CHAPTER 34

Contrast-Enhanced Renal Ultrasound

Antoine Guillaume Schneider and Jean-Yves Meuwly

OBJECTIVES

This chapter will:
1. Present contrast-enhanced ultrasonography (CEUS) as an imaging modality.
2. Describe current clinical indications for renal CEUS.
3. Describe renal perfusion quantification with CEUS, its technique, validation, and limitations.

BACKGROUND

Given the intimate relationship between perfusion and function in renal physiology, alterations of renal perfusion are thought to play a role in the pathophysiology of acute kidney injury (AKI). However, the frequency, importance, and clinical relevance of such alterations in critical illness remain largely unknown.[1] This knowledge gap is explained largely by the inaccuracy or lack of applicability of currently available tools to measure renal perfusion (para-aminohippurate [PAH] clearance, Doppler ultrasound, magnetic resonance imaging [MRI] or scintigraphy) in the context of critical illness.[1–6]

Contrast-enhanced ultrasound (CEUS) is a recent, ultrasound-based imaging modality, which makes use of dedicated contrast agents.[6,7] CEUS is applicable at the bedside, is minimally invasive, and could represent an ideal technique to evaluate renal perfusion in critical illness. In addition, CEUS is not associated with renal toxicity and therefore is not contraindicated in AKI.

This chapter presents technical aspects of CEUS, possible clinical indications, current level of validation in critical care nephrology and related settings, and the limitations and pitfalls of CEUS.

CONTRAST-ENHANCED ULTRASONOGRAPHY

Ultrasound Contrast Agents

The first reported ultrasound contrast agent (UCA) was based on air microbubbles created by agitating saline. Such technique still is used widely to detect cardiac right-to-left shunt. Gases represent ideal contrast agents for ultrasound because they are highly compressible and their density is 1000 less than the blood; thus the large difference in impedance generates high ultrasound contrast. Technical progress has enabled the production of stable gas microbubbles, which are small and uniform in size. These microbubbles (Fig. 34.1) consist of inert, poorly soluble perfluorinated gases embedded in phospholipids or albumin shells.[8] They behave as pure blood agents because their size (1–6 μm) prevents them from diffusing through the endothelium (Fig. 34.2).[9] After intravenous injection, UCA microbubbles can cross the pulmonary circulation and be visualized in arteries or capillary beds. Their half-life in the circulation is a few minutes, and the gas present in the microbubbles is excreted totally by the lungs.[10] Several UCA preparations have been developed and licensed for use throughout the world (Table 34.1).

Ultrasound Equipment and Settings

To optimize UCA visualization, dedicated imaging modes must be used when performing CEUS. UCA have the unique property of emitting an acoustic signal enriched with new harmonic frequencies when insonated. Harmonic B mode, power modulation, phase or pulse inversion, coherent pulse sequencing, and power pulse inversion are some of the contrast-specific imaging modes (also designated as "nonlinear" imaging modes) available in modern ultrasound equipment.[11] These dedicated modes aim at minimizing microbubble destruction by high acoustic pressures and make use of low mechanical index (MI) imaging or intermittent imaging (e.g., MI < 0.7). Today, contrast-specific modes are available on most mid- to high-end ultrasound devices.

Safety

As for any other drug, ultrasound contrast agents have been submitted to extensive clinical investigations for safety and efficacy, before approval by national health authorities. Postmarketing studies in more than 1 million patients[12–14] have established CEUS as a safe procedure. Wei et al.[15] reported a rate of severe reactions of 0.01% and no death in 78,383 patients, including 10,000 acutely ill patients (either in the ICU or with acute chest pain of possible cardiac origin) who had received UCA. As for any drug or contrast agent, the risk of anaphylactic reaction remains present, and the use of these products in unstable patients should be restricted to centers with full resuscitation capacities.

As discussed in the next paragraph, the blood flow quantification requires use of high mechanical index US for very short period of time (flashes). Some concerns have been raised about the safety of this procedure. Jimenez[16] showed in a porcine model that repeated insonification of the kidney at high MI did not produce any histologic change neither immediately after the procedure nor 4 hours later. There are, in particular, no signs of inflammatory response and no signs of extravasation of erythrocyte from the capillary system.

CLINICAL APPLICATIONS FOR RENAL CONTRAST-ENHANCED ULTRASONOGRAPHY

Most clinical applications for CEUS are related to the liver[17]; however, there is growing interest for nonhepatic indications.

TABLE 34.1

Commercially Available Ultrasound Contrast Agents

CONTRAST AGENT	SHELL	GAS	REGISTERED IN
Optison	Human albumin	Perfluoropropane	United States, Canada
Definity (Luminity)	Phospholipids	Perfluoropropane	United States, Europe, Canada
Sonovue	Phospholipids	Sulfur hexafluoride	Canada, Europe, China, India, Korea
Sonazoid	Phospholipids	Perfluorobutane	Japan

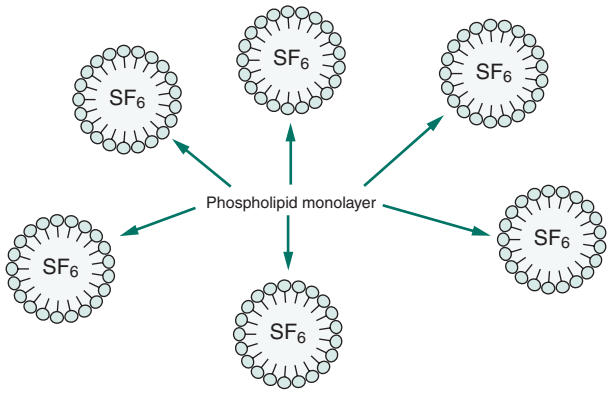

FIGURE 34.1 Schematic illustration of a microbubble contrast agent: Sonovue. *SF,* Sulfur hexafluoride.

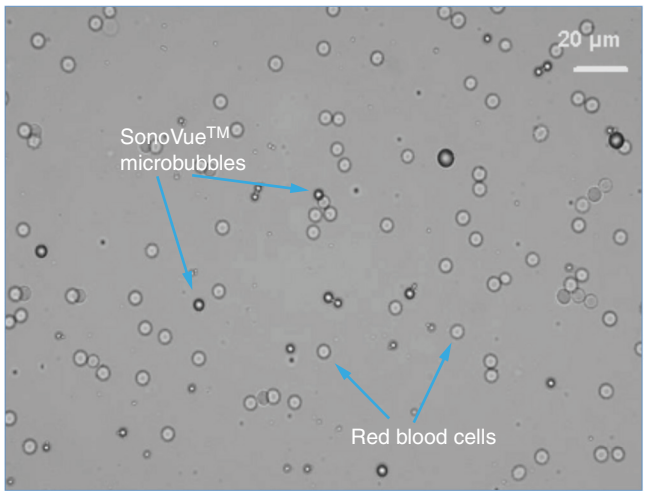

FIGURE 34.2 See also color plates. Optical microscopic view of microbubbles in rabbit blood. (Courtesy of Bracco SpA.)

The 2011 updated European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) has edited guidelines and recommendations on the clinical practice of nonhepatic CEUS.[18] The recommended renal indications are presented in Box 34.1, and those related to vascular problems are reviewed briefly in this chapter.

Vascular Imaging With Contrast-Enhanced Ultrasonography

CEUS enables vascular bed visualization with detailed granularity. After a bolus administration of UCA, kidneys enhance quickly and intensively (Fig. 34.3). Enhancement occurs first in arteries, followed a few seconds later by the cortex. Medullary enhancement occurs next, first in the outer medulla, then the pyramids gradually fill in. The renal medulla eventually will appear nearly isoechoic relative to cortex. As microbubble concentration in the general circulation decreases, contrast enhancement fades within 3 to 6 minutes, depending on sensitivity of the equipment used and on the amount of microbubbles injected.

BOX 34.1

Clinical Indications for Contrast-Enhanced Ultrasound as Recommended by the European Federation of Societies for Ultrasound in Medicine and Biology

Suspected vascular disorders, including renal infarction and cortical necrosis. (Recommendation Level: A)

Differential diagnosis between solid lesions and cysts presenting with equivocal appearance at conventional US. (Recommendation Level: B)

Differentiation between renal tumors and anatomic variations mimicking a renal tumor ("pseudo-tumors") when conventional US is equivocal. (Recommendation Level: B) However, both CEUS and CECT have limitations in rare, very small isoenhancing tumors.

Characterization of complex cystic masses as benign, indeterminate, or malignant to provide information for the surgical strategy. (Recommendation Level: A)

Additional aid, when necessary, in the follow-up of nonsurgical complex masses. (Recommendation Level: C)

Identification of clinically suspected renal abscesses in patients with complicated urinary tract infection. (Recommendation Level: C)

In patients undergoing renal tumor ablation under US guidance, CEUS may be used to improve lesion visualization in difficult cases and to detect residual tumor either immediately or later after ablation. When CEUS is planned, preablation assessment of lesion vascularity is important. (Recommendation Level: B)

Modified from Piscaglia F, Nolsoe C, Dietrich et al. The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. *Ultraschall Med.* 2012;33(1):33–59.
CECT, Contrast-enhanced computed tomography; *CEUS,* contrast-enhanced ultrasound; *US,* ultrasound.

Renal Infarction

CEUS can help diagnose renal infarction. Such a condition is related most commonly to trauma but can be observed in nontraumatic situations, such as renal artery thromboembolism, renal artery aneurysms and pseudoaneurysms, vasculitides, antiphospholipid syndrome, nephrotic syndrome, loin-pain hematuria syndrome, and cocaine abuse.

In such situations, CEUS can demonstrate absence of enhancement of the affected renal tissue (Fig. 34.4). Acute

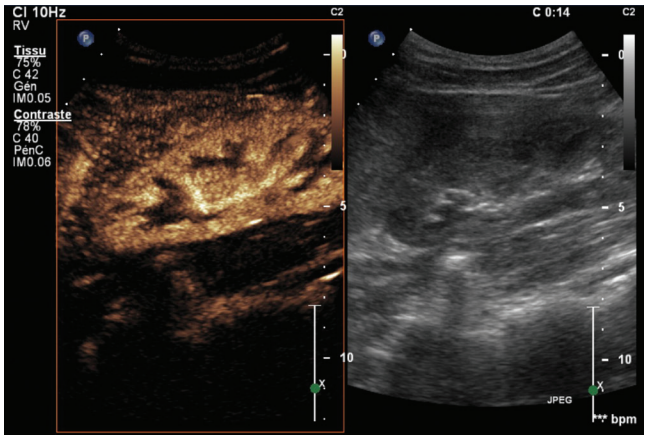

FIGURE 34.3 See also color plates. Normal contrast-enhanced ultrasound (CEUS) perfusion image. Longitudinal view of the right kidney in a 39-year-old woman, investigated for suspicious renal mass at the upper pole. No mass is visible, neither on fundamental image *(right)* nor on CEUS *(left)*. The CEUS image shows a homogeneous arterial perfusion of the kidney. In the arterial phase, because of predominant portal phase, the liver remains hypoperfused in comparison with the kidney.

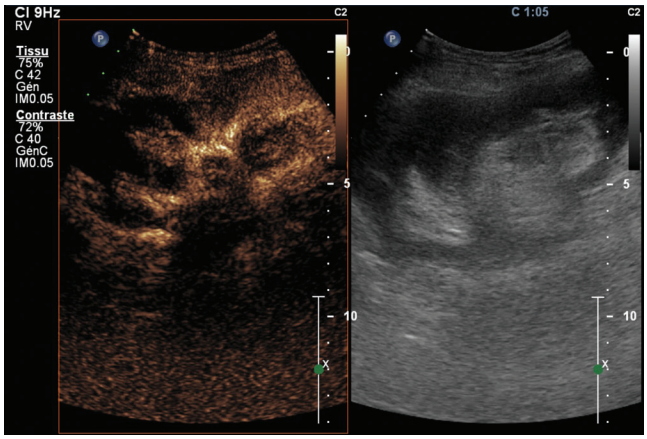

FIGURE 34.4 See also color plates. Renal infarction. Longitudinal view of a renal allograft in the left iliac fossa in a 72-year-old man. Three years after the graft, sudden pain in the left lower quadrant, with fever and acute decrease of the renal function. The fundamental image on the *right* does not show any anomaly. The CEUS image on the *left* clearly depicts a triangular avascular region of the upper pole: infarct.

infarcts typically are seen as wedge-shaped, nonenhancing areas within an otherwise normal-appearing kidney. Renal shape is preserved. A thin subcapsular rim of viable, enhanced cortex can be preserved as a result of collateral blood supply from the renal capsule, equivalent to the cortical rim sign, frequently described as a sign of renal infarction on computed tomography CT. When unilateral infarction is detected in the context of AKI, arteries must be investigated with other imaging techniques to refute or confirm renal artery stenosis.

Although of interest, CEUS is not the recommended first-line imaging in trauma. Indeed, even under optimal conditions, major solid organ injuries may be missed, vascular injuries could be difficult to detect, and intestinal or mesenteric injuries cannot be identified. A CT scan remains the gold standard in such situations.

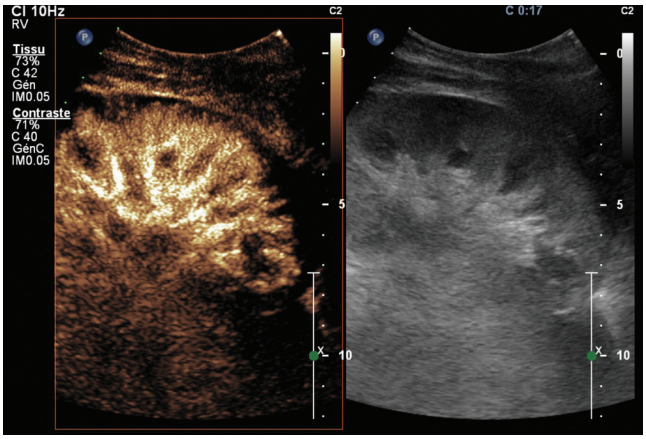

FIGURE 34.5 See also color plates. Cortical necrosis. Longitudinal view of a renal allograft in the right iliac fossa in a 7-year-old boy with an allograft dysfunction in the first 24 hours after implantation; suspicion of cortical necrosis. The *right* part of the image shows fundamental imaging at low energy. The *left* part shows contrast-enhanced ultrasound. An avascular rim is clearly visible at the periphery of the kidney, characteristic of cortical necrosis.

Acute Cortical Necrosis

Prolonged renal ischemia as induced by hemorrhagic shock, major surgery, or as a complication of an endovascular intervention, may result in a necrosis restricted to the renal cortex. This condition is referred to as *cortical necrosis*. The process is often bilateral and can be either multifocal or diffuse. Acute cortical necrosis also can be caused by renal artery spasm, microvascular injury, and diffuse intravascular coagulation.

CEUS allows differentiation between cortical necrosis (Fig. 34.5) and renal infarction. In such cases, enhancement of interlobar and arcuate arteries is observed without enhancement of corresponding cortex. Again, a rim of subcapsular cortical enhancement can be seen resulting from collateral flow from the renal capsular vessels.

Cholesterol Emboli Syndrome

Acute renal failure in a context of recent invasive vascular procedure should prompt consideration of cholesterol emboli syndrome, particularly in the presence of arterial hypertension and signs of distal ischemia. This diagnosis is suggested further by the presence of livedo reticularis and cholesterol crystals on a dilated funduscopic examination. A definitive diagnosis may be made by visualization of cholesterol crystals in a biopsy specimen of the skin or kidney.

Imaging can be indicated to rule out renal infarction or other vascular disorders. Color Doppler ultrasound examination is not specific. After microbubble administration, patients with recent atheroembolic episodes usually present with multiple triangular cortical areas of delayed enhancement. Enhancement is reduced only during the early phase and can be increased in later stages. Perfusion abnormalities usually are normalized within a few weeks of the embolization, despite clinically documented irreversible renal parenchymal damage. Although unproven, the progressive disappearance of perfusion defects is thought to be due to progressive volume reduction of the cortical ischemic areas.

Renal Transplant

In renal transplant medicine, a detailed evaluation of blood flow in the subcapsular capillaries is highly desirable because the latter are involved primarily in acute rejection. Fisher et al.[19] examined 32 patients 5 to 7 days after kidney transplantation and were able to show that a temporal difference in the contrast agent arrival slopes between two main territories allowed the differentiation of acute graft rejection from a normal clinical course (where the slopes were uniform).

Blood flow quantification with CEUS may help to differentiate between acute tubular necrosis and acute rejection in the immediate postoperative period. This technique also has a high accuracy for the diagnosis of chronic allograph nephropathy.[20,21]

BLOOD FLOW QUANTIFICATION WITH CONTRAST-ENHANCED ULTRASONOGAPHY

Overview

Because microbubbles remain confined to the intravascular space and have a rheology similar to that of red blood cells, contrast uptake as a function of time can be used to estimate quantitative perfusion parameters. Techniques have been derived to make use of these properties and enable blood flow quantification with CEUS. Most of these rely upon the ability of a flash (a few frames of high mechanical index ultrasound) to destroy all UCA microbubbles in the scan plan. Indeed, if UCA is administered as a continuous infusion, the organ reperfusion after microbubbles destruction can be observed and analyzed (Fig. 34.6). These perfusion quantification techniques are based on the works of Wei et al.,[22,23] a technique further modified by Tiemann et al.[24] and Arditi et al.[25] The latter approach was implemented in software enabling offline data processing. Using this software, video data are first linearized to compute an echo-power signal whose amplitude is proportional to the local contrast agent concentration. As described in the approach by Tiemann et al.,[24] fitting of these signals after destruction allows perfusion quantification. Here, the perfusion parameters considered are relative blood volume (rBV), mean transit time (mTT), and blood flow (rBV/mTT). An example of data analysis output provided by VueBox (Bracco, Milano, Italy) is depicted in Fig. 34.7.

Clinical Use of Contrast-Enhanced Ultrasonography to Quantify Renal Perfusion

Kishimoto et al.[26] used CEUS to evaluate the effect of an infusion of dopamine on renal microcirculation in nine healthy subjects. They subsequently used the same technique[27] to study to effect of valsartan on renal perfusion in seven healthy volunteers and found a significant increase in microbubble velocity after oral administration of valsartan, which correlated well with the increase in total renal blood flow determined by PAH clearance ($p < .05$). Kalantarinia et al.[28] tested the utility of CEUS to monitor the expected increase in renal blood flow after a high protein meal in healthy adults. They found a statistically significant increase (by 42.8%) in renal blood flow ($A \times \beta$ parameter) compared with baseline ($p = .002$).

We performed a study in 10 healthy volunteers evaluating changes in perfusion index (PI: a variable that is proportional to blood flow) seen during intravenous infusion of angiotensin II and after oral captopril. We found a statistically significant and dose-dependent decrease in PI during increasing doses of angiotensine II (ATII) as compared with baseline. The decreases in PI were already detectable when the renal plasma flow (as estimated by PAH clearance) decreased by 15%.[29]

Our next study represented the first utilization of CEUS to quantify renal perfusion in critically ill patients.[30] This study has demonstrated the feasibility and safety of CEUS in critically patients. Twelve patients intended for elective cardiac surgery underwent renal CEUS with destruction-reperfusion sequences before the procedure and 6 and 24 hours postprocedure. Despite occasional hemodynamic instability and invasive monitoring, no adverse event was recorded during or after the administration of Sonovue as UCA. Destruction-replenishment data were analyzed blindly by two independent radiologists whose analyses were in agreement.

Potential clinical uses of renal perfusion evaluation with CEUS was then evaluated in two clinical settings: circulatory shock[30] and hepatorenal syndrome.[31] The first study[30] aimed at determining changes in CEUS-derived parameters induced by a noradrenaline-induced increase in mean arterial pressure from 60 to 80 mm Hg in patients with circulatory shock. This study did not demonstrate an overall effect of a noradrenaline-induced increase in mean arterial pressure on perfusion parameters. However, on an individual level, such response was heterogeneous and unpredictable.

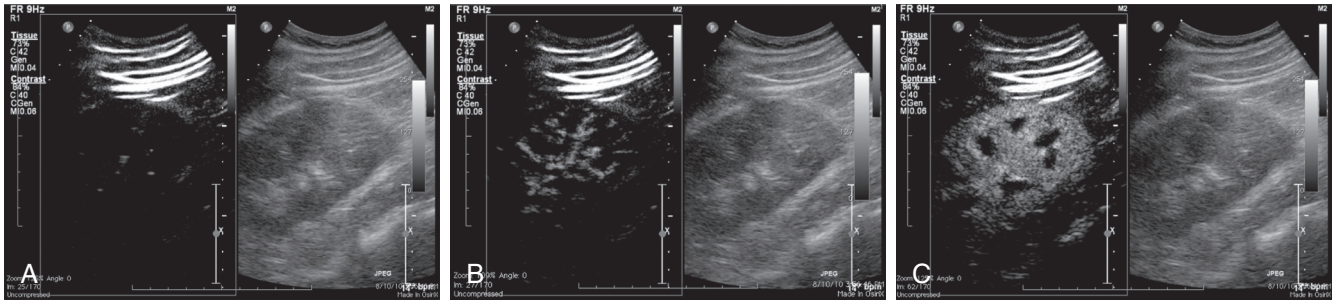

FIGURE 34.6 Example of destruction refilling sequences obtained in a 60-year-old male patient, 1 hour after coronary artery bypass surgery. Each part of the figure is divided in two; the left parts show contrast-specific images and the right parts show standard B mode images. After the destruction flash (4a left), no signal is detectable in the contrast specific image (i.e., all the microbubbles have been destroyed). Five seconds after destruction (4b left), partial replenishment of the main arteries with contrast can be noticed. Ten seconds after destruction, the kidney is replenished fully with contrast (4c left). No significant changes are observed in B-mode images (4a-c right). (Modified from Schneider A, Johnson L, Goodwin M, Schelleman A, Bellomo R. Bench-to-bedside review: Contrast enhanced ultrasonography—a promising technique to assess renal perfusion in the ICU. *Crit Care.* 2011;15[3]:157.)

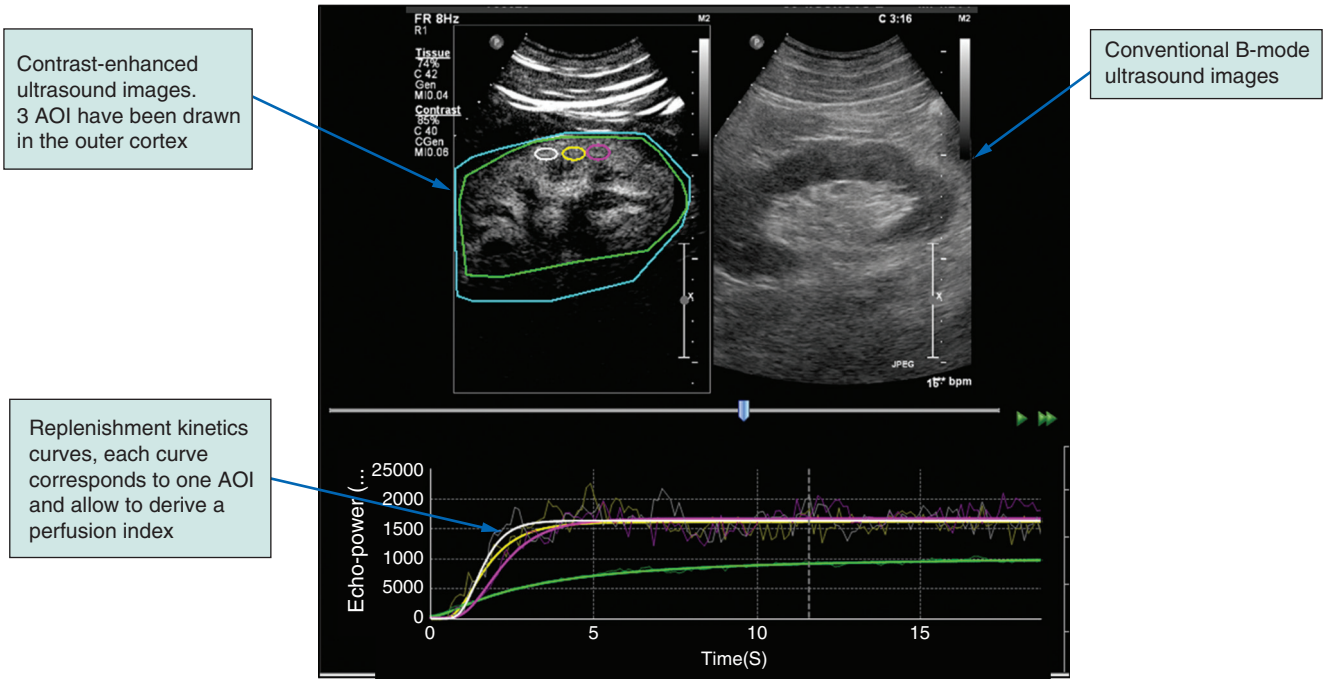

FIGURE 34.7 See also color plates. Renal perfusion index measurement using dedicated quantification software (Screenshot). Screenshot of Sonotumor™, shown as an example of software allowing perfusion quantification in CEUS sequences. The *upper segments* show the contrast-enhanced images *(left)* as well as the conventional ultrasound images *(right)*. This is where the reader can draw an area of interest (AOI) that will be analyzed by the software. Replenishment curves *(lower segment)* then are generated for each AOI. These curves represent the intensity of the echo-power as a function of time after the flash. *Bold lines* are fitted curves of the actual measured data represented by the clear lines. The fitted curves allow the derivation of a perfusion index (PI) for each AOI. (Modified from Schneider A, Johnson L, Goodwin M, et al. Bench-to-bedside review: contrast enhanced ultrasonography—a promising technique to assess renal perfusion in the ICU. *Crit Care.* 2011;15(3):157.)

A similar study evaluated the effect of the administration of terlipressin; a potent vasoconstrictor with preferential effect on mesenteric vasculature on renal cortical CEUS-derived parameters in patients with hepato-renal syndrome (HRS), a condition thought to be caused purely by renal perfusion alterations. Although of limited size, this study suggested that an increase in CEUS-derived parameters could be associated with clinical response in HRS.

Limits and Pitfalls

All together, these studies have demonstrated CEUS feasibility and safety in critically ill patients and suggested some potential indications. However, before renal perfusion quantification enters clinical practice, several issues must be resolved and several limitations clarified.

One of the most obvious limitations is related to cost and availability. UCA are currently relatively expensive and CEUS requires mid- to high-end equipment. In addition, a shortage of UCA was observed in some countries because of distribution issues. Equally, not all UCA are approved by regulating agencies throughout the world (Table 34.1).

On another level, given the pure intravascular properties of UCAs and their lack of urinary excretion, no data can be directly extrapolated from CEUS regarding kidney excretory function. The relationship between perfusion and function is a largely unanswered question. CEUS may contribute to our knowledge in this field, but CEUS-derived parameters should not to be viewed as a surrogate for renal function evaluation.

CEUS quantification of renal perfusion remains associated with high variability in results. Indeed, minute change in insonification angle or imprecise positioning of the US probe may result in dramatically modified results. Very strict anatomic landmarks must be identified to limit this variability. This may prove difficult in certain patients. The measurements can be made even more difficult in spontaneously breathing patients in whom renal incursion may be large during the respiratory cycle. This issue may be overcome in some sedated patients by using an inspiratory pause, provided it is tolerated.

Finally, CEUS enables only semiquantification of perfusion. Indeed results are not expressed in flow units but in arbitrary units. Therefore only changes between values can be interpreted, and a patient needs to serve as its own control. With this in mind, reproducibility of measures is paramount.

Future Research

Further studies are required to establish the relative importance of flow parameters as evaluated by CEUS. For instance, the mTT parameters, an indicator of time to replenishment, may be associated with less variability than the RBV parameter, which could be more dependent on the angle of insonification. Perhaps, the use of 3D probes as suggested by some authors[32] could overcome some of these limitations.

Technical issues limiting measurement reproducibility need to be sorted before clinical studies aiming to establish clinical indications for CEUS can be organized.

CONCLUSION

CEUS is a safe, noninvasive, and reliable technique with recognized indications in some forms of AKI and after renal transplant. In many ways, it is ideally designed to evaluate and monitor renal blood flow in ICU patients. Blood flow quantification with CEUS remains associated with important pitfalls. Further studies and technologic refinement are required to overcome these limitations.

Key Points

1. Contrast-enhanced ultrasound (CEUS) is a recent imaging modality making use of gas microbubbles as a contrast agent.
2. CEUS is safe, is feasible at the bedside, and enables renal vascular beds visualization.
3. CEUS can play a role in the diagnosis of renal infarction and cholesterol emboli syndrome and in the evaluation of renal transplant.
4. Techniques for renal perfusion quantification have been proposed but must be refined and validated before entering clinical practice.

Key References

6. Schneider A, Johnson L, Goodwin M, et al. Bench-to-bedside review: contrast enhanced ultrasonography - a promising technique to assess renal perfusion in the ICU. *Crit Care*. 2011;15(3):157.
15. Wei K, Mulvagh SL, Carson L, et al. The safety of deFinity and Optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. *J Am Soc Echocardiogr*. 2008;21(11):1202-1206.
18. Piscaglia F, Nolsoe C, Dietrich CF, et al. The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. *Ultraschall Med*. 2012;33(1):33-59.
23. Wei K, Le E, Bin JP, et al. Quantification of renal blood flow with contrast-enhanced ultrasound. *J Am Coll Cardiol*. 2001;37(4):1135-1140.
29. Schneider AG, Hofmann L, Wuerzner G, et al. Renal perfusion evaluation with contrast-enhanced ultrasonography. *Nephrol Dial Transplant*. 2012;27:674-681.

A complete reference list can be found online at ExpertConsult.com.

References

1. Prowle JR, Ishikawa K, May CN, et al. Renal blood flow during acute renal failure in man. *Blood Purif*. 2009;28(3):216-225.
2. Selkurt EE. Renal blood flow and renal clearance in hemorraghic shock. *Am J Physiol*. 1946;145:699-799.
3. Wan L, Yang N, Hiew CY, et al. An assessment of the accuracy of renal blood flow estimation by Doppler ultrasound. *Intensive Care Med*. 2008;34(8):1503-1510.
4. Prowle JR, Molan MP, Hornsey E, et al. Cine phase-contrast magnetic resonance imaging for the measurement of renal blood flow. *Contrib Nephrol*. 2010;165:329-336.
5. Hofmann L, Simon-Zoula S, Nowak A, et al. BOLD-MRI for the assessment of renal oxygenation in humans: acute effect of nephrotoxic xenobiotics. *Kidney Int*. 2006;70(1):144-150.
6. Schneider A, Johnson L, Goodwin M, et al. Bench-to-bedside review: Contrast enhanced ultrasonography - a promising technique to assess renal perfusion in the ICU. *Crit Care*. 2011;15(3):157.
7. de Jong N, Ten Cate FJ, Lancee CT, et al. Principles and recent developments in ultrasound contrast agents. *Ultrasonics*. 1991;29(4):324-330.
8. Klibanov A. Ultrasound contrast agents: development of the field and current status. *Top Curr Chem*. 2002;222:73-106.
9. Cosgrove D. Angiogenesis imaging–ultrasound. *Br J Radiol*. 2003;76(Spec1):S43-S49.
10. Morel DR, Schwieger I, Hohn L, et al. Human pharmacokinetics and safety evaluation of SonoVue, a new contrast agent for ultrasound imaging. *Invest Radiol*. 2000;35(1):80-85.
11. Schneider M. Bubbles and microcirculatory disorders. *Eur Radiol*. 2001;11(suppl 3):E1-E5.
12. Kusnetzky LL, Khalid A, Khumri TM, et al. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent: results in 18,671 consecutive studies. *J Am Coll Cardiol*. 2008;51(17):1704-1706.
13. Dolan MS, Gala SS, Dodla S, et al. Safety and efficacy of commercially available ultrasound contrast agents for rest and stress echocardiography a multicenter experience. *J Am Coll Cardiol*. 2009;53(1):32-38.
14. Main ML, Ryan AC, Davis TE, et al. Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent (multicenter registry results in 4,300,966 consecutive patients). *Am J Cardiol*. 2008;102(12):1742-1746.
15. Wei K, Mulvagh SL, Carson L, et al. The safety of deFinity and Optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. *J Am Soc Echocardiogr*. 2008;21(11):1202-1206.
16. Jimenez C, de Gracia R, Aguilera A, et al. In situ kidney insonation with microbubble contrast agents does not cause renal tissue damage in a porcine model. *J Ultrasound Med*. 2008;27(11):1607-1615.
17. Anaye A, Perrenoud G, Rognin N, et al. Differentiation of focal liver lesions: usefulness of parametric imaging with contrast-enhanced US. *Radiology*. 2011;261(1):300-310.
18. Piscaglia F, Nolsoe C, Dietrich CF, et al. The EFSUMB Guidelines and Recommendations on the Clinical Practice of Contrast Enhanced Ultrasound (CEUS): update 2011 on non-hepatic applications. *Ultraschall Med*. 2012;33(1):33-59.
19. Fischer T, Dieckhofer J, Muhler M, et al. The use of contrast-enhanced US in renal transplant: first results and potential clinical benefit. *Eur Radiol*. 2005;15(suppl 5):E109-E116.
20. Schwenger V, Korosoglou G, Hinkel UP, et al. Real-time contrast-enhanced sonography of renal transplant recipients predicts chronic allograft nephropathy. *Am J Transplant*. 2006;6(3):609-615.
21. Benozzi L, Cappelli G, Granito M, et al. Contrast-enhanced sonography in early kidney graft dysfunction. *Transplant Proc*. 2009;41(4):1214-1215.
22. Wei K, Jayaweera AR, Firoozan S, et al. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. *Circulation*. 1998;97(5):473-483.
23. Wei K, Le E, Bin JP, et al. Quantification of renal blood flow with contrast-enhanced ultrasound. *J Am Coll Cardiol*. 2001;37(4):1135-1140.
24. Tiemann K, Becher H, Lohmeier S. Real-Time assessment of tissue perfusion following bubble destruction at low emission-power - first experimental results using power pulse inversion imaging. *J Am Coll Cardiol*. 2000;35:426A.
25. Arditi M, Frinking PJ, Zhou X, et al. A new formalism for the quantification of tissue perfusion by the destruction-replenishment method in contrast ultrasound imaging. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2006;53(6):1118-1129.
26. Kishimoto N, Mori Y, Nishiue T, et al. Renal blood flow measurement with contrast-enhanced harmonic ultrasonography: evaluation of dopamine-induced changes in renal cortical perfusion in humans. *Clin Nephrol*. 2003;59(6):423-428.
27. Kishimoto N, Mori Y, Nishiue T, et al. Ultrasound evaluation of valsartan therapy for renal cortical perfusion. *Hypertens Res*. 2004;27(5):345-349.
28. Kalantarinia K, Belcik JT, Patrie JT, et al. Real-time measurement of renal blood flow in healthy subjects using contrast-enhanced ultrasound. *Am J Physiol Renal Physiol*. 2009;297(4):F1129-F1134.
29. Schneider A, Meuwly BM, Vogt B. Renal perfusion quantification with CEUS, a pilot study on 10 healthy subjects. *Man*. 2010.
30. Schneider AG, Goodwin MD, Schelleman A, et al. Contrast-enhanced ultrasound to evaluate changes in renal cortical perfusion around cardiac surgery: a pilot study. *Crit Care*. 2013;17(4):R138.
31. Schneider AG, Schelleman A, Goodwin MD, et al. Contrast-enhanced ultrasound evaluation of the renal microcirculation response to terlipressin in hepato-renal syndrome: a preliminary report. *Ren Fail*. 2014;1-5.
32. Feingold S, Gessner R, Guracar IM, et al. Quantitative volumetric perfusion mapping of the microvasculature using contrast ultrasound. *Invest Radiol*. 2010;45(10):669-674.