinical improvement of the patients that is apyrexia and gradual discontinuation of vasopressors.

The 13 (24.5%) patients exhibiting ≥2 imaging findings but not AAC were managed successfully by applying measures including gastric drainage and modulation of antibiotic

Table 2: Ultrasound results in the 25 patients who exhibited at least one finding.

Total number of patients with at least one finding	25/53 (47.2%)
Gallbladder wall thickening (>3 mm)	19/25 (76%)
Gallbladder distention (long axis > 100 mm, short axis > 50 mm)	8/25 (32%)
Striated gallbladder wall	3/25 (12%)
Pericholecystic fluid	5/25 (20%)
Gallbladder sludge	19/25 (76%)

therapy to cover possible pathogens originating from the gallbladder and/or interruption of enteral or parenteral nutrition, under the guidance of evolving ultrasound, clinical, and laboratory findings. None of these patients exhibited AAC, while hepatic dysfunction was present only in 2 cases (15.4%).

Finally, 19 patients (35.8%, 14 with US findings) did not have any liver function tests abnormalities and 34 patients (64.2%) had liver function tests abnormalities, of whom only 11 (32.4%) had concomitant US findings. Only 5 (9.4%) patients had both normal liver function and normal ultrasound findings of the GB during their ICU stay.

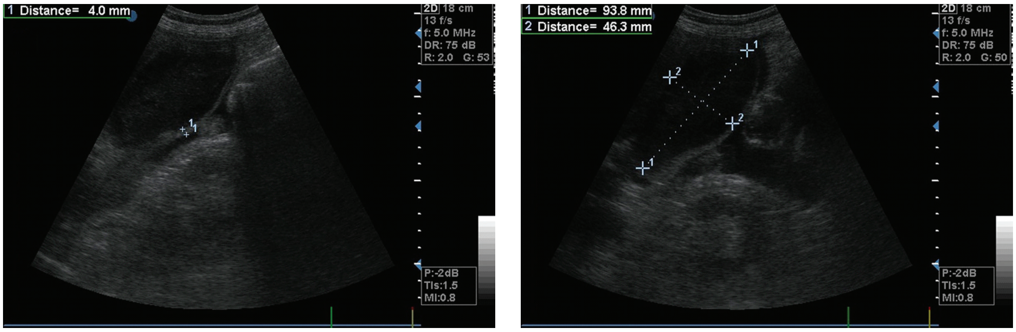
4. Discussion

AAC poses major diagnostic challenges in critical care patients.GB abnormalities and AAC are one of the many potential causes in the differential diagnosis of systemic inflammatory response syndrome and sepsis or jaundice and no other obvious source of infection [11]. Notably, gallbladder ischemia can progress rapidly to gangrene and perforation with detrimental effects. Indeed physical examination and laboratory evaluation are unreliable in AAC [16]. Abdominal pain and tenderness may be masked by analgesia and sedation. Fever is generally, present but other physical findings may not be consistent and/or reliable, particularly physical examination of the abdomen [17]. Leukocytosis and jaundice are commonplace, but nonspecific in the setting of critical illness. Also, a number of pitfalls can be encountered in the interpretation of common liver function tests [18, 19]. Alterations of hepatic enzymes reflecting the extent of hepatocellular necrosis (i.e., transaminases) or cholestasis (i.e., bilirubin) could be attributed to various causes such as extrahepatic infection and sepsis, ischemia/reperfusion injury, total parenteral nutrition, trauma, and drug adverse effects. Diagnosis of intra-abdominal pathology and AAC often rests on imaging studies and clinical suspicion [11]. Computed tomography scans are useful but can be ambiguous, while oftentimes the patient is too unstable to be safely transferred. Ultrasound by-the-bed examination represents not only an alternative imaging method, but also a lifesaving diagnostic tool in the detection of intra-abdominal pathology and remains the screening procedure of choice for depicting GB abnormalities [15–22].

In this study, almost half of our patients (47.2%) exhibited at least one GB abnormality on ultrasound examination and 30.2% of them had ≥2 findings. In fact, anomalies of GB are extremely common and could be found in up to 84% of the critically ill as a result of various causes [1, 2, 23]. However, we found that only 5.7% of the patients developed AAC requiring surgical intervention which is higher than that reported in the literature [6–8]. In a previous study, 14 out of 28 critical care patients (50%; 19 intubated) were found to have one of the three major sonographic criteria for AAC, but none of these subjects needed any intervention [23]. It was suggested that thickening of the gallbladder wall is the single most reliable criterion, with reported specificity of 90% at 3 mm and 98.5% at 3.5 mm wall thickness and sensitivity of 100% at 3 mm and 80% at 3.5 mm [24–26]. Accordingly, gallbladder wall thickness greater than or equal to 3.5 mm is generally accepted to be diagnostic of AAC [24–26]. In our cohort, 19 patients had gallbladder wall thickening >3 mm, but only 3 developed AAC compatible with the clinical condition of the patients. Other helpful sonographic findings for AAC such as pericholecystic fluid, striated gallbladder wall, and distention of the gallbladder of more than 5 cm were found in five, three and eight patients, respectively. In this study, all patients who exhibited AAC presented with GB wall thickening >3.5 mm and pericholecystic fluid; however, the recorded rate of AAC was too low to justify routine ultrasound examination of the GB on a weekly basis. The present findings suggest that on the grounds of clinical suspicion for AAC (i.e., unexplained sepsis syndrome), even in the absence of liver dysfunction, a sonographic examination could alter the decision making and could be potentially lifesaving for the individual patient.

Furthermore, 13 (24.5%) of our patients who presented with ≥2 ultrasound findings, of whom only 2 had liver dysfunction, were medically managed (gastric drainage, antibiotics, interruption of enteral nutrition, etc.) under the guidance of evolving ultrasound, clinical, and laboratory parameters.

Nevertheless, alterations in liver function tests were not correlated to pertinent ultrasound findings in this cohort of critical care patients. It is worth mentioning that ≈64% (34/53) of our patients had liver dysfunction of which only 32% (11/34) had concomitant gallbladder US findings. That is, for 23 patients having liver dysfunction, US examination was crucial to exclude GB abnormalities. On the contrary, in the 3 patients with AAC only one presented with concomitant hepatic dysfunction. Surely, routine evaluation of liver function tests for diagnosing AAC is neither specific nor sensitive. AAC represents an underdiagnosed entity in the ICU, and this may be partially due to the complexity of underlying medical and surgical problems and lack of reproducible signs and biochemical parameters [1, 6, 9]. Diagnosis of AAC and GB anomalies in general relies on a high level of clinical suspicion. Moreover, AAC is considered an ischemic rather than an infectious disorder, and any abdominal pain in a critically ill patient, or even unexplained fever or hemodynamic instability, warrants consideration of this diagnosis [2]. Prompt application of ultrasound investigations could confirm clinical suspicions and guide consequently therapeutic options [1, 9, 27, 28].



(a) (b)

Figure 1: Gallbladder ultrasound depicting one patient with acute acalculous cholecystitis exhibiting wall thickening (4 mm) in the presence of sludge (a) and marginally increased dimensions (93 × 46.3 mm) with pericholecystic fluid (b).

4.1. Limitations. This study has many limitations. Ultrasound is a method with inherent technical limitations; moreover increased body mass index, subcutaneous edema, and/or air and mechanical ventilation may affect the clarity of ultrasound images in the ICU [23, 24, 28]. Also, the sample of patients was rather small to perform any meaningful subgroup analysis and to draw definite conclusions about the correlation of laboratory and imaging findings in patients with GB anomalies. Future larger prospective studies are required to investigate further the issues raised in this study. Despite the aforementioned limitations, ultrasound is a useful diagnostic tool for detection of AAC and GB abnormalities in the ICU. Its prompt application may aid in altering therapeutic strategies, operative or conservative, and could prove lifesaving for the individual patient.

4.2. Conclusions. In this study, alterations in liver function tests were not correlated to pertinent ultrasound findings in critical care patients with GB abnormalities. Standardized ultrasound monitoring of the GB facilitated the diagnosis of 3 cases of AAC and thus guided prompt surgical treatment. The former accordingly guided the medical management of 13 patients who exhibited two or more imaging findings without ACC and excluded GB abnormalities in 23 patients having abnormal liver function test alone. However, the low rate of AAC observed in this small series could not justify routine ultrasound examination of the GB to identify AAC in the ICU. On the other hand routine ICU ultrasound examination was found useful in almost 75% of ICU patients for differential diagnosis, monitoring of abnormalities found or therapies applied, or excluding GB abnormalities. Taking into account this high rate in combination with the bedside availability of US examination, the capability to investigate other organs such as heart, vessels, and lungs, and the low related costs, ultrasound examination can be an examination of choice in most critically ill ICU patients.

Conflict of Interests

There are no potential conflicts of interests.

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Research Article

Sonographic Lobe Localization of Alveolar-Interstitial Syndrome in the Critically Ill

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Introduction. Fast and accurate diagnosis of alveolar-interstitial syndrome is of major importance in the critically ill. We evaluated the utility of lung ultrasound (US) in detecting and localizing alveolar-interstitial syndrome in respective pulmonary lobes as compared to computed tomography scans (CT). *Methods*. One hundred and seven critically ill patients participated in the study. The presence of diffuse comet-tail artifacts was considered a sign of alveolar-interstitial syndrome. We designated lobar reflections along intercostal spaces and surface lines by means of sonoanatomy in an effort to accurately localize lung pathology. Each sonographic finding was thereafter grouped into the respective lobe. *Results*. From 107 patients, 77 were finally included in the analysis (42 males with mean age = 61 ± 17 years, APACHE II score = 17.6 ± 6.4, and lung injury score = 1.0 ± 0.7). US exhibited high sensitivity and specificity values (ranging from over 80% for the lower lung fields up to over 90% for the upper lung fields) and considerable consistency in the diagnosis and localization of alveolar-interstitial syndrome. *Conclusions*. US is a reliable, bedside method for accurate detection and localization of alveolar-interstitial syndrome in the critically ill.

1. Introduction

Pulmonary diseases with involvement of the alveolar space and the interstitium (alveolar-interstitial syndrome) are common in the critically ill. Diagnostic assessment of the alveolar-interstitial syndrome includes chest radiography and computed tomography (CT). Chest CT is considered the "gold standard" test for the diagnosis of most pulmonary disorders in the intensive care unit (ICU). However, serial CT examinations may be required to followup the clinical course of pulmonary disorders and the results of therapy increasing radiation exposure. Also, this may be time consuming and hazardous as critically ill patients who oftentimes suffer from severe respiratory insufficiency are transferred to another unit.

Historically, lung was considered a poorly accessible organ for ultrasound (US) assessment mainly due to abundance of air. However, in patients with lung disease extending to the pleura, US can be particularly useful for a wide range of applications [1, 2]. Recent studies have shown the significant role of lung US in detecting pulmonary diseases [3–15]. Areas of ground-glass adjacent to the pleura, areas of consolidation and areas of thickening of the interstitium can be easily detected using lung US [3–13]. The sonographic imaging of pulmonary diseases is based on the detection and quantification of "comet-tails" lines known as "B-lines" or lung rockets [5], generated by reverberation of the US beam. Previous studies have shown that the presence of multiple lines perpendicular to the pleura with a distance of 3 mm or less and a distance of 7 mm and more are representative of ground-glass areas and of subpleura interlobular septa thickening, respectively [3–5]. Although there have been several studies reporting the possible role of lung US in detecting the alveolar-interstitial syndrome [3–13], its application in routine ICU practice remains unclear.

The aim of this study was to investigate the utility of a simple lung US protocol in detecting and localizing areas of alveolar and/or interstitial involvement in respective pulmonary lobes as compared to thoracic CT scans in critical care patients.

2. Materials and Methods

2.1. Study Population. We enrolled 107 consecutive patients with respiratory failure necessitating mechanical ventilation who were admitted to our medical ICU during a 12-month period. Patients with an ICU stay longer than 48 hours who underwent chest CT for diagnostic purposes were included in this study. Patients with pneumothorax, subcutaneous emphysema, mesothelioma, massive effusion, pneumonectomy, and body mass index (BMI) ≥40 kg/m^2 (class III obesity) were excluded. All patients were sedated under mechanical ventilation set at the volume assist-control mode. Informed consent was obtained from all patients or their relatives and the study was approved by institutional ethics committee.

2.2. Study Protocol. Lung US was performed before CT scan, within an interval of 30 min, by an independent expert radiologist who was blinded to the subjects' identity and to the CT results. The portable US system Vivid 7 (GE, Wauwatosa, WI, USA) equipped with a sector array probe (1.5–3.8 MHz) was utilized. All patients were examined in supine or semirecumbent position. US examinations consisted of bilateral scanning of the anterior and lateral chest of the right and left hemithorax. Lung US was performed from the second to the fifth intercostal space from parasternal to midaxillary line, for the right lung; from the second to the fourth intercostal space from parasternal to midaxillary line, for the left lung, respectively (Figures 1, 2, and 3). This also included sonographic depiction of the fissures. Along the posterior axillary line, scanning was performed at the level of seventh and eighth intercostal space. Notably, examination of the left fifth intercostal space was not performed since the heart blocks the visibility of the wall interface. All patients were examined in end-expiration to avoid displacements of the lower borders of the lung. The intercostal spaces which were scanned along the lines were grouped into respective pulmonary lobes (Table 1). Results of US scanning in each pulmonary lobe were recorded and compared with CT findings in the same lobe. Presence of A-lines was considered normal [3]. Alveolar-interstitial syndrome in each lobe was defined as the presence of more than two comet-tail artifacts perpendicular to the pleural line [3–5]. Alveolar pattern

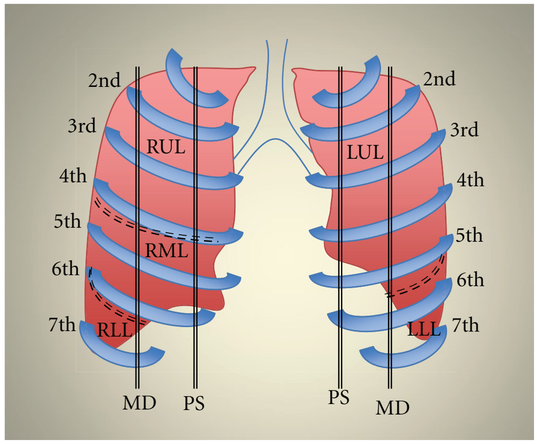

Figure 1: Anterior view of the lung. Schematic representation of pulmonary lobes in relation to ribs and intercostal spaces along parasternal (PS) and midclavicular (MD) lines, respectively. Dashed lines correspond to major and minor lung fissures (RUL: right upper lobe; RML: right mid lobe, RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe).

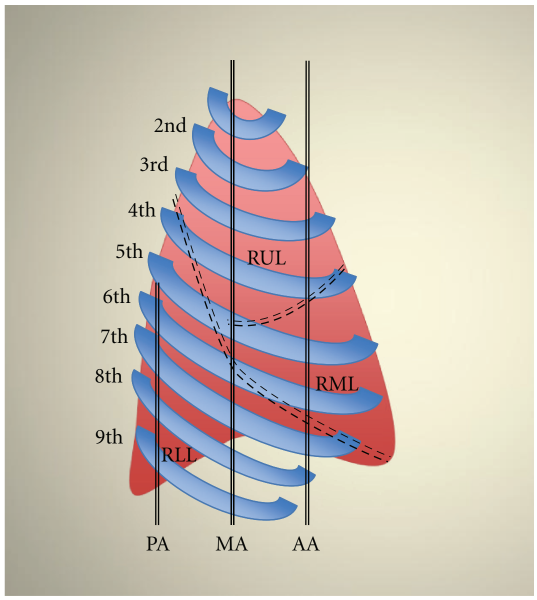

Figure 2: Lateral view of the right lung. Schematic representation of pulmonary lobes in relation to ribs and intercostal spaces along anterior axillary (AA), midaxillary (MD), and posterior axillary (PA) lines, respectively.

included also pleural-based consolidations described sonographically as heterogeneous tissue-like patterns resembling the echogenicity of the liver with hyperechoic punctiform or linear artifacts, corresponding to air bronchograms [3–5].

Thoracic CT scans were performed from the apex to the diaphragm using a Tomoscan (GE, WI, USA). All images were observed and photographed at a window width of 1,600 HU and a level of −600 HU. An independent radiologist, who was blinded to subjects' identity and to lung US results, was assigned to interpret the CT results. All findings

TABLE 1: Ultrasound scanned intercostal spaces grouped in respective pulmonary lobes.

	PS	MDC	AA	MA	PA
			Right lung		
RUL	2nd, 3rd LIS	2nd, 3rd LIS	2nd, 3rd LIS	2nd, 3rd, 4th LIS	—
RML	4th, 5th LIS	4th, 5th LIS	4th, 5th LIS	5th LIS	—
RLL	—	—	—	—	7th, 8th LIS
			Left lung		
LUL	2nd, 3rd, 4th LIS	2nd, 3rd, 4th LIS	2nd, 3rd, 4th LIS	2nd, 3rd LIS	—
LLL	—	—	—	4th LIS	7th, 8th LIS

RUL: right upper lobe, RML: right mid lobe, RLL: right lower lobe; LUL: left upper lobe, LLL: left lower lobe, PS: parasternal line, MDC: midclavicular line, AA: anterior axillary line, MA: mid axillary line, PA: posterior axillary line, LIS: lung intercostal space.

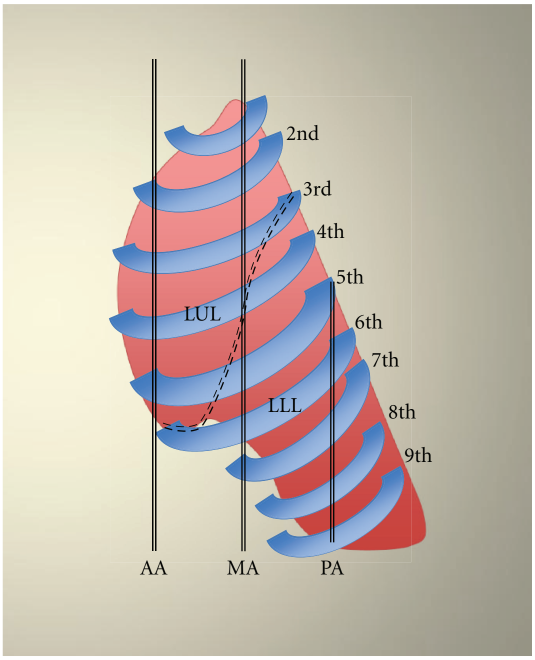

FIGURE 3: Lateral view of the left lung. Schematic representation of pulmonary lobes in relation to ribs and intercostal spaces along anterior axillary (AA), midaxillary (MD), and posterior axillary (PA) lines, respectively.

were recorded and assigned to the appropriate pulmonary lobe. Alveolar-interstitial syndrome was defined according to the Fleischner Society's recommendations [16] as the presence of one or the combination of ground-glass opacities, consolidation, reticulation, and septal thickening.

2.3. Statistical Analysis. Continuous variables are presented as mean ± standard deviation (SD). The accuracy of lung US in detecting alveolar-interstitial syndrome was evaluated by means of sensitivity = (true positive/(true positive + false negative)); specificity = (true negative/(true negative + false positive)); positive predictive value = (true positive/(true positive + false positive)); negative predictive value = (true negative/(true negative + false negative)); and diagnostic accuracy = (true positive + true negative)/(true positive + true negative + false positive + false negative). Cohen's weighted kappa was calculated to express the degree of agreement between lung US and thoracic CT scan in diagnosing and localizing the alveolar-interstitial syndrome in all respective pulmonary lobes [17], while 2.5th and 97.5th percentiles of 5,000 bootstrap replicates estimated 95% confidence intervals. The bootstrap is a resampling method used for estimating a distribution, from which various measures of interest can be calculated [18, 19]. A P-value (two-sided in all tests) of <0.05 was considered significant. Analysis was performed with the R2.10.1 statistical package (R Development Core Team, 2009. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

3. Results

From 107 consecutive patients studied, 77 were finally enrolled (42 males with mean age = 61 ± 17 years, acute physiology and chronic health evaluation score (APACHE) II = 17.6 ± 6.4, and lung injury score = 1.0 ± 0.7). Thirty patients were excluded from the study. The causes were an ICU stay less than 48 hours ($n = 18$), subcutaneous emphysema ($n = 8$), pneumonectomy ($n = 2$), and a BMI ≥40 ($n = 2$). Various causes of admission in the ICU were recorded such as multiple organ dysfunction syndrome ($n = 23$), trauma ($n = 17$), postsurgical complications ($n = 15$), exacerbation of chronic obstructive pulmonary disease (COPD, $n = 6$), and miscellaneous ($n = 16$).

Hence, a total of 144 hemithoraces were evaluated both by US and CT scans according to the study protocol (Figure 4). Alveolar-interstitial syndrome was diagnosed by CT scans in 42/77 (54%), 49/77 (64%) and 61/77 (79%) patients for the upper, mid-, and lower right lobes, respectively. In the left lung, alveolar-interstitial syndrome was diagnosed by CT scans in 38/77 (49%) and 65/77 (84%) patients for the upper and the lower lobe, respectively. US detected alveolar-interstitial syndrome in 39/77 (50%), 47/77 (61%) and 50/77 (65%) patients for the upper, mid-, and lower right lobes, respectively. In the left lung, sonographic alveolar-interstitial syndrome was detected in 36/77 (47%) and 56/77 (73%) patients for the upper and the lower lobe, respectively. Diagnostic accuracy of lung US in detecting alveolar-interstitial syndrome is presented on Table 2.

Agreement between lung US and CT scans was evaluated according to kappa values and 95% confidence intervals

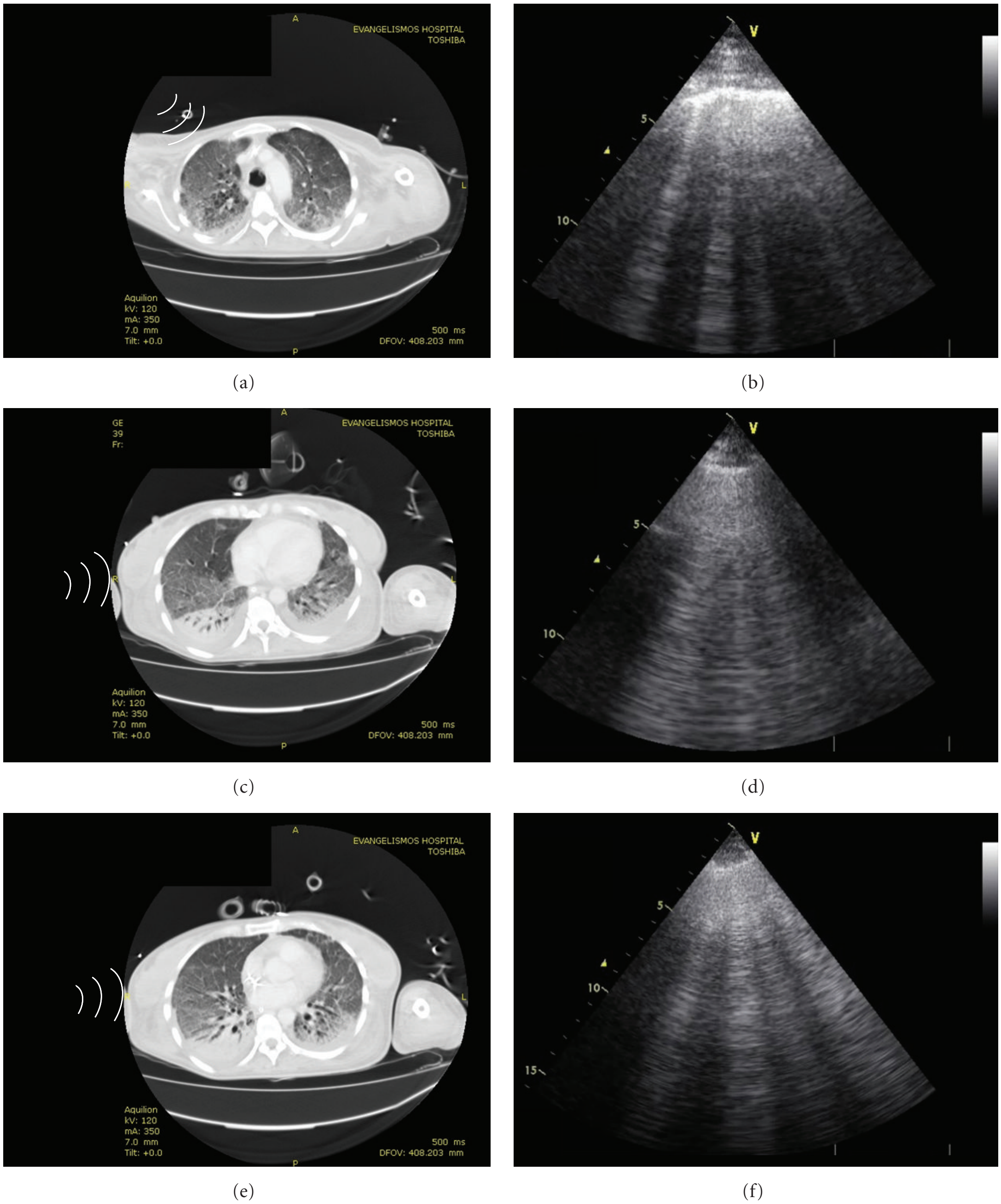

Figure 4: Computed tomography (CT) scans showing areas of "ground glass" opacification and bilateral-dependent areas of dense consolidation in a patient with acute respiratory distress syndrome (right panel). Lung ultrasound scans in the same patient depicting B-lines arising from the pleural line, confirming thus a pattern of diffuse alveolar-interstitial syndrome (left panel).

Table 2: Accuracy of lung ultrasound in diagnosing alveolar-interstitial syndrome in respective pulmonary lobes.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	DA (%)
RUL	93	91	83	91	92
RML	96	96	98	93	96
RLL	82	87	96	56	83
LUL	95	87	88	94	91
LLL	86	92	98	55	87

PPV: positive predictive value; NPV: negative predictive value; DA: diagnostic accuracy; RUL: right upper lobe; RML: right mid lobe, RLL: right lower lobe; LUL: left upper lobe; LLL: left lower lobe.

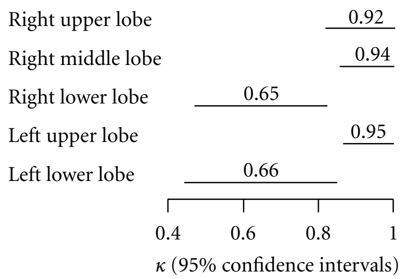

Figure 5: Cohen's kappa values by lobe of lung, with lines displaying bootstrap 95% confidence intervals.

were calculated by bootstrap analysis, for all respective pulmonary lobes: right upper 0.92 (0.82–1.00), mid 0.94 (0.86–1.00), lower 0.65 (0.47–0.82); left upper 0.95 (0.87–1.00), lower 0.66 (0.45–0.85), respectively (all $P < 0.01$) (Figure 5).The overall agreement, involving all lung fields bilaterally, between US and CT in the diagnosis and appropriate lobe localization of the alveolar-interstitial syndrome, was substantial: 0.78 (0.66–0.89; $P < 0.01$).

4. Discussion

In this study, lung US showed high sensitivity and specificity in the detection of alveolar-interstitial syndrome. The present results revealed substantial agreement between lung US and CT scans in detecting alveolar-interstitial syndrome in critical care patients.

The comet-tail artifact, a form of reverberation of echoes, was first described by Ziskin [20]. Since then, this repetition artifact noted at the lung surfaces in normal and pathologic clinical conditions [9], was sonographically correlated with the detection of alveolar-interstitial syndrome [3–8]. In previous reports studying the alveolar-interstitial syndrome, the chest wall was divided into anterior and lateral chest wall or into four areas divided for each hemithorax, two anterior, (upper and lower) and two lateral, (upper and basal) [3–5]. We designated lobar reflections along intercostal spaces and surface lines by means of sonoanatomy in an effort to accurately localize lung disease. Our results confirmed high sensitivity and specificity of lung US in diagnosing alveolar-interstitial syndrome as others have previously reported [3]. In patients with acute respiratory distress syndrome (ARDS) the presence of B-lines yielded an accuracy of 97% in the diagnosis of alveolar-interstitial syndrome [5]. B-lines were correlated with subpleural interstitial oedema and were suggested as potential non-invasive measures of pulmonary artery occlusion pressure in the critically ill [21]. In addition, two US studies that investigated the detection of alveolar-interstitial syndrome for the diagnosis of lung contusion presented 94% and 86% sensitivity and 96% and 97% specificity, respectively [12, 13]. In a recent study of 42 critical care patients, lung US presented a sensitivity, specificity and diagnostic accuracy of 94%, 93%, and 94% for detecting interstitial syndrome, respectively [7]. The efficacy of lung US in detecting areas of consolidations has been reported in previous studies [7–10]. Also, B-lines were used in the differential diagnosis between acute cardiogenic pulmonary oedema and ARDS, acute pulmonary oedema and exacerbation of COPD and in dyspnoea diagnostic protocols such as the Blue Protocol [22–24]. Interpretation of lung US artifacts can be helpful in various clinical scenarios (i.e., presence of comet-tails artifacts excludes the existence of pneumothorax) [14]. Study of these artifacts according to several research groups, allows evaluation of lung aeration in patients with ARDS [25, 26]. The association of B-lines with the presence of extravascular lung water [27, 28] may extend the role of lung US in assessing lung aeration. B-lines have been studied in cardiogenic and high-altitude pulmonary oedema [29, 30], following medical treatment of patients with acute decompensated heart failure [31], in patients undergoing hemodialysis [32], and in patients with community-acquired and ventilator-associated pneumonia [33]. Taking into account all previous reports, the present results reinforce the significance of lung US utility in the diagnosis of alveolar and interstitial pathology. Additionally, we were able to localize pulmonary disease of the alveolar space and/or the interstitium to respective lobes. A simple reproducible protocol had good diagnostic accuracy compared to the gold standard of CT scan. Localization to particular pulmonary lobes could be useful to aid in the differential diagnosis of respiratory disease. Moreover, a bedside test that can localize pulmonary disease could potentially be useful to guide diagnostic procedures such as bronchoscopy.

Limitaions. This study has several limitations. Lung US was performed on the anterior and lateral chest areas and not on dorsal areas to avoid displacement of patients. This might have increased the false negative cases especially for posterior disease processes. Indeed, our results revealed lower sensitivity and specificity values for lung US in the lower pulmonary lobes and decreased extent of agreement with CT scan findings in these areas. Dorsal scans could have improved the efficacy of lung US in detecting areas of ground-glass, consolidation, and areas of interstitial involvement in the posterior lung. If clinically warranted and attention is paid to patient safety, a more complete exam could be performed which included the dorsum though the accuracy of such an exam is unknown. Another issue that could explain imperfect diagnostic accuracy is the limited capability of US to detect pulmonary pathology that does not reach the pleura [34]. However, alveolar-interstitial syndrome is generally extended to the lung periphery. Our designated sonoanatomical correspondence of the intercostal spaces with the appropriate pulmonary lobe also represents a methodology limitation. The somatotype of the patient and underlying pulmonary pathology such as atelectasis and diaphragm paralysis may alter the anatomical correspondence of the pulmonary lobes with the intercostal spaces [27]. The performance in patients with anatomic variants such as accessory fissures is unknown. Since obese patients were excluded, results cannot be extrapolated to such patients. Finally, in this study, a single experienced observer performed all the US examinations to reduce bias. Lung US is considered an operator dependent test; however, high degree of inter- and intraobserver reproducibility has been previously reported for several indications [3, 4].

Despite the aforementioned limitations, this study demonstrated a high accuracy of lung US in diagnosing the alveolar-interstitial syndrome in the ICU. US exhibited substantial agreement with thoracic CT and showed consistency in the localization of lung pathology to respective lobes, even if the dorsal areas of the lung were not scanned. Sonography can be easily performed at the bedside, free of radiation exposure; hence, it may represent a promising alternative to CT in the monitoring of pulmonary disorders [35]. In conclusion, we provided evidence that lung US represents a reliable and accurate bedside test for assessing and localizing pulmonary disease of the interstitium and/or the alveolar space in critical care patients.

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Clinical Study

Left Ventricular Longitudinal Function Assessed by Speckle Tracking Ultrasound from a Single Apical Imaging Plane

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Background. Transthoracic ultrasonography of the heart is valuable in monitoring and treatment of critically ill patients. Speckle tracking ultrasound (STU) has proven valid in estimating left ventricular systolic deformation. The aims of the study were to compare conventional and automated STU and to determine whether left ventricular systolic deformation could be estimated from one single imaging plane. *Methods*. 2D-echocardiography cine-loops were obtained from 20 patients for off-line speckle tracking analysis, consisting of manually tracing of the endocardial border (conventional method) or automatically drawn boundaries (automated method). *Results*. We found a bias of 0,6 (95% CI −2.2−3.3) for global peak systolic strain comparing the automated and the conventional method. Comparing global peak systolic strain of apical 4-chamber cine-loops with averaged Global Peak Strain obtained from apical 4, 2 and long axis cine-loops, showed a bias of 0.1 (95% CI −3.9−4.0). The agreement between subcostal 4-chamber and apical 4-chamber global peak systolic strain was 4.4 (95% CI −3.7−12.5). *Conclusion*. We found good agreement between the conventional and the automated method. STU applied to single apical 4-chamber cine-loops is in excellent agreement with overall averaged global peak systolic strain, while subcostal 4-chamber cine-loops proved less compliant with speckle tracking ultrasound.

1. Introduction

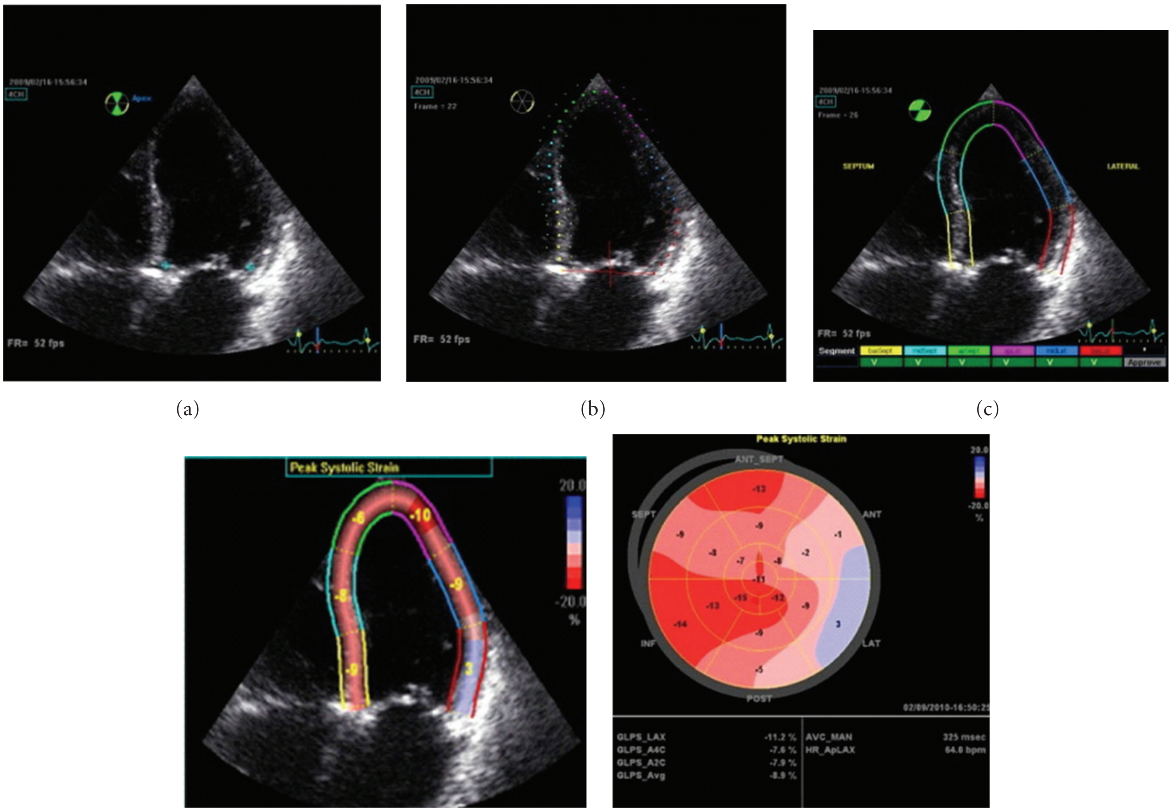
Bedside transthoracic ultrasound protocols have won wide spread use for monitoring and guiding treatment of the critically ill patients [1–7]. Evaluation of left ventricular systolic function is a key element in focused protocols [1, 2] as well as standard echocardiography [8]. Visual estimation (eyeballing) and wall motion index (WMI), Simpsons Biplane method, and Doppler tissue imaging are used for quantification of left ventricular systolic function, but they are either subjective, dependent upon operator experience, or time consuming [9–17]. Speckle Tracking Ultrasound (STU) is a novel method allowing assessment of both regional and global left ventricular function [18–21] in dedicated semiautomatic software, thereby making this method fast and potentially available for online real-time analysis in the critical setting where time is crucial.

Two different STU algorithms are available in the Echopac software (GE Healthcare, Horten Norway). One is conventional quantitative strain analysis (Q-analysis) in which manual tracing of the endocardial border is necessary and secondly a less time-consuming automated function imaging (AFI) where the endocardial borders are automatically traced. Quite often the image quality from the AP4C view is poor in critically ill patients for different reasons: positive pressure ventilation, catheters, wires, surgical dressing, and posture among the most important. Therefore we set out to examine whether GLPS could be estimated from a single subcostal view.

Thus the purpose of this study was to compare the two methods and secondly to evaluate whether left ventricular deformation could be estimated from a single imaging plane by means of STU.

2. Materials and Methods

2.1. Patients. The study was approved by the Danish Data Protection Agency (no. 2011-41-6010) with a waiver of informed consent. Bedside ultrasonography is a standard component of clinical care at the site of investigation.



(a) (b) (c)

(d) (e)

Figure 1: Steps involved in the sequence of Automated Functional Imaging (AFI) analysis and conventional analysis using the apical four chamber view (AP4C). (An example, see also text.) (a) Two points have been applied on both sides of the Mitral valve. The apical point has yet to be placed. (b) Myocardial wall of the left ventricle has been outlined defining a region of interest (ROI), consisting of 3 concentric lines delineating the endocardial and epicardial borders and a midmyocardial layer and end systole is automatically marked by aortic valve closure. (c) ROI is divided into 6 segments and good alignment is confirmed within each segment. (d) Peak systolic strain values of each segment have been calculated by the computer algorithm. (e) Bulls Eye plot presenting segmental peak systolic strain values (17 segment model) and global peak systolic strain values of each view (GLPS LAX: apical long axis; GLPS 4C: apical four-chamber; GLPS 2C: apical 2 chamber) and an overall averaged peak systolic strain value average GLPS.

20 patients (13 women and 7 men), mean age 66 (range 25–90) years, who previously underwent comprehensive conventional 2-dimensional echocardiography were studied. Two patients underwent coronary artery bypass grafting and 15 aortic valve replacement surgery due to either aortic valve stenosis (13) or aortic valve regurgitation (2), while three patients had no known cardiac disease.

2.2. Data Acquisition and Analysis. Transthoracic ultrasonography images were obtained by an experienced ultrasonographer using General Electric Vivid 9 system equipped with an M4S probe (frequency range: 1.5–4.0 MHz). Grey-scale 2-dimensional (2D) ECG-triggered, apical 2-chamber (AP2C), apical long axis (APLAX), apical 4-chamber (AP4C), and subcostal 4-chamber (SU4C) cine-loops were recorded with frame rates ranging from 42 to 70 fps for offline analysis.

From each view one cardiac cycle was selected for analysis of 2D strain with the two methods. First is *Q-analysis* (*conventional method*): the myocardial wall of the left ventricle was outlined by manually applying successive points along the endocardial border followed by automated tracing of the epicardial border and thus defining a region of interest (ROI). *AFI (automated function imaging) method*: two points were applied on each side of the mitral valve and a third point at the apex of the left ventricle followed by automated tracing of endocardial and epicardial borders defining ROI. Manual readjustment of endocardial tracing and ROI were performed in both methods in order to achieve optimal alignment if necessary. Aortic valve closure marked end systole and was defined automatically in the apical long axis view at the end of the T-wave of the corresponding electrocardiographic tracing and used as a reference for the subcostal, four- and two-chamber views. Time of aortic valve closure was also visually confirmed and adjusted if necessary.

In both methods, the region of interest outlining the entire left ventricular wall was divided into 6 segments. A computer algorithm calculated peak systolic strain values within each segment together with global peak systolic strain (GLPS) from each view and lastly overall averaged global peak systolic strain (aGLPS) of the AP4C, AP2C, and APLAX views (Figure 1). Cine-loop analysis of the SU4C was conducted with the same algorithm used for analysis of AP4C

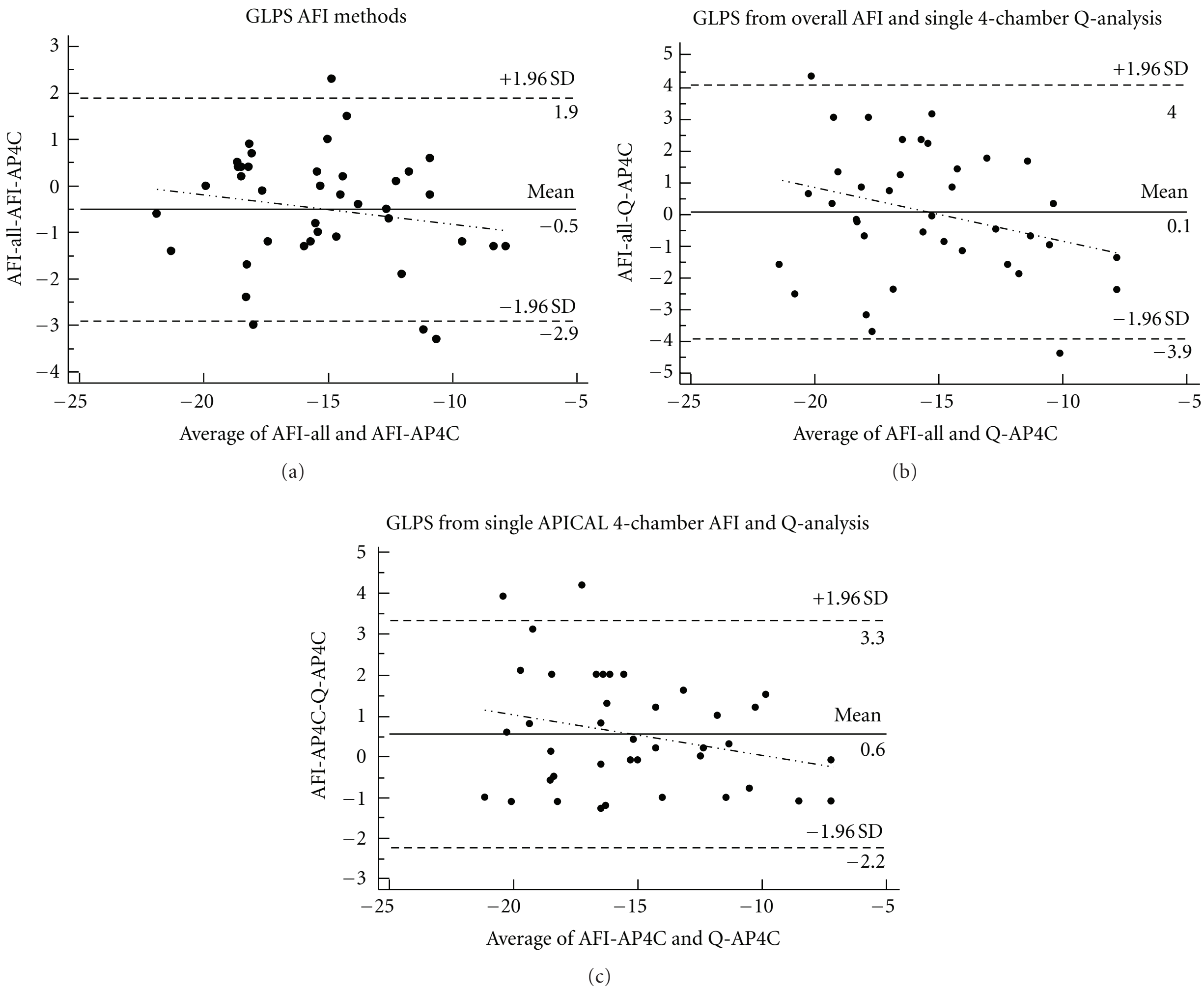


Figure 2: Bland Altman plot with mean difference and limits of agreement between overall averaged global peak systolic strain (aGLPS) of the AP4C, AP2C, and APLAX views using AFI method (AFI-All) compared to single apical 4-chamber GLPS using AFI method (AFI-AP4C) (a), AFI-all compared to single apical 4-chamber view using conventional Q-analysis (Q-AP4C) (b), and GLPS comparing AFI of an apical single 4-chamber view (AFI-AP4C) and Q-analysis of an apical single 4-chamber view (Q-AP4C) (c).

views. All analysis was done by two independent observers to estimate interobserver variability.

2.3. Statistical Analysis. Bland-Altman analysis was used to calculate the bias and limits of agreement between corresponding measurements. Analysis was done with MedCalc software version 11.5.1 (Mariakerke, Belgium).

3. Results

80 cine-loops were analyzed representing a total of 480 segments of which none were excluded. Bland Altman analysis of aGLPS (AFI-all) and GLPS from a single apical four-chamber view (AFI-AP4C) showed a mean difference of −0.5 with 95% confidence limits (95% CI) between −2.9 and 1.9 (Figure 2).

Bland Altman analysis of aGLPS using the AFI method (AFI-All) against GLPS obtained from conventional Q-analysis of single apical 4-chamber view (Q-AP4C) showed a mean difference of 0.1 (95% CI −3.9–4.0), while comparison of conventional Q-analysis of a single apical 4-chamber and AFI analysis of a single apical 4-chamber view showed a mean difference of 0.6 (95% CI −2.2–3.3) (Figure 2).

The mean difference comparing conventional Q-analysis of GLPS (Q-SU4C) and GLPS using the AFI method (AFI-AP4C) from single subcostal 4-chamber view was 4.4 (95% −3.7–12.5) (Figure 3).

The agreement between the two observers using the AFI showed a mean difference of −0.19 with 95% limits of −1.74–1.36 (Figure 4). For the conventional analysis of apical 4-chamber view, the mean differences, was −0.5 (95% CI −4.2–3.1), while the conventional analysis of subcostal 4-chamber view was −1.5 (95% CI 8.0–11.0).

4. Discussion

We found good agreement between average global peak systolic strain obtained by the conventional method and the

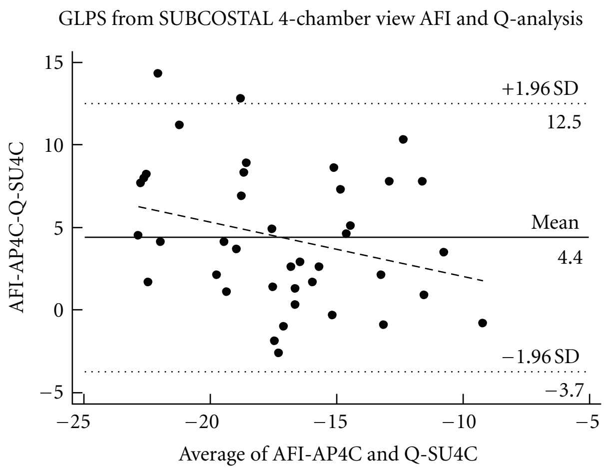


FIGURE 3: Bland Altman plot with mean difference and limits of agreement between Q-analysis of global peak systolic strain from the subcostal 4-chamber view (Q-SU4C) view compared to AFI global peak systolic strain (AFI-AP4C).

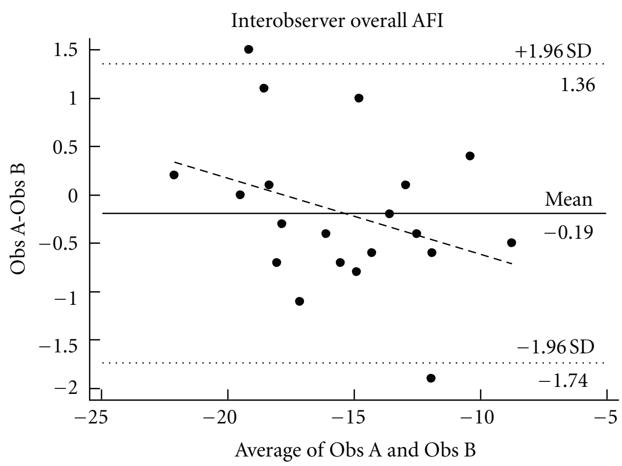


FIGURE 4: Bland Altman plots comparing observer A with observer B using AFI.

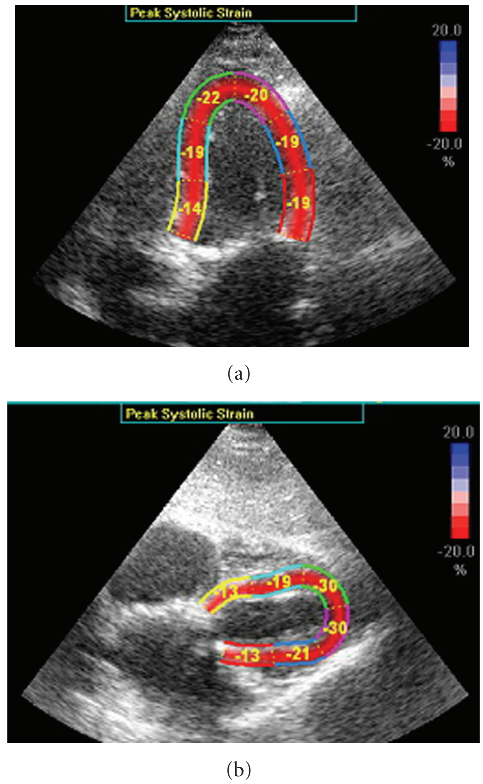


FIGURE 5: Apical (a) and subcostal (b) four-chamber view from the same patient. Segmental peak systolic strain values are indicated. Apex of the heart can be difficult to recognize in the subcostal view and peak systolic strain values appear to be significantly higher at the apex of the subcostal view than the apical view. See text for further explanation.

AFI method, although the two methods basically utilize the same algorithm calculating strain and the fact that the two methods are interchangeable is extremely relevant in critical care because the time consumption is very different for the two methods.

Our study showed that left ventricular systolic deformation could be estimated using the AFI method from one cineloop of a single AP4C view. This has also tremendous critical care application since the apical two- and long-axis view are both time demanding and difficult to achieve in the critical scenario. This finding also applies to most of the focussed echo protocols which disregard the apical 2- and long-axis view [1–3]. Recently we have shown that the AP4C view can be achieved even with the patient in the sitting position [4]. The fact that AFI is already available on several high-end ultrasound machines makes these results even more attractive.

In critical care, most patients are placed supine for different reasons making the subcostal four-chamber view the a priori best choice. Unfortunately our results showed that GLPS from Sub4C significantly overestimates GLPS from both AP4C and aGLPS. First of all it was difficult to obtain GLPS from SU4C using the AFI method because this required substantial correction of ROI making this analysis no different from the conventional method and thereby eliminating the time advantage of the AFI method. Secondly we noticed that overestimation primarily was presented at apical segments (Figure 5). One reason could be that interposition of inflated lung often blurs the apex of the heart in the subcostal view. Another reason could be that the algorithm used to calculate strain from AP4C is not appropriate for the Sub4C, because the images are tilted approximately 90 degrees from having the axis of the heart at the center of the ultrasound beam to a lateral position. Sivesgaard et al. [22] demonstrated that STU is independent of insonation angle, but reliability was dependent upon speckle tracking number (STN). STN describes the relation between displacement, frame rate, and sector depth, and beyond a certain value peak strain cannot be reliably measured. One could speculate that the subcostal view represents STN values beyond the critical value. The subcostal view requires greater sector depth compared to apical views and this could be the reason why STU applied to cine-loops of the subcostal view results in substantial overestimation of systolic peak strain values. Future software optimisation might improve the assessment of STU from SU4C.

Using a single view is limited by not describing regional differences in myocardial motion and this must be taken into consideration. Reduced myocardial motion will not be detected in the posterior or anterior wall leading to an overestimation of left ventricular systolic function. Conversely underestimation will likely take place if reduced myocardial motion occurs in the septal or lateral wall.

We found good agreement between the experienced and the novel observer using either conventional Q-analysis or AFI. This indicates that emergency physicians with limited experience can perform analysis, but results are dependent upon good quality ultrasonographic images, which can be difficult for the inexperienced to obtain. Studies have shown that the task of performing focused bedside transthoracic ultrasonography can be learned fast even with little or no previous ultrasonography experience [5, 20].

5. Conclusion

This study shows that global peak systolic strain based on AFI is in good agreement with conventional Q-analysis for the single apical 4 chamber. STU applied to the subcostal four-chamber view cannot replace the apical four-chamber view. AFI method has the potential to become the method of choice in clinical settings, because it is fast and more objective opposed to visual eyeballing and can be performed with even limited experience of ultrasonography.

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Research Article

Optimization of Cannula Visibility during Ultrasound-Guided Subclavian Vein Catheterization, via a Longitudinal Approach, by Implementing Echogenic Technology

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Objective. One limitation of ultrasound-guided vascular access is the technical challenge of visualizing the cannula during insertion into the vessel. We hypothesized that the use of an echogenic vascular cannula (EC) would improve visualization when compared with a nonechogenic vascular cannula (NEC) during real-time ultrasound-guided subclavian vein (SCV) cannulation in the ICU. *Material and Methods*. Eighty mechanically ventilated patients were prospectively enrolled in a randomized study that was conducted in a medical-surgical ICU. Forty patients underwent EC and 40 patients were randomized to NEC. The procedure was ultrasound-guided SCV cannulation via the infraclavicular approach on the longitudinal axis. *Results*. The EC group exhibited increased cannula visibility as compared to the NEC group ($92\% \pm 3\%$ versus $85 \pm 7\%$, resp., $P < 0.01$). There was strong agreement between the procedure operators and independent observers ($k = 0.9$, 95% confidence intervals assessed by bootstrap analysis = 0.87 to 0.93; $P < 0.01$). Access time ($12.1\,\mathrm{s} \pm 6.5$ versus $18.9\,\mathrm{s} \pm 10.9$) and the perceived technical difficulty of the ultrasound method (4.5 ± 1.5 versus 7.5 ± 1.5) were both decreased in the EC group compared to the NEC group ($P < 0.05$). *Conclusions*. Echogenic technology significantly improved cannula visibility and decreased access time and technical complexity optimizing thus real-time ultrasound-guided SCV cannulation via a longitudinal approach.

1. Introduction

Real-time ultrasound-guided central venous cannulation has been associated with higher success rates, faster access times, and a reduction in mechanical complications, when compared to landmark techniques [1–6]. Mechanical complications occur more frequently when accessing the subclavian vein (SCV) compared to the other sites of central venous access [6–8]. We recently demonstrated that ultrasound-guided SCV cannulation, while technically demanding, was superior to landmark methods in a cohort of intensive care unit (ICU) patients [6]. Our ultrasound method was based on the implementation of a step-by-step guided technique [6]. Cannula visualization is fundamental to the safety and efficacy of all ultrasound-guided methods, but no single technology meant to improve cannula echogenicity has been

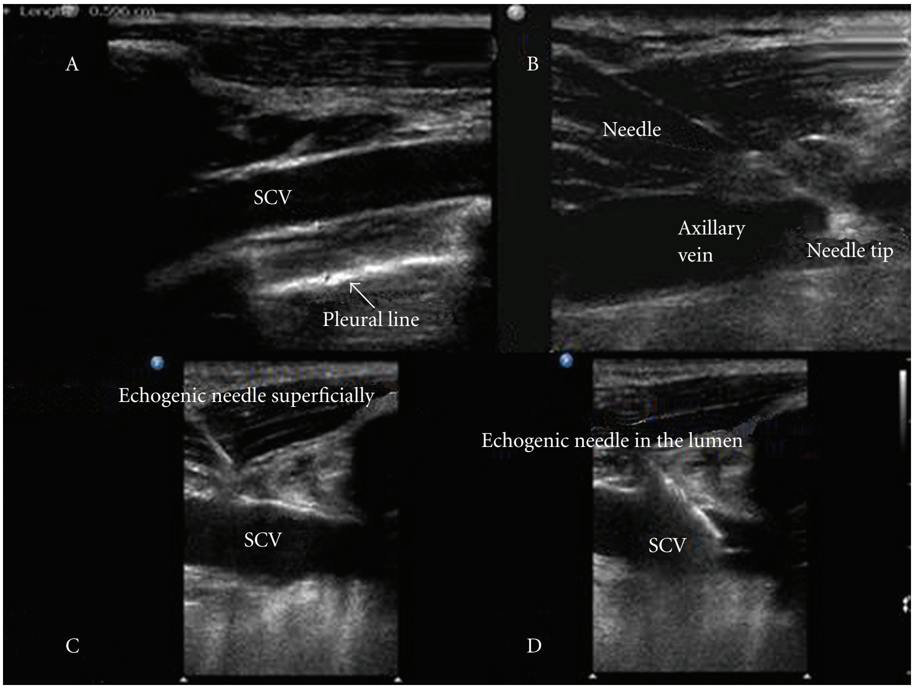

Figure 1: The subclavian vein (SCV) scanned just above the pleural line (A); axillary vein cannulation by nonechogenic cannula on the longitudinal axis (B); snapshots of SCV cannulation by echogenic cannula depicting its tip superficially (C) and in the vessel's lumen (D), respectively.

widely adopted [9–14]. The value of this technology has not been formally studied in the ICU setting [9, 11, 12, 15]. Recently, a vascular cannula (VascularSono, Pajunk, GmbH, Medizintechnologie, Geisingen, GermanyVascular-Sono) incorporating "Cornerstone" reflectors on the distal 2 cm, to increase echogenicity, was developed based on technology previously used in regional anesthesia needles [16]. We hypothesized that the use of an echogenic vascular cannula (EC) would improve visualization when compared with a nonechogenic vascular cannula (NEC) (Arrow Howes, PA, U.S.A) during real-time ultrasound-guided SCV cannulation in the ICU.

2. Materials and Methods

During 2011, eighty patients who required central venous access were prospectively enrolled in this randomized study that was conducted in a medical-surgical ICU. Forty patients underwent EC and 40 patients were randomized to NEC. The procedure was ultrasound-guided SCV cannulation via the infraclavicular approach on the longitudinal axis. All patients were sedated and mechanically ventilated. Randomization was performed by means of a computer-generated random-numbers table, and patients were stratified with regards to age, gender, and body mass index (BMI). Block randomization was used to ensure equal numbers of patients in the above groups [3]. All physicians who performed the procedures had at least five years of experience in central venous catheter placement. The study was approved by the institutional ethics committee, and appropriate informed consent was obtained.

Chest radiography was used to assess catheter placement after the procedure, as previously described [6, 17]. Mechanical complications were defined as arterial puncture, hematoma, hemothorax, pneumothorax, injury to the brachial plexus as well as to the phrenic nerve, catheter misplacement, and cardiac tamponade [6].

2.1. Real-Time Ultrasound-Guided SCV Cannulation. All patients were placed in Trendelenburg position and were cannulated as described in detail by Fragou et al. [6]. Triple-lumen catheters were used in all cases and all procedures were performed under controlled and nonemergent conditions in the ICU. Standard sterile precautions were utilized. The EC and NEC were both 18 gauge cannulas specifically intended for use in vascular access. Ultrasonography was performed with an HD11 XE ultrasound machine (Philips, Andover, MA, USA) equipped with a high-resolution 7.5–12 MHz transducer, which was covered with sterile ultrasonic gel and wrapped in a sterile sheath (Microtec medical intraoperative probe cover, 12 cm × 244 cm). Using the infraclavicular approach, on the longitudinal axis, sonoanatomic landmarks (such as the acoustic shadows of the underlying first thoracic rib and of the sternum) were identified, as well as, the axillary and SCV vein (Figures 1 and 2). Doppler techniques were utilized to confirm the two-dimensional (2D) findings. Vessels were cannulated using the Seldinger technique under real-time ultrasound guidance.

2.2. Data Acquisition, Study Protocol, and Outcome Measures. The cannulation was performed by a single operator and was

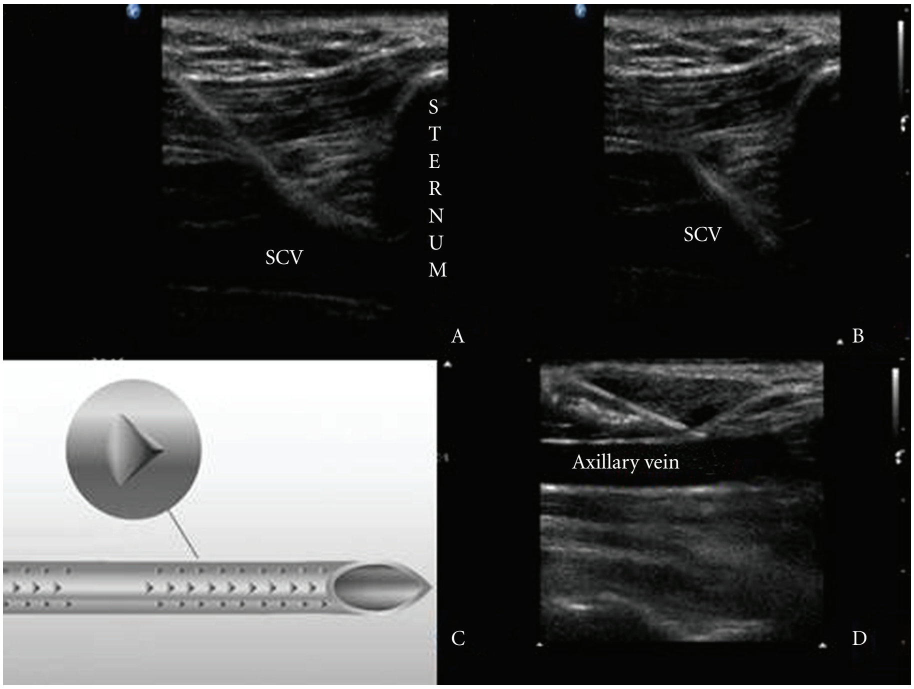

Figure 2: Echogenic cannula entering the SCV just adjacent to the sternum (A B); the former incorporates "Cornerstone" reflectors mainly arranged at its distal 2 cm (C), which increase significantly its visibility (D).

observed by a second physician. The operators and observers were blinded to the cannula used. Following each procedure, the operator and the observer were asked to score the percentage of time they were able to continuously visualize the cannula; a 10-point scale was used (ranging from 1 equals 0%–10%, to 10 equals 90%–100%). Operators were asked to rate the perceived technical difficulty and complexity of the task also using a 10-point scale, in which 0 was most simple and 10 was most complex [6]. The observer measured access time, number of attempts, and complications. Access time was defined as the time between penetration of skin and aspiration of venous blood.

Data was collected using a standardized form and was entered in a database. We documented baseline patient characteristics, side of catheterization, presence of risk factors for difficult venous cannulation, previous difficulties during cannulation, previous mechanical complications, known vascular abnormalities, and untreated coagulopathy (international normalization ratio > 2; activated partial thromboplastin time > 1.5; platelets < 50×10^9 litre^{-1}).

2.3. Statistical Analysis. Data were expressed as mean ± standard deviation (SD). Student's t-test for independent means, χ^2 analysis, or Fisher's exact test where appropriate were used to identify differences between the two groups. A P value (twosided in all tests) of <0.05 was considered significant. Study power was based on data from a previous needle visibility study and was adjusted for our intervention [18]. Assuming data to be nonparametric, power sample analysis gave a minimum sample size of 40 cannulations. Wilcoxon rank-sum test was used to compare tip visibility data for the 2 groups. The agreement between the operator and the observer cannula visibility results was evaluated by Cohen's weighted kappa, while 2.5th and 97.5th percentiles of 5,000 bootstrap replicates estimated 95% confidence intervals. The bootstrap is a resampling method used for estimating a distribution, from which various measures of interest can be calculated [19]. Statistical analysis was performed using SPSS software, version 11.0 (SPSS Inc. Chicago, IL, USA).

3. Results

Baseline characteristics of the study population are presented in Table 1. There were no significant differences in age, gender, body mass index (BMI), and presence of risk factors for difficult venous cannulation between the NEC and the EC groups. No cases of preexisting thrombosis were identified.

Results of cannula visibility are presented in Figure 3. Operators reported improved cannula visualization in the EC group when compared to the NEC group (92% ± 3% versus 85 ± 7%, respectively; $P < 0.01$). The agreement between the operators and observers was statistically significant (k equal 0.9, 95% confidence intervals assessed by bootstrap analysis = 0.87–0.93; $P < 0.01$).

Results of the secondary outcomes are presented in Table 2. There were no statistically significant differences noted in mechanical complications between the two groups. Access time (12.1 s±6.5 versus 18.9 s±10.9) and the perceived technical difficulty of the procedure (4.5±1.5 versus 7.5±1.5) were both decreased in the EC group compared to the NEC group ($P < 0.05$). Examples of cannula visibility of EC and NEC during ultrasound-guided SCV and axillary vein

Table 1: Baseline characteristics of the study population; values are presented either in percentages or as mean ± SD.

Characteristics	EC group (n = 40)	NEC group (n = 40)
Age (years)	50 ± 10.5	51 ± 9.9
Gender (male/female ratio)	0.51 ± 0.4	0.52 ± 0.5
APACHE II score	20.2 ± 3.1	20.3 ± 3.3
Diagnosis upon admission		
Trauma without brain injury	5 (12.5%)	7 (17.5%)
Trauma with brain injury	15 (37.5%)	11 (27.5%)
Burn	2 (5%)	3 (7.5%)
ARDS	3 (7.5%)	5 (12.5%)
Sepsis	5 (12.5%)	7 (17.5%)
Postsurgical complications	10 (25%)	7 (17.5%)
Side of catheterization (left/right)	19/21	18/22
Body mass index (kg/m^2)	22.9 ± 5.1	23.8 ± 4.2
Prior catheterization	10 (25%)	10 (25%)
Limited sites for access attempts	3 (7.5%)	3 (7.5%)
Previous difficulties during	5 (12.5%)	5 (12.5%)
Catheterization		
Previous mechanical complications	2 (5%)	2 (5%)
Known vascular abnormality	1 (2.5%)	1 (2.5%)
Untreated coagulopathy	0 (0%)	1 (2.5%)
Skeletal deformity	1 (2.5%)	0 (0%)

APACHE II score: acute physiology and chronic health evaluation score II; ARDS: acute respiratory distress syndrome; NEC: nonechogenic cannula, EC: echogenic cannula.

Table 2: Secondary outcome measures in the EC group versus the NEC group.

Outcome measures	EC group (n = 40)	NEC group (n = 40)
Access time (sec)	12.1 ± 6.5 (5.5–20.4)*	18.9 ± 10.9 (9.5–29.4)
Success rate (%)	40 (100%)	40 (100%)
Average number of attemptsartery puncture	1 ± 0.3 (1–1.5) 0 (0%)	1.1 ± 0.5 (1–1.8) 1 (2.5%)
Hematoma	0 (0%)	1 (2.5%)
Pneumothorax	0 (0%)	0 (0%)
Hemothorax	0 (0%)	0 (0%)
Catheter misplacement	0 (0%)	0 (0%)
Damage of the brachial plexus	0 (0%)	0 (0%)
Phrenic nerve injury	0 (0%)	0 (0%)
Technical difficulty (scale 1 to 10)	4.5 ± 1.5*	7.5 ± 1.5

EC: echogenic cannula, NEC: nonechogenic cannula; Comparisons between the NEC and the EC group of patients; $P < 0.05$*; access time and average number of attempts are expressed as mean ± SD (95% confidence intervals).

cannulation, on the longitudinal axis, are shown in Figures 1 and 2.

4. Discussion

Our study demonstrated improved cannula visibility with the use of EC during ultrasound-guided SCV cannulation. The likelihood of visualizing the cannula during a longitudinal approach is already reasonably high [6]; nevertheless, the use of EC statistically increased the likelihood of continued successful cannula visualization. In addition, the utilization of EC resulted in significantly reduced access times and perception of technical difficulty. EC represents a brightly echogenic vascular puncture cannula which incorporates “Cornerstone” reflectors mainly arranged at the distal 2 cm of the needle. These reflectors guarantee the visibility of the cannula shaft, independent of the puncture angle according to the manufacturer. The principle is the same as that used in bicycle reflectors, where light is reflected back to its source regardless of the angle at which it approaches [15–17]. The present results suggested that the echogenic technology significantly improved cannula visibility during real-time ultrasound-guided SCV cannulation. Our methodology was designed to test EC in actual clinical practice in the ICU, where image acquisition is affected or limited by the presence

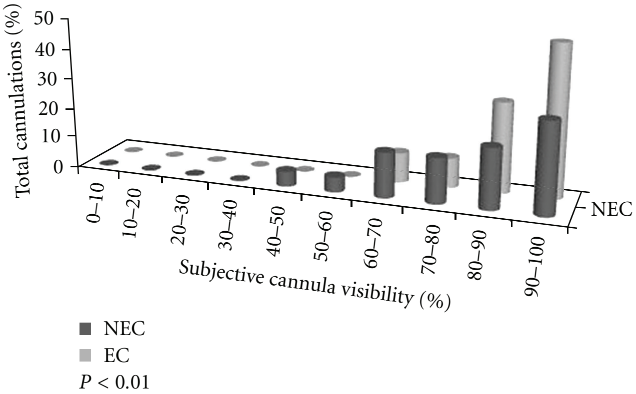

Figure 3: Subjective percentage of cannula visibility assessments (echogenic cannula, EC: gray; nonechogenic cannula, NEC: black).

of various factors such as obesity, subcutaneous air, edema, trauma and mechanical ventilation [1–8]. The use of EC may improve image acquisition and success rates in technically challenging cases of vascular access.

There is no definitive method for objective assessment of cannula visibility. Previous studies used scoring systems with skilled observers rating static images [9–14]. Other groups have suggested objective measures of cannula visibility in still images [15, 18]. We aimed to examine cannula visibility during central venous cannulation, under real-time clinical conditions.

Although interpretation of dynamic 2D ultrasound images remains subjective, we used an analytical 10-point scale, along with a "dual" evaluation model of operators and observers. We demonstrated that, high operator and observer agreement existed between the subjective estimations of cannula visibility rates.

The study has several limitations. Despite the fact that the operators were blinded at the initiation of the procedure, the two vascular cannulas inherently exhibited different ultrasonographic appearance and could possibly be differentiated. The dimensions of the Cornerstone reflectors are determined by the frequency of the ultrasound with which they are designed to work. Lower frequencies may require broader dimensions, but these are limited by the wall thickness of the cannula [9–15] In this study, the echogenic cannulas used were specifically designed for central venous access.

We failed to find any significant reduction of mechanical complications. This may be due to the fact that an in-plane technique was used in all cases, moreover our baseline mechanical complication rate was extremely low (given the fact that our study group is highly skilled in ultrasound-guided vascular access), and that the sample size was rather small. Finally, let us underline that complications exist even with ultrasound-guidance (i.e., hematoma resulting from inadvertent arterial damage either to the adjacent main artery or some of the many branches in this area) during SCV cannulation [6, 20].

In conclusion, our investigation demonstrated that the use of EC significantly improved THE cannula visibility and decreased the vascular access time as well as perceived technical complexity during real-time ultrasound-guided SCV cannulation. Our data provide clinical rationale to study the evolving field of enhanced echogenic ultrasound technology. Further studies are required to determine if EC is cost-effective and changes overall outcomes in the ICU.

Conflict of Interests

The authors declare that they have no financial or other interest in the echogenic vascular cannula, nor do they have any financial or other affiliation with Pajunk.

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Review Article

Can Transthoracic Echocardiography Be Used to Predict Fluid Responsiveness in the Critically Ill Patient? A Systematic Review

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Introduction. We systematically evaluated the use of transthoracic echocardiography in the assessment of dynamic markers of preload to predict fluid responsiveness in the critically ill adult patient. *Methods*. Studies in the critically ill using transthoracic echocardiography (TTE) to predict a response in stroke volume or cardiac output to a fluid load were selected. Selection was limited to English language and adult patients. Studies on patients with an open thorax or abdomen were excluded. *Results*. The predictive power of diagnostic accuracy of inferior vena cava diameter and transaortic Doppler signal changes with the respiratory cycle or passive leg raising in mechanically ventilated patients was strong throughout the articles reviewed. Limitations of the technique relate to patient tolerance of the procedure, adequacy of acoustic windows, and operator skill. *Conclusions*. Transthoracic echocardiographic techniques accurately predict fluid responsiveness in critically ill patients. Discriminative power is not affected by the technique selected.

1. Introduction

Our primary concern in the management of the critically ill patient is the optimisation of tissue oxygen delivery. Insufficient intravascular loading in the early resuscitation of acute sepsis results in tissue underperfusion, organ dysfunction, and acidosis. Excessive fluid administration has also been shown to be detrimental in the perioperative setting and in acute lung injury, prolonging both time on mechanical ventilation and time in intensive care [1].

It has been reported that as few as 40 percent of critically ill patients thought to be intravascularly deplete gain an improvement in cardiac output after a standard fluid bolus, exposing more than half of patients to the risks of excessive fluid administration [2].

Knowledge of static measures of preload such as central venous pressure, pulmonary artery wedge pressure, end-diastolic volumes, and intrathoracic blood volume has not translated into patient benefit [3–6]. This suggests that measurement of preload does not foretell preload responsiveness.

Contemporary investigation has therefore focussed on the search for clinical markers which predict a useful response to a fluid bolus. These "dynamic" markers make use of provoked cardiac reaction assessed without the need for a fluid bolus, instead utilizing either the consequences of heart-lung interaction during ventilation or the response to postural change to mimic the effect of a fluid bolus on stroke volume.

Firstly, in mechanically ventilated patients who have no spontaneous respiratory effort, the change in intrathoracic pressure has a cyclical effect on both the left and right heart (as shown in Figure 1). A rise in intrapleural pressure compresses the pulmonary vasculature and in turn causes compression of the venous inflow vessels and the heart itself. This reduces both right ventricular (RV) preload and left ventricular (LV) afterload whilst conversely both RV afterload and LV preload are increased. These effects are accentuated by hypovolaemia implying variation in stroke volume with cyclical respiratory changes can be used to predict whether stroke volume will alter if preload is increased. This is the basis of the increasingly ubiquitous stroke volume variation monitoring systems but can also be examined using Doppler echocardiography of flow through valves, vessels, or outflow tracts. If the cross-section at the point of measurement can be visualized or accurately estimated, then the product of that

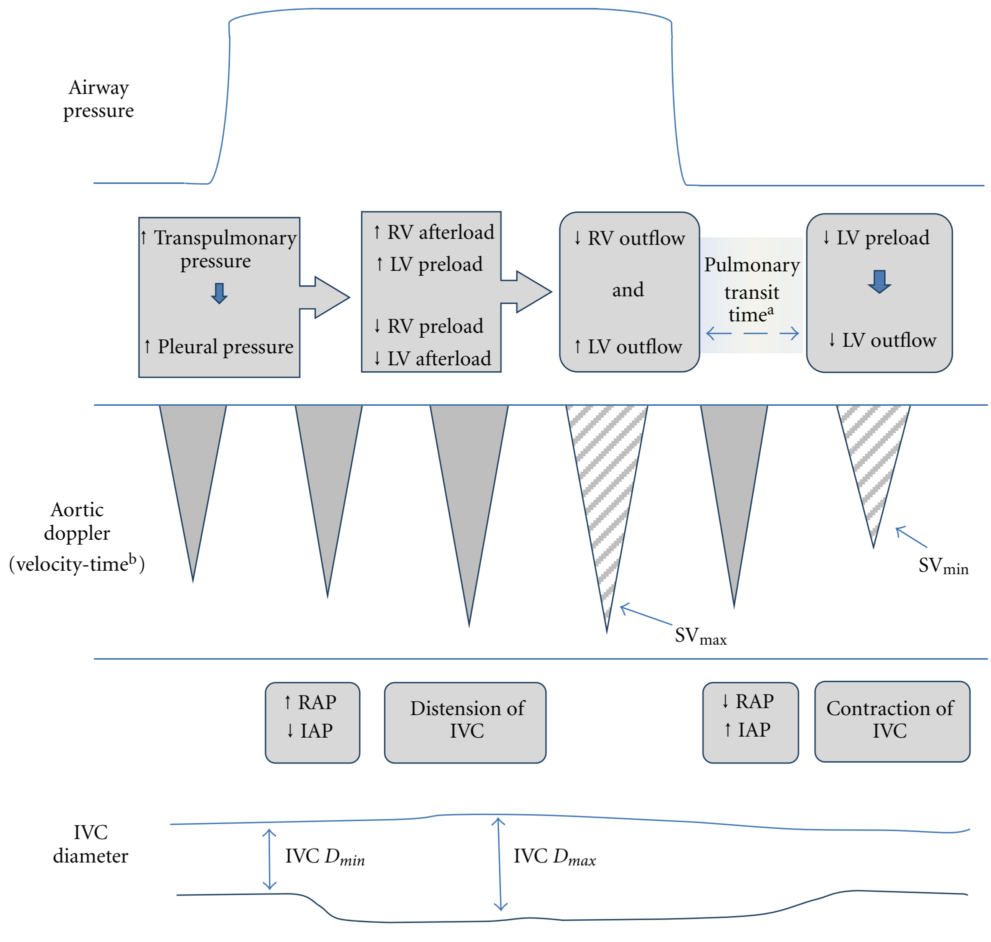

Figure 1: The physiological explanation for the changes in stroke volume and IVC diameter caused by mechanical ventilation. RV right ventricle, LV left ventricle, SV_{max} and SV_{min} maximum and minimum stroke volume, RAP right atrial pressure, IAP intraabdominal pressure, IVC D_{max} and IVC_{min} maximum and minimum inferior vena cava diameter during the cycle. [a]The pulmonary transit time represents the time taken for blood to travel through the pulmonary circulation. [b]SV is the product of the velocity-time integral (area under the Doppler signal curve) and the diameter of the vessel at the point the reading was taken.

area and the integral of the flow-time curve (generated by the Doppler signal) is equal to the stroke volume.

Secondly, in the spontaneously ventilating subject, negative intrapleural pressure during inspiration results in a reduction in the diameter of the abdominal inferior vena cava (IVC). The degree of collapse during tidal volume breaths is known to reflect the right atrial pressure with reasonable accuracy in health [2]. To a degree, the reverse effect is seen in patients who are being ventilated with positive pressure.

Thirdly, raising the legs from the horizontal position to 45 degrees causes the gravitational movement of lower limb venous blood towards the heart. This provides a transient volume load of between 150 and 300 millilitres to the central circulation, lasting for a few minutes [7, 8]. The use of Doppler echocardiography to assess the change in cardiac outflow after this surrogate volume load provides an intuitive means of forecasting response to an administered fluid bolus.

Modern intensive care is increasingly concerned with the avoidance of unnecessary invasive procedures which contribute to patient morbidity either directly or more often through the associated risk of catheter-related bloodstream infection [9].

Transoesophageal echocardiography may provide superior image quality in some cases and is increasingly utilised for cardiovascular monitoring on intensive care units. Nonetheless, it requires equipment, time, and skills that are less abundant on many intensive care units. It is contraindicated in some patients with upper airway or oesophageal surgery and also usually necessitates sedation which is not always achieved without adverse consequence.

Accordingly, the objective of this review is to systematically evaluate the literature examining the use of transthoracic echocardiography in the assessment of dynamic markers of preload used to predict fluid responsiveness in the critically ill patient.

2. Methods

An electronic literature search was carried out using Medline, EMBASE, CINAHL, and the Cochrane database of systematic

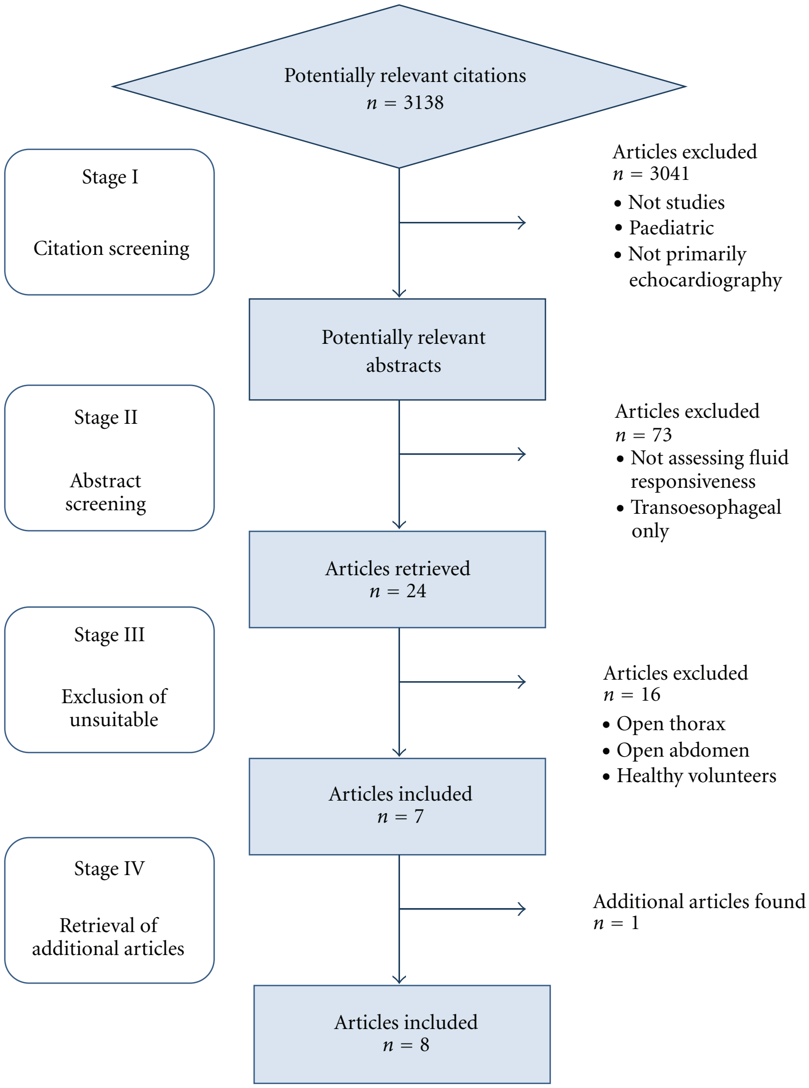

Figure 2: Citation filtering process.

reviews. The search terms used were ((fluid) OR (volume) OR (preload) OR (filling)) AND ((respons*) OR (status) OR (assess*)) AND ((echocardiograph*) OR (echog*)). The search was limited to "human" and "English language." Figure 2 shows the process of filtering the studies selected for review.

Transoesophageal echocardiography studies were excluded, as were those in which the sample group, the equipment used and the reference test cut-off criteria implied the conclusions were not applicable to the critically ill patient in a high dependency of critical care environment.

2.1. Definitions of Fluid Responsiveness. "Fluid responsiveness" refers to a predefined rise in stroke volume or cardiac output after rapid fluid loading with a predetermined volume of fluid. Between investigators, there are inevitable differences in the choice of stroke volume or cardiac output, the volume of fluid given, the duration over which the fluid load was given, and the type of fluid given.

The diagnostic test or equivalent of the index test in these studies is defined as the echocardiographic test done to give a prediction of fluid responsiveness. In this review, this test will be termed the "predictive test." The test done to assess the response to a fluid bolus once given is similar to a reference test but for the purposes of this review will be called the "response test."

Responders are those patients in whom the cardiac output or stroke volume rises by the threshold amount after a given bolus of fluid.

2.2. Statistical Analysis. The Standards for Reporting of Diagnostic Accuracy (STARD) initiative developed a guide for assessing the quality of reporting of studies of diagnostic accuracy [10]. In this review, the STARD score was adapted to

Table 1: Modified STARD criteria assessment [10].

Criteria	Specific question
1	Was the study population described (inclusion and exclusion criteria included)?
2	Is there a description of the sampling (e.g., consecutive patients, if not why not?)?
3	Is it clear whether the tests were done prospectively or retrospectively?
4	Is there a description of the response test (including fluid bolus)?
5	Is there a detailed description of the equipment and techniques used in the tests?
6	Is the rationale for cut-offs and ranges given?
7	Is there detail of the operators in terms of number and training?
8	Is there detail of what information was available to the readers of the response ?
9	Were the statistical methods for comparing diagnostic accuracy detailed?
10	Are there details of tests of reproducibility?
11	Are the patient demographics and comorbidities shown?
12	Is there detail of those meeting inclusion criteria but not undergoing either test?
13	Was there detail of the interval between predictive and response tests?
14	Is there a report cross-tabulating predictive and response test results?
15	Is diagnostic accuracy described, including likelihood ratios or data to calculate them?
16	Is there mention of how missing values were dealt with (i.e., unobtainable values)?
17	Are the estimates of accuracy variability between operators/readers included?
18	Are there estimates of reproducibility?
19	Is the clinical applicability of the study findings discussed?

judge the quality of the investigation in each article selected (Table 1). A 19-point score was devised using 19 of the 25 STARD criteria. Each criterion was assigned one point and the overall score divided into categories: poor (score 0–10), adequate (11–15), and good (16–19).

The results of the selected studies were not meta-analysed due to the heterogeneity of methodologies, as well as the differences in patient selection, modes of ventilation and definition of fluid response. There was insufficient data for the construction of summary receiver-operator characteristic (SROC) curves or for the calculation of Q star statistics, and the simple average of sensitivity and specificity data is not an informative approach. Furthermore, the usage of a fixed-effects model such as SROC would be expected to produce exaggeratedly high levels of reported accuracy for a test that is to be put to use in the complex environment of the critically ill patient [11].

3. Results

Of the 3138 articles identified through the search terms, eight studies were included for review. The quality scores ranged between 13 and 15, indicating an adequate standard throughout. The studies were all small but of appropriate intensive care unit setting (Tables 2 and 3).

3.1. Assessment of Fluid Responsiveness Using Transaortic Stroke Volume Increment to Passive Leg Raising. Five studies used transaortic stroke volume variation to predict fluid responsiveness using passive leg raising to mimic a fluid bolus [12–16]. Overall quality of the studies was adequate. All were done in intensive care patients with shock of various aetiologies. Three were carried out in medical intensive care units, one in a surgical unit, and the other in a mixed unit. Studies by Biais et al. [15], Lamia et al. [14], Maizel et al. [13], and Prèau et al. [12] included only patients with spontaneous respiratory effort, whether or not they were mechanically ventilated.

Important differences between studies were evident in the study protocols. Maizel et al. [13] and Prèau et al. [12] used a 30 to 45 degree leg raise from the supine position where all others started with the patient semirecumbent at 30 to 45 degrees before tilting the bed until the patient was supine with legs raised (Figure 3). These two methods have been shown to result in different volumes of caudal surge of blood which potentially affects the validity of the test. Maizel et al. [13] had no second baseline measurement prior to fluid delivery. In all studies, the pretest baseline measurements of stroke volume were similar before the passive leg raise and before the assessment of a response to fluid bolus.

All studies showed good sensitivity (77 to 100 percent) and specificity (88 to 99 percent) using a threshold of 10 to 15 percent increment of stroke volume or cardiac output.

Strikingly, stroke volume change with PLR predicted the correct response to volume expansion in 16 of the 18 patients with arrhythmia [16].

3.2. Assessment of Fluid Responsiveness Using Transaortic Stroke Volume Variation with Respiration. A single study by Biais et al. looked at the use of stroke volume variation for prediction of fluid responsiveness [19]. In this study, stroke volume variation measured across the aortic valve was used to predict a fluid response which was delivered as a 20 mL/kg/m^2 bolus of 4% albumin. Stroke volume variation was calculated using the formula:

$$\frac{SV_{max} - SV_{min}}{SV_{mean}}. \quad (1)$$

All patients were receiving mandatory ventilation and had no spontaneous respiratory effort.

The area under the receiver operator characteristic (ROC) curve was used to ascertain a threshold of nine percent stroke volume variation as being the most useful for discerning responders from nonresponders. Using this cut-off, there was excellent sensitivity and specificity (100 and 88 percent, resp.).

TABLE 2: Characteristics of studies selected.

Study	Technique	Patient group	Selection	Ventilation	Rhythm	Volume and type	Time (min)	Response criteria
Barbier et al. [17]	IVC DI	Mixed ICU	Shock (sepsis) and acute lung injury	All mand	Any	7 mL/kg colloid	30	>15% CO TTE
Feissel et al. [18]	ΔD_{IVC}	Medical ICU	Shock (sepsis)	All mand	Any	8 mL/kg colloid	20	>15% CO TTE
Lamia et al. [14]	PLR	Medical ICU	Shock (sepsis or hypovolaemia)	All spont	Regular SR, or AF	500 mL crystalloid	15	>15% SV TTE
Maizel et al. [13]	PLR	Mixed ICU	Shock (unspecified)	All spont	Regular SR	500 mL crystalloid	15	>12% CO TTE
Biais et al. [15]	PLR	Surgical ICU	Shock (sepsis or haemorrhage)	All spont	Any	500 crystalloid	15	>15% SV TTE
Biais wt al. [19]	SVV	Surgical ICU	Post-operative (liver surgery)	All mand	Regular SR	20 mL/kg/m^2 colloid	20	>15% CO TTE
Thiel et al. [16]	PLR	Medical ICU	Shock (unspecified)	Mixed	Any	500 mL crystalloid or colloid	Unspec	>15% SV TTE
Préau et al. [12]	PLR	Medical ICU	Shock (sepsis or acute pancreatitis)	All spont	Regular SR	500 mL colloid	<30	>15% SV TTE

Selection: inclusion criteria summary, PLR: passive leg raising, spont: spontaneous respiratory effort whether or not on mechanical ventilation, mand: ventilator giving mandatory breaths only and patient fully adapted to ventilator, SR: sinus rhythm, AF: atrial fibrillation, TTE: transthoracic echocardiography, SV: stroke volume, CO: cardiac output, ΔD_{IVC} change in IVC diameter adjusted by the mean (see text), IVC DI: IVC distensibility index (see text), and unspec: unspecified time.

TABLE 3: Collated results of all included studies.

Study	Number of tests	Predictive test	Threshold	Resp %	Intra-obs %	Inter-obs %	AUC (ROC)	Sens	Spec	PLiR	NLiR	PPV	NPV	r
Lamia et al. [14]	24	PLR SVI or CO rise	≥12.5%	54	2.8 ± 2.2	3.2 ± 2.5	0.96 ± 0.04	77	99	77	0.23			0.79
Maizel et al. [13]	34	PLR CO rise	≥12%	50	4.2 ± 3.9	6.5 ± 5.5	0.90 ± 0.06	63	89	5.73	0.42	85	76	0.75
		PLR SV rise	≥12%		4.2 ± 3.9	6.2 ± 4.2	0.95 ± 0.04	69	89	6.27	0.35	83	73	0.57
Biais et al. [15]	34	PLR SV rise	≥13%	67		SI	0.96 ± 0.03	100	80	5.00	0.00			
Thiel et al. [16]	102	PLR SV rise	≥15%	46		SI	0.89 ± 0.04	81	93	11.57	0.20	91	85	
Préau et al. [12]	34	PLR SV rise	≥10%	41		SI	0.90 ± 0.04	86	90	8.60	0.16	86	90	0.74
		PLR dVF rise	≥8%				0.93 ± 0.04	86	80	4.30	0.18	75	89	0.58
Biais et al. [15]	30	SVV	≥9%	47		SI	0.95	100	88	8.33	0.00			0.80
Barbier et al. [17]	23	IVC DI	≥18%	41	8.7 ± 9	6.3 ± 8	0.91 ± 0.07	90	90	9.00	0.11			0.90
Feissel et al. [18]	39	ΔD_{IVC}	≥12%	41	3 ± 4	SI						93	92	0.82

Threshold: cut-off between responders and nonresponders, Resp: proportion responding to fluid load, Intra-obs: intraobserver variability, Inter-obs: interobserver variability, AUC(ROC): area under the receiver-operator curve, Sens: Sensitivity, Spec: Specificity, PLiR: positive likelihood ratio, NLiR: negative likelihood ratio, PPV: positive predictive value, NPV: negative predictive value, r: correlation coefficient, PLR: Passive leg raising, SI: single investigator/reader, CO: cardiac output, SV: stroke volume, dVF: change in femoral artery velocity as measured by Doppler, SVI: stroke volume index, LVEDAI: left ventricular end-diastolic area, E/E_a: mitral E-wave velocity/mitral annulus E velocity measured by tissue Doppler, ΔD_{IVC}: change in IVC diameter (D) as calculated by $(D_{\max} - D_{\min})/0.5(D_{\max} + D_{\min})$, IVC DI: IVC distensibility index calculated by $(D_{\max} - D_{\min})/D_{\min}$.

3.3. Assessment of Fluid Responsiveness through Respiratory Variation of IVC Diameter. Two studies by Barbier et al. and Feissel et al. used respiratory variation of the diameter of the IVC to predict fluid responsiveness [17, 18]. Both studies included only mechanically ventilated patients, without spontaneous respiratory effort. Each study compared the maximum and minimum diameter of the IVC just distal to the hepatic vein: $D_{\max}$ and $D_{\min}$, respectively (see Figure 1). Both studies expressed the distensibility of the IVC as a percentage index.

Barbier et al. used a "distensibility index" calculated by

$$\frac{(D_{\max} - D_{\min})}{D_{\min}}, \tag{2}$$

whereas Feissel et al. corrected the mean of the two values:

$$\frac{(D_{\max} - D_{\min})}{0.5(D_{\max} + D_{\min})}. \tag{3}$$

Barbier et al. showed a sensitivity and specificity of 90 percent using a cut-off distensibility index of 18 percent to indicate

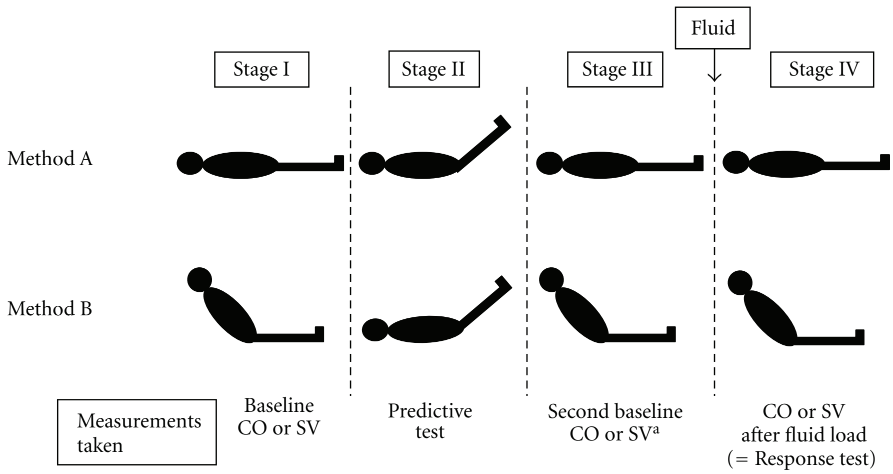

Figure 3: The stages of the two different methods of passive leg raising. CO cardiac output, SV stroke volume. [a]Measurements at this stage were not taken in one study (Maizel).

fluid responsiveness. Feissel et al. demonstrated a correspondingly high positive and negative predictive value, 93 and 92 percent, respectively, using an IVC diameter variation of 12 percent [18].

4. Discussion

This review shows that TTE is a highly discriminative test for the prediction of the stroke volume or cardiac output response to volume loading in critically ill patients, thus highlighting the potential for expansion of its role in quantitative assessment.

Importantly, TTE techniques appear useful in patients with spontaneous respiratory effort and those with arrhythmias: this is in contrast to many of the techniques that involve invasive monitoring which have been shown to be inaccurate in these situations [5].

Although TTE does not provide continuous monitoring which can be managed by nursing staff at the bedside, in reality, most clinical questions regarding fluid management arise intermittently. With equipment close at hand the time taken for a focussed TTE assessment rarely takes more than few minutes [20]. In addition, much of the data derived from pulmonary artery catheter measurement can be obtained using TTE, obviating the need for an invasive monitor that has been shown not to alter outcome [4].

The techniques of IVC diameter assessment, transaortic stroke volume variability with respiration and stroke volume increment with passive leg raising all provided strong predictive ability for response to a fluid bolus. The area under ROC curves was greater than 0.9 in all articles that presented the statistic. Although a clear threshold value for discriminating responders from nonresponders seems intuitively advantageous, clinicians are adept at coping with non-discriminatory results and using them to inform decisions made on the basis of the whole clinical picture.

None of the three TTE techniques is convincingly the best and if possible all three should be used to minimize the impact of their limitations. On occasion, this may not be achievable for a number of reasons. Local pain or delirium may preclude all or part of a TTE exam in a small minority of cases. In the 260 scans attempted within the studies selected, just 13 could not be performed for these reasons making this a well-tolerated procedure in the main. Thoracic or abdominal wounds may sometimes make views impossible to achieve. Obesity or rib prominence can also make TTE acoustic windows difficult to obtain but it is rare that at least a single usable view cannot be obtained in an individual. In the reviewed studies, only nine of the 260 attempted scans were abandoned due to difficulty with anatomy. Additionally, the applicable techniques will depend on the presence or absence of mechanical ventilation or dysrhythmias. For example, in a patient with atrial fibrillation who is fully ventilated, transaortic Doppler assessment is inaccurate but subcostal measurement of the IVC diameter variation can be safely used.

4.1. Clinical Application. The concept of "wet" and "dry" intensive care units has long been debated. The apparent benefits of goal-directed aggressive fluid resuscitation in the early stages of sepsis must be balanced with evidence for reduced morbidity when "restrictive" fluid regimes are used [21]. The literature lacks agreement on definitions of "wet" and "dry," or "liberal" versus "restrictive" fluid protocols, and consequently, it is difficult to be certain of applicability to a particular setting. Brandstrup provided compelling evidence in colorectal surgical patients and the ARDSNET group in the subset of acute lung injury, but there is a paucity of further evidence [1, 22].

It is important to recognize that this review neither allows assumptions about the longevity of the response to fluid, nor the value of a continuous fluid infusion thereafter. It also follows that a forecast suggesting the patient will be fluid responsive in no way guarantees the safety of a delivered bolus in terms of increasing extravascular lung water or worsening regional organ oedema and function.

The literature contains a growing body of work on optimising haemodynamics using other echocardiographic parameters, beyond simple measures of contractility and structural pathology. Patterns of flow across the mitral valve and tissue velocity of the annulus have proved useful, principally when assessed in combination. Tissue velocity, particularly that measured close to the mitral valve annulus, assessed using Doppler imaging (TDI) provides an accurate estimation of diastolic function of the left ventricle irrespective of preload changes [23, 24]. Pulmonary artery occlusion pressure can be estimated by a number of methods, chiefly by tissue Doppler imaging but also by examining the pattern of movement of the interatrial septum [25]. Subtleties of the sonographic representation of interlobular septa can be used to assess extravascular pulmonary water and also correlate with pulmonary artery occlusion pressure [26]. An assessment using as many parameters as possible will provide valuable information at many stages of the patient's stay whether in managing the acute and unstable periods, or when weaning from the ventilator is troublesome [27].

Although detailed examination of the heart requires an experienced echocardiography practitioner, there is an increasing acceptance of the value of focussed echocardiographic assessments to answer common clinical questions arising in critical illness. This has arisen in tandem with the emergence of a number of courses and training programmes centred on evaluation of the critically ill patient by those less experienced in echocardiography. Jensen showed that with only limited training, a diagnostic transthoracic window was achieved 97 percent of the time when used in the evaluation of shock [20]. In the UK, a consultation process to provide a training template and curriculum for focussed echocardiography in critical care is currently underway [28].

4.2. Limitations. This review was restricted to the specific question of fluid response. In reality, echocardiographic assessment of the critically ill aims to gain as complete a picture as possible of the cardiovascular state. Ideally, this should also involve a full structural study in addition to inspection of left ventricular filling state and perhaps even ultrasonic examination of the lungs.

Furthermore, studies using transoesophageal echocardiography (TOE) were not selected for this review and, although it would seem intuitive that flow or diameter measurements techniques taken with one kind of echocardiography could be safely extrapolated to another, this ignores the differing technical restrictions of each technique. Transoesophageal echocardiography has its own growing evidence base for its application in intensive care and clearly where it is available provides invaluable haemodynamic information to inform clinical decisions.

A significant limitation of this review is the small size of the study groups since only a single study included more than 40 patients [16]; this is typical of studies of diagnostic accuracy. Meta-analysis was not performed, due to the heterogeneity of the methods and patient characteristics. In addition due to the similarity of the sensitivity and specificity data, it was felt that further statistical analysis would not add useful information.

It is conspicuous that only one article reported on the time between the initial predictive test and the subsequent assessment of a response to a fluid bolus [12]. Patients with haemodynamic instability can undergo rapid changes in cardiovascular parameters mandating that the period between the predictive and confirmatory tests should be as short as possible.

The amount of fluid used, the type used, and the rate at which it was given all impact upon the response test in these studies. Unfortunately, there is no agreed formulation for a standard fluid load although almost all studies use approximately the same formulation.

Although no specific details were given about the qualifications of the echocardiography operator or reader most studies inferred they were experienced. Furthermore, blinding of the operator or reader, to the measurements taken after volume loading was rare and this is, therefore, a source of observer bias within the data.

Intraobserver variability was considered by the majority of studies and attempts were made to measure it with variable success. An intuitively more useful measurement of reproducibility was achieved by examining the variability of repeated measurements of distensibility by Feissel et al. [18]. This showed a greater degree of intraobserver concordance at 3.4 percent. Any concern about the reproducibility of observations should however be viewed in the context of the consistent results achieved throughout the reviewed studies which is unlikely to have arisen by chance.

Of note, whilst the effects of varying tidal volumes on echocardiographic parameter assessment are minimal, the impact of raised intra-abdominal pressure and of different positive end expiratory pressure is largely unstudied [29].

4.3. Future Developments. The clinical question that was not addressed in any of the articles was that of the "real-world" value of echocardiographic approaches to assessing fluid responsiveness. The studies reviewed do not provide us with information about translation into effects on morbidity or mortality, nor is there yet such a current evidence base in the literature. This evidence may well originate in the context of future investigation into the dilemma of conservative versus liberal fluid management.

Transpulmonary microsphere contrast has already been shown to dramatically improve volumetric assessment and its use in the critically ill would intuitively improve the clinical utility of the modality still further [30]. Three-dimensional echo remains in its infancy within the intensive care unit but the promise of increased, automated volumetric accuracy, and improved diagnostic clarity will also undoubtedly be examined in the near future [31, 32].

5. Conclusion

Transthoracic echocardiography is becoming a powerful noninvasive tool in the daily care of the critically ill. This review brings together the evidence for employing TTE to predict fluid responsiveness. Assuming there is equipment and local expertise TTE is a repeatable and reliable method of predicting volume responsiveness in the critically ill.

Transaortic stroke volume variation with the respiratory cycle, stroke volume difference following passive leg raising, and IVC diameter changes with respiration all provide good prediction of the likelihood of a response to a fluid bolus. The techniques can be used individually to address the needs of different patients and in combination to triangulate clinical information where uncertainties may occur.

The studies reviewed form a robust platform of physiological data on which to base further studies involving larger numbers of patients which engage with clinically relevant outcomes, such as inotrope use, blood pressure, length of stay, and time to weaning from mechanical ventilation.

Improved access to clinician-echocardiographers through a defined training process will facilitate such clinical studies and give patients access to accurate noninvasive information in answer to the daily clinical conundrum of fluid responsiveness.

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