Editorial

Contrast-Enhanced Ultrasonography: A Promising Method for Blood Flow and Perfusion Evaluation in Critically Ill Patients

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Introduction

The microcirculation is attracting more and more attention due to its central role in prognosis of critically ill patients. Monitoring perfusion of patients on intensive care units is of highest priority to guide diagnostic and treatment strategies to optimize organ perfusion, subsequently leading to an individualized therapy. The most often used parameter to detect alterations in the microcirculation is serum lactate; there is still lack of bedside monitoring methods for direct observation of microcirculation. With the noninvasive, convenient, and unique value in the quick diagnosis and dynamic monitoring during the course of treatment, bedside critical ultrasonography has been widely used, regarded as the "visual stethoscope." Contrast-enhanced ultrasonography (CEUS) is a competing technology that enables real-time observation of vascular perfusion; the basic composition of the contrast agents is microbubbles made of gases embedded within a shell characterized by safety, high tolerance, and lack of radiation, which can reflect ultrasound and avoid destruction during circulation and allow for continuous imaging of the vasculature and microcirculation. Therefore, CEUS can be used for the assess tissue microcirculation of critically ill patients, particularly in visceral organs.[1]

Evaluation of Blood Flow and Perfusion in Important Organs

CEUS is widely used in various kidney diseases such as acute kidney injury (AKI), kidney transplantation, cortical necrosis, trauma-induced lesions, and differential diagnosis of renal masses.[2] AKI is an independent predictor of mortality in critically ill patients. Although the exact pathogenesis remains poorly understood, the alteration of renal perfusion is considered to play a pivotal role. Whether renal perfusion is closely linked to its function or not, it is still not clear. Monitoring renal microcirculation may theoretically allow individualized hemodynamic optimization that could improve function and prevent the progression of AKI. CEUS is a promising approach to real-time quantification of renal perfusion both in specific region and on the macroscopic scale. Renal perfusion could be estimated accurately by CEUS, consistently matched the pathological changes in the kidney. CEUS could be used for the noninvasive evaluation of renal microvascular perfusion under different disease settings such as ischemia/reperfusion injury, intra-abdominal hypertension, chronic renal ischemic injury, and global hypoxia.[3] CEUS could detect renal cortical changes following angiotensin II or captopril administration; these changes were parallel to those of estimated by para-aminohippurate clearance. It can also assess renal cortical perfusion in Intensive Care Unit (ICU) patients with AKI; CEUS-derived parameters suggest a decrease in renal perfusion occurring within 24 h of surgery in patients at risk of AKI. CEUS-derived parameters in patients with AKI demonstrated that high heterogeneity in renal perfusion in response to a similar change in MAP, a predetermined mean arterial pressure (MAP) target, might not be suitable for critically ill patients. These findings open up new possibilities for the bedside assessment of renal microcirculation in ICU patients; CEUS parameters could be alternative indexes of tissue perfusion other than common

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parameters.[4] Renal cortical necrosis (RCN) is an uncommon irreversible renal lesion with poor outcome characterized by patchy or diffuse ischemic necrosis of renal cortex; causes of RCN include sepsis, extensive burns, pancreatitis, and diabetic ketoacidosis. The diagnosis of RCN is challenging due to lack of safe bedside methods to detect it. In McKay's study, CEUS was shown to be a safe point-of-care method to differentiate RCN from acute tubular necrosis with properties of simplicity, inexpensiveness, quick-accessibility and noninvasiveness. This method overcomes many of the limitations encountered by Doppler assessment such as attenuation, poor sensitivity, and angle dependency.[5]

It is crucial for critically ill patients to detect impairment of cerebral perfusion before occurrence of irreversible damage, and the effects of interventions can be assessed to evaluate and adjust the therapy. Several CEUS methods have been used to visualize and evaluate cerebral perfusion in patients with cerebral ischemia or acute brain injury. In patients who have undergone decompressive craniectomy,[6] CEUS is able to visualize changes in cerebral perfusion induced by systemic hemodynamic changes and ventilation manipulation in real time at the bedside.[7] The occurrence and severity of cerebral hypoperfusion, the effects of hemodynamically active drugs, and CO_2 on cerebral perfusion can be detected by this imaging technique.[8] The sensitivity and specificity of the detection of size and localization of infarction ranged from 75% to 96% and from 60% to 100%, respectively, compared with computed tomography (CT) or magnetic resonance imaging (MRI). With the bolus technique, time-related ultrasound perfusion parameters were similar to those of MRI. Therefore, CEUS is a safe, dynamic, precise, repeatable bedside approach to monitor brain microcirculation and analyze cerebral autoregulation function in patients with intracranial hypertension or unilateral brain lesion.

The Use of Contrast-Enhanced Ultrasonography in Trauma Patients

The use of the focused assessment with sonography for trauma in blunt abdominal trauma for the recognition of hemoperitoneum is well established with high specificity, but it is not sufficient to exclude parenchymal injuries, as the parenchymal injury may present without hemoperitoneum. CEUS allows to be performed in real time, increasing the capability to identify parenchymal injuries, optimizing imaging quality, such as lesion extension, margins, and its relationship with capsule and vessels.[9] CEUS has the ability to detect lesions in liver, spleen, and kidneys and also to identify active bleeding with almost as sensitive as CT.[10,11] In the study of Miele *et al*.[12], 203 patients with abdominal trauma were examined with baseline US and CEUS and a spiral CT as the standard of reference; CEUS correctly identified all of the liver lesions detected by conventional ultrasound, recognizing confluent lesions measuring up to 3 cm in diameter in two patients, missed on conventional ultrasound, and in other four patients, it identified one traumatic lesion not visible with basal ultrasound. Sessa *et al*.[11] described the CEUS findings of the traumatized spleen, 256 patients with a history of blunt abdominal trauma were retrospectively evaluated, CEUS identified 34/35 splenic injuries with CT as the standard of reference, demonstrating that CEUS was accurate as CT in the detection and staging of traumatic splenic injuries. CEUS was able to correctly identify 28/28 renal parenchymal lesions in trauma patients with or without perirenal or retroperitoneal hematoma.[13] Blunt traumatic pancreatic injury is relatively rare and accurate and quick diagnosis of this lesion is very important since unrecognized complications may have serious consequences. Serum amylase and CT are the common modalities to detect pancreas injury. Ultrasound has been used for the screening of abdominal blunt injuries; its sensitivity has been only moderate in the assessment of pancreatic trauma. In a patient with pancreatic trauma from a blunt abdominal injury, traditional two-dimensional ultrasound failed to detect the abnormality, while the injury was well recognized by CEUS, as well as by CT and MRI.[14] CEUS may be a potential tool for recognition and follow-up of pancreatic injury. For active bleeding, CEUS can easily detect contrast extravasation immediately after vessel opacification, as Catalano *et al*.[15] demonstrated that CEUS correctly identified 20 cases of active bleeding; this technique has 100% of sensitivity and specificity for active bleeding diagnosis.

Clinical Diagnosis of Ischemic Disease in Critically Ill Patients

Acute ischemic injury often occurs in severe patients such as thrombosis and related embolism which include pulmonary embolism (PE), spleen infarction, renal infarction, intestinal necrosis, and cerebral embolism. The organs may become infarcted due to an embolic event or due to a thrombus of the artery or one of these terminal branches. It is difficult to identify the infarcted region with conventional ultrasound in acute phase because the region of infarction is isoechoic. With CEUS, the boundaries of infarcted lesion could be clearly outlined as microbubbles could not be taken up in non-perfused region.[16] CEUS is considered as accurate as CT for the detection of vascular defects of the infarcted organs, and this technique is easily applicable to critically ill patients at the bedside.[17]

Acute acalculous cholecystitis (AAC) is a disease characterized by severe gallbladder inflammation without cystic duct obstruction due to gallstones; AAC occurs most frequently in critically ill patients and is associated with high morbidity and mortality. The symptom of AAC is usually covered by other severe complications and is often ignored. The complications of AAC are life-threatening, including gallbladder perforation, gangrene, empyema, sepsis and even MODS. Thus, timely diagnosis of AAC is extremely crucial.[18] Therefore, investigating the perfusion and differentiation between acute gangrenous and nongangrenous cholecystitis is so important. Transabdominal ultrasound is considered

as the primary bedside investigation technique. However, non-contrast ultrasonography could not discriminate necrosis from non-necrotic tissues. Reduced signal intensity or decreased perfusion of gallbladder on CEUS tends to indicate gangrenous cholecystitis with high specificity.[19]

The diagnosis of acute PE in critically ill patients, especially with hemodynamic instability is one of the most important and difficult problems; multiorgan ultrasound has been used to diagnosis PE and has been shown to have high sensitivity. In patients with compromised hemodynamic status and suspected PE, echocardiographic signs of right ventricular dysfunction enable the avoidance of computed tomography angiography and allow an immediate initiation of PE treatment. Peripheral embolic consolidations cannot be distinguished from infectious pleurisy lung by conventional lung ultrasound; pleural lesions may be much better visualized and differentially diagnosed on CEUS; the region of embolized is characterized by peripheral wedge-shaped areas with a complete or incomplete lack of enhancement; these CEUS patterns could be interpreted as a sign of local infarctions of the peripheral lung.[20]

Perspective

Point-of-care ultrasound is increasingly used in intensive care units, which has changed the paradigm of diagnosis and treatment of critically ill patients. As the role of ultrasound in the ICU continues to expand, it will become "visual stethoscope" incorporated into our clinical works. CEUS is a competing technology that enables real-time observation of perfusion and continuous imaging of the vasculature and microcirculation, which has been used in diagnosis of ischemic lesion and evaluation of perfusion of various organs. With this bedside technology, it becomes possible to evaluate tissue perfusion in real time which is essential for critical care.

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