Article published online: 2023-04-18

The Use of Ultrasound Contrast in Interventional Radiology

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Arab J Intervent Radiol 2023;7:12–21.

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Abstract

Ultrasound contrast agents have gained increasing popularity due to the high level of safety, real-time improved visualization, and ability to detect vascularity. As a result, contrast-enhanced ultrasound lends itself well to interventional radiology including in preprocedure assessment, intraprocedural guidance, and postprocedure evaluation. The authors aim to demonstrate the wide utility of contrast-enhanced ultrasound in both vascular and nonvascular intervention.

Keywords
- contrast agent
- contrast medium
- ultrasound

Introduction

The use of ultrasound (US) in intervention is well established and widespread practice due to inherent benefits. These include a dynamic examination, absence of radiation as well as being inexpensive and available at a bedside. As a result, many interventions have become solely US-guided (e.g., biopsies) or have an US-guided element (e.g., vascular puncture). However, US is conventionally only able to provide a static assessment of the macrovascular circulation, limiting visceral assessment and that of physiological and nonphysiological cavities. A further potential downfall is the reliance on operator technique, and thus variability, which may limit operator confidence. In many cases difficulty may be due to the lack of inherent contrast in grayscale US.

Contrast-enhanced US (CEUS) is a technique that has been developed over the last 3 decades with increasing popularity. The microbubble contrast agent consists of an inert gas (sulfur hexafluoride) encased in a phospholipid shell approximately the size of a red blood cell. When exposed to low acoustic pressure in contrast-specific mode this causes microbubble resonation and nonlinear signal which is displayed after static signal cancellation giving a true micro- and macrovascular image. The microbubbles have transpulmonary stability and are true blood pool agents meaning they recirculate to a capillary bed level within the blood stream until they are excreted via the pulmonary circulation, with the phospholipid shell metabolized within the liver. As a result, there is no hepatic or renal toxicity and no blood tests are required prior to use.[1] Studies have shown safety of US contrast agents (UCA) in both the adult and pediatric population, as well as more recent depiction of safety in pregnancy.[2,3] Benefits of CEUS also include those inherent to conventional US, including dynamic real-time visualization and lack of radiation exposure. It is also suitable for patients who are unable to tolerate magnetic resonance imaging (MRI) due to claustrophobia or implanted devices.

CEUS lends itself well to use in interventional radiology (IR) and can be used either to aid diagnosis preintervention, guide intervention interprocedurally, or confirm endpoint postprocedure. Typically, this is through better visualization of a lesion (including viable/necrotic areas), determining critical structures and planning a pathway, confirming placement/communication of cavities, determining endpoint of a procedure, or identifying complications. Diagnostically, CEUS may also be used in surveillance.

Procedure

Procedural technique will be based on requirements broadly speaking these are either intravascular or intracavity.

article published online
April 18, 2023

DOI https://doi.org/10.1055/s-0043-1764437.
ISSN 2542-7075.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Intravascular administration is typically via a peripheral or central venous access and will usually require between 1.2 and 4.8 mL UCA (typically SonoVue [Bracco]) followed by a normal saline flush. Doses are dependent on the area evaluated and probe used as the contrast resonates best at 3 to 5 MHz meaning higher doses are needed at higher frequencies. It is important to use correct dosing to avoid excessive flair artifact inhibiting visualization. Less frequently, intraarterial administration can be performed via an indwelling catheter when targeting a specific region, e.g. prostatic artery. Lower doses are required due to lack of systemic circulation (typically less than 1 mL followed by saline flush).

Intracavity CEUS requires an indwelling tube, for example, gastrostomy, nephrostomy, etc. Due to the small comparative volume to the circulating blood only 0.1 mL UCA is required diluted in 20 mL normal saline to allow volume for administration.[4]

CEUS is typically done preprocedure along with optimized grayscale imaging and, if needed, intraprocedural for real-time guidance. After optimized grayscale imaging contrast-specific mode is entered and UCA administered. An onscreen timer is started and video clip recorded usually using a split screen or overlay mode for concurrent grayscale imaging.

A vial of contrast is viable for 6 hours so can be reused for multiple patients once infection control protocols are performed adequately.

Nonvascular CEUS in IR

Biopsy

Increasingly, histological confirmation is required in diagnosis and frequently subtyping is needed to guide treatment. US-guided biopsy offers the benefit of no radiation or iodinated contrast exposure, with real-time imaging. CEUS can provide four areas of benefit in biopsies; increasing diagnostic certainty, increasing lesional conspicuity, avoiding nonviable tissue/critical structures, and identifying complications.

Preprocedure diagnostic CEUS is advised to identify and characterize a focal lesion, including in the diseased liver. In some cases characterization of a benign or regressing lesion may prevent the need for biopsy.

Lesions may be difficult to identify at grayscale mode US, similarly computed tomography (CT)-guided biopsy may become landmark-based once an appropriate contrast phase has passed. CEUS provides tissue contrast and can be evaluated continuously to determine peak visualization and allow accurate target identification. This can be facilitated in the arterial phase by a short high mechanical index pulse to burst the microbubbles in the field of view and identify early phase replenishment (►**Fig. 1**). The well recognized safety of US contrast in both adults and pediatrics means repeated injection can be performed.[2,3,5] In patients with chronic liver disease and multiple nodules CEUS has been shown to increase biopsy sensitivity.[6,7] CEUS has also been shown in thoracic biopsies to distinguish central lung tumors from adjacent atelectasis as well as mediastinal structures facilitating lesional biopsy.[8] Evaluation of the surrounding tissue can also be performed and identification of significant intervening structures, such as arteries or compressed bowel, can be performed without the need of artifact associated with Doppler mode.

As UCA are pure intravascular agents, they are able to define clearly viable portions of lesion increasing the ability to target vascularized lesions. Studies demonstrating CEUS to facilitate US-guided biopsy of lesions not visible on B-mode US, or targeted biopsy of heterogeneous lesions with enhancing and necrotic components, emerged over a decade ago.[7] Use of CEUS has changed biopsy pathway trajectory in up to 80% of cases as conventional US poorly visualizes necrosis by comparison.[8] Peak target visualization can be achieved on temporal overlay imaging with CEUS, whereby the postcontrast images are stacked to demonstrate overlapping vasculature over time. Potentially, this may decrease the number of passes required and improve sample integrity.[9]

Drainage CEUS

CEUS can be used via the intravascular or endocavity route to support US-guided drainage procedures. Grayscale appearances of collections may create diagnostic difficulty, with echogenic contents giving the impression of solid tissue, which may be further confounded if needle aspirate fails to yield fluid. CEUS clearly delineates the nonenhancing areas of the collection compared with adjacent vascularized tissue or viscera (►**Fig. 2**). Vascularized septations may be present and often shown a typical honeycomb appearance, while perilesional hypervascularity and early washout can also be seen in abscesses. The fluid aspect of the collection can be

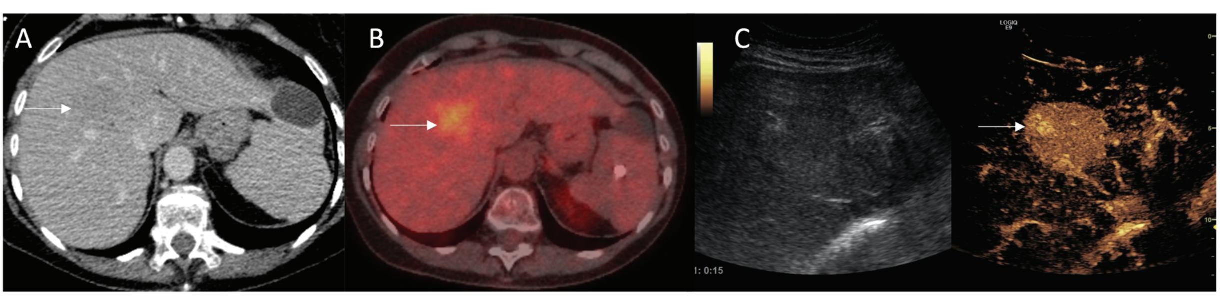

Fig. 1 (**A**) Axial contrast-enhanced (CE) computed tomography (CT) showing a subtle hepatic lesion (arrow) which was confirmed on (**B**) positron emission tomography (PET)-CT scan (arrow). The lesion was not seen on grayscale ultrasound but on (**C**) simultaneous CEUS in split screen mode arterial enhancement is seen (arrow) and the lesion was could be targeted for biopsy in the arterial phase with reinjection.

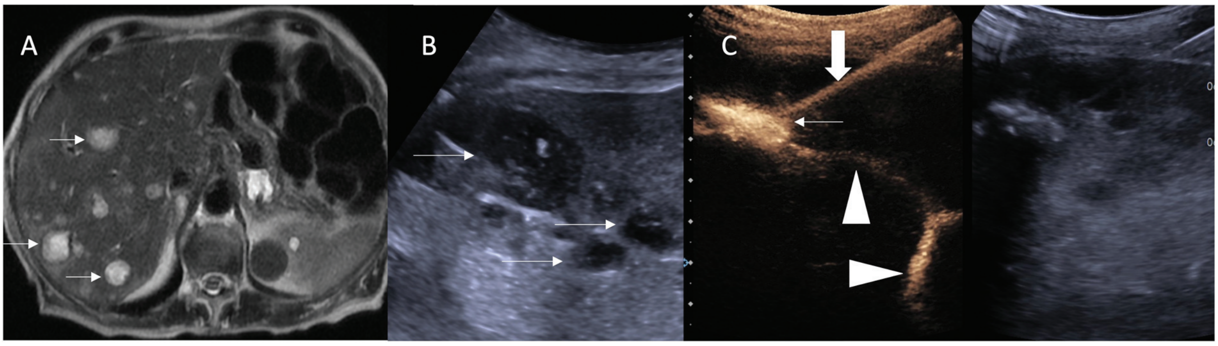

Fig. 2 (**A**) T2-weighted axial magnetic resonance (MR) sequence showing multiple cystic areas with internal debris (arrow). (**B**) Grayscale ultrasound (US) image showing multiple hepatic lesions (arrows). (**C**) Simultaneous grayscale and contrast-enhanced US (CEUS) performed with dilute contrast via the access needle (thick arrow) which showed filling of the collection (thin arrow) communication with the biliary tree (arrowheads) indicating biliary abscesses.

easily differentiated allowing operator confidence for drainage. In addition, preprocedure CEUS can delineate adjacent vascular structures and abnormality such as mycotic pseudoaneurysm formation. In selected cases of gallbladder wall perforation, the drain can be sited through the preexisting wall defect if appropriate to avoid further loss of wall integrity. This may be useful in percutaneous management of perforated cholecystitis[10] (►**Fig. 3**).

Once percutaneous cavity access has been obtained endocavity UCA administration can be used to determine the degree of communication between multiple collections or within one loculated collection. This can be used to help determine if thrombolytic therapy or mechanical disruption will be required to allow maximal drainage. Communication with multiple adjacent collections can also be evaluated preventing the requirement for multiple drains. CEUS clearly delineates the drain lumen and tip as well as better highlights residual fluid component of the collection and potential fistulation. Fistulous communications can subsequently be delineated in recurrent collections to facilitate tract closure. This includes oral ingestion of UCA or enteric administration to highlight fistulous communication.

Postprocedure a drain which no longer has output often requires assessment of position and patency. Grayscale images may be difficult to identify the drain tip and as a result require cross-sectional imaging. Endocavitary CEUS clearly delineates the drain lumen and tip as well as better highlights residual fluid component of the collection and potential fistulation. Intravascular CEUS can be used to assess for residual nonenhancing abscesses.[4]

Ablation CEUS

CEUS-guided ablation can be performed using similar principles to CEUS-guided biopsy and is a well-recognized alternative to other imaging modalities as it allows delineation and accurate depiction of further sites of disease.[11] In

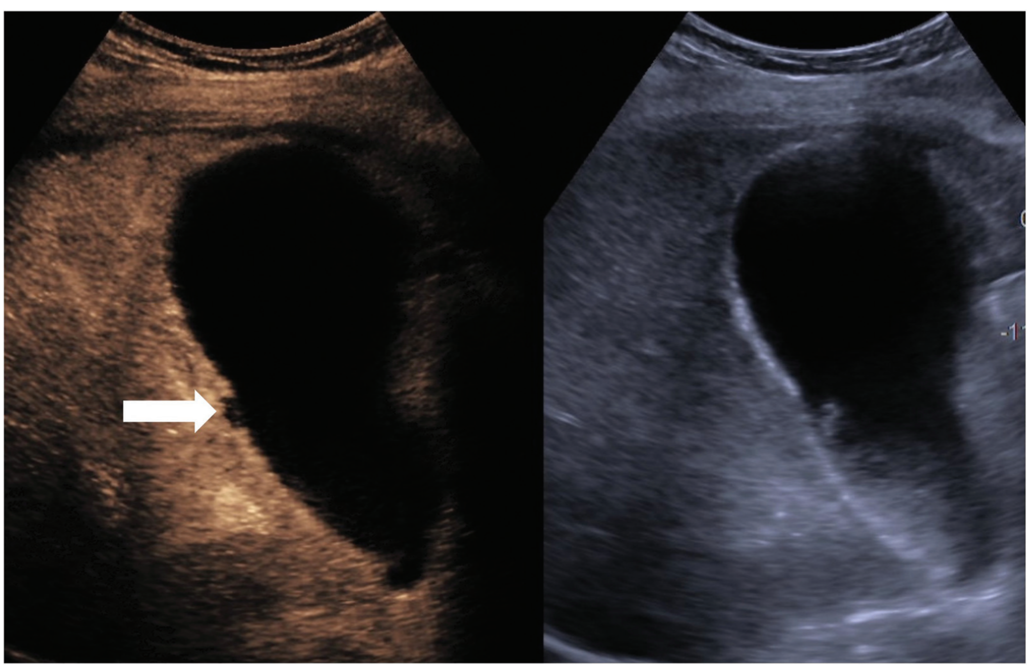

Fig. 3 Simultaneous grayscale and contrast-enhanced ultrasound (CEUS) of the gallbladder showing a mildly thick-walled gallbladder with focal perforation on the medial aspect with loss of wall integrity (arrow).

addition to radiation and contrast sparing, the technique allows continuous imaging throughout the procedure and can confirm the successful ablation zone.[12]

CEUS-guided ablation has been used in a multitude of regions, including the liver,[13] kidneys,[14] thyroid,[15] parathyroids,[16] retroperitoneum,[17] uterine fibroids, and abdominal wall endometriosis.[18,19] CEUS has been applied in a range of ablative modalities, including microwave ablation, alcohol ablation, radiofrequency ablation, cryoablation, and irreversible electroporation.[20,21] Solbiati et al demonstrated much lower partial ablation rates using CEUS than conventional means (16.1% vs. 5.9%).[22]

CEUS can supplement ablative therapy by facilitating add-on ablation of the feeding artery in hypervascular tumors to reduce perfusion.[23] It can also be used to detect complications during and following ablation.[24] Detectable vascular complications include bleeding, pseudoaneurysm formation, and thrombosis. Some operators have used US guidance to treat bleeding after microwave ablation with glue embolization.[25]

Surveillance postablation to monitor for recurrence has been shown to be possible following different ablative therapies in different tissues[26] (►**Fig. 4**).

Nephrostomy and Nephrostograms with CEUS

Fluoroscopy-guided nephrostomy is a relative contraindication in several clinical scenarios, including pregnancy and iodinated or gadolinium contrast allergy. Differentiation of the collecting system from renal parenchyma may be difficult when there is increased calyceal echogenicity such as in urosepsis, collecting system hemorrhage, or malignancy. Intravenous CEUS can delineate the nonenhancing collecting system to be targeted and subsequent confirmation of successful collecting system access in these cases can be achieved by instillation of dilute UCA via the access needle (►**Fig. 5**).[27] Should there be failure of collecting system access, injecting UCA does not result in obscuration of the target as the microbubbles can be burst using short-duration high mechanical index imaging, unlike fluoroscopic-guided puncture.

When nondilated collecting systems require a nephrostomy (e.g., urinary diversion), several techniques can be performed. Initially, intravenous CEUS can better demonstrate the nonenhancing renal calyces through the access needle or the collecting system may be expanded by retrograde instillation of dilute microbubble contrast by retrograde ureteral contrast injection. These approaches reduce the number of punctures

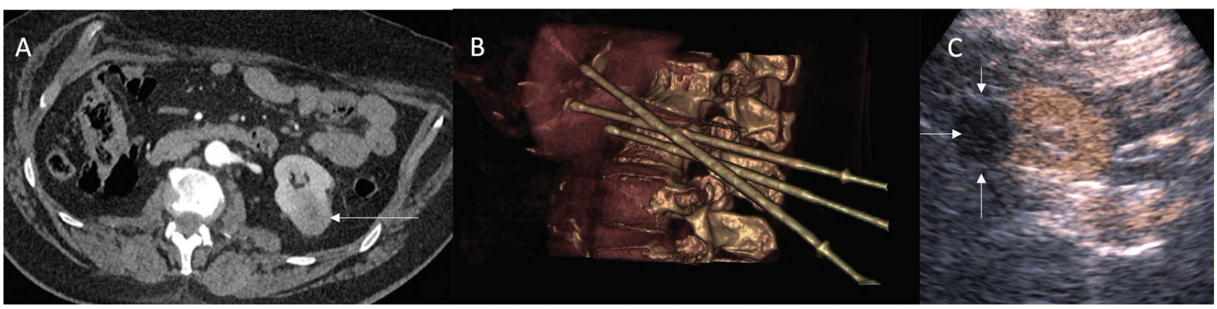

Fig. 4 (**A**) Axial computed tomography (CT) showing a left renal tumor. (**B**) Placement of cryoablation probes on three-dimensional (3D) reconstructed CT images. (**C**) Contrast-enhanced ultrasound (CEUS) 1 year later showing no enhancement and reduced size of the lesion in keeping with adequate ablation.

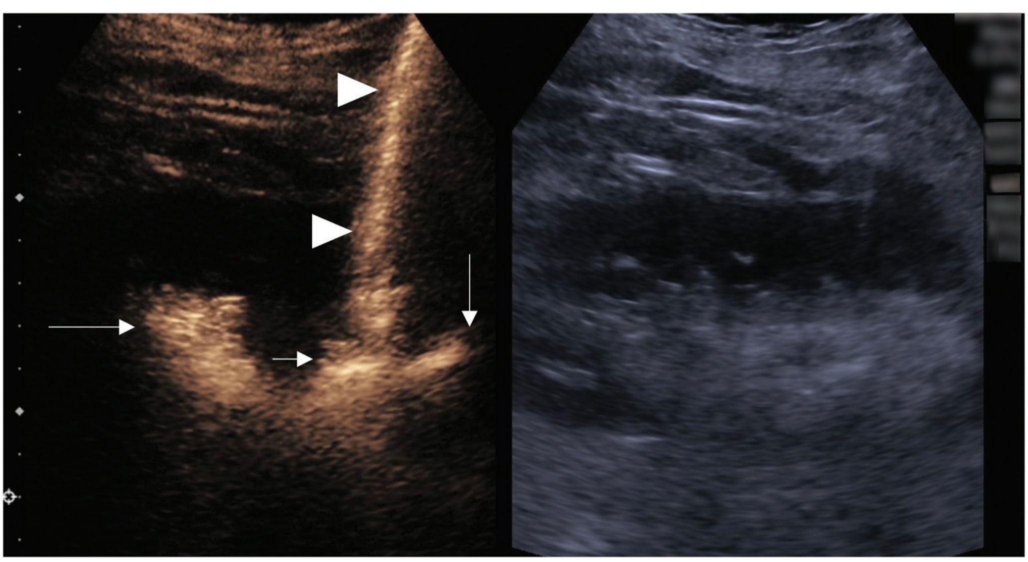

Fig. 5 Contrast-enhanced ultrasound (CEUS) image with simultaneous on grayscale imaging. After Chiba needle access (arrowhead) dilute ultrasound contrast administered fills the collecting system (thin arrow) indicating appropriate placement in a patient too unwell for transfer to the interventional radiology facility.

needed to achieve access, improve puncture site accuracy, and reduce procedural bleeding.[28]

Following collecting system access or nephrostomy placement, a nephrostogram may be performed by endocavitary UCA to confirm correct nephrostomy position, delineate the ureter and confirm contrast passage to the urinary bladder, and is potentially more sensitive than conventional iodinated contrast.[29] There is also the potential to evaluate ureteric strictures or fistulation.

Percutaneous Transhepatic Cholangiography CEUS

The use of the microbubble contrast agent to perform percutaneous transhepatic cholangiography (PTC) has been successfully reported for both puncture confirmation and assessment of biliary drainage.[30] The major benefits are reduced radiation burden and the ability to perform PTC in patients with iodinated and gadolinium contrast agent allergy. CEUS PTC is used as an alternative to fluoroscopy-guided biliary puncture with radiodense contrast which may obscure the image. While CEUS has been shown to be a good alternative to fluoroscopically guided PTC, it is limited mainly when wire manipulation is required.[30] Intravenous administration can be particularly helpful in the nondilated system to better visualize the biliary system, while when given through the access needle allows confirmation of position without creating poor visualization as occurs with iodinated contrast. CEUS through the biliary tree can also confirm enteric biliary drainage. Endobiliary UCA administration has been used to demonstrate biliary leakage following T-tube removal[31] and identified an occult biliary-arterial fistula.[32]

Lymphatics CEUS

Lymphatic system evaluation and intervention is emerging. Currently, the evidence is being driven by case reports and series; however, some techniques such as sentinel node localization are well established.[33] Breast cancer patients with lymphoedema following axillary dissection may also benefit from CEUS lymphatic mapping before lymphaticovenous anastomosis surgery.[34]

Early work has also shown feasibility of improved lymphatic needle placement for MRI lymphangiography in pediatrics with CEUS confirmation.[35] Retrograde pyelography has been used to delineate a fistula between the kidney and the lymphatic system in a child with nonparasitic chyluria.[36] Intranodal CEUS administration matches conventional lymphangiography in the assessment of thoracic duct patency[37] and treatment of lymphatic malformations.[38]

Vascular IR

Angioplasty

Peripheral vascular disease is a common condition, often symptomatic through claudication or progressive to critical limb ischemia. Revascularization through angioplasty is often performed and the result assessed through Doppler US, symptom improvement, or visual improvement on angiography postprocedure. While CEUS can provide angiographic assessment of a focal stenosis it can also be used to assess muscle perfusion. Amarteifio et al[39] performed CEUS after revascularization and showed a decreased time to maximum enhancement as well as a shorter time to maximum improvement predicting more successful outcome.

Dialysis Fistula

For US-guided percutaneous endovascular treatment of arteriovenous fistula, the superficial location lends itself well to US guidance and can be done without iodinated contrast given to the renally impaired population. Taurisano et al have demonstrated the potential effectiveness of CEUS providing detail on the likelihood of restenosis post-percutaneous transluminal angioplasty. Similarly to angioplasty the angiographic nature means CEUS can guide intervention in hemodialysis fistulas and detect complications such as rupture.[40] Reinjection can be performed as required given the absence of nephrotoxicity and excellent safety profile.

Vascular and Lymphatic Malformation

Vascular malformations (VMs) are complex congenital or iatrogenic lesions with quiescent endothelium often involving multiple tissues planes. While MRI is the default imaging modality used in their assessment, CEUS using intravascular contrast agent can offer additional information on the mapping of these lesions.

In the setting of intracranial arteriovenous malformations (AVM) repair, CEUS has been employed to provide the surgeon with real-time adjunctive information to distinguish between involved, feeding vessels and normal vessels in the intraoperative setting, particularly as increasing intraoperative edema can blur margins.[41]

IR is well-established in the definitive management of VMs. CEUS has been demonstrated to add to the safety and efficacy profile of cornerstone IR procedures such as embolization and sclerotherapy in the management of VMs.[42]

Similar to the evaluation in venous malformations, CEUS can be performed prior to sclerotherapy of lymphatic malformations. UCA can be injected into cystic spaces to glean further detail on the structure of the malformation prior to sclerosis. This is particularly useful as often these lesions can comprise of multiple adjacent but separate cystic components which each require sclerosis for definite treatment of the lesion or to determine whether multiple treatments will be required. Furthermore, as a pure intraluminal agent the absence of vascular filling on CEUS can provide confidence as nontarget treatment will be a low risk.

CEUS can also be used to quantify the perfusion in VM before and after embolization treatment. This is done through time-intensity curve (TIC) analysis and calculation of time to peak (TTP) as well as area under the curve (AUC). TTP increase and AUC decrease indicate therapy-induced changes post-embolization. With this, dynamic CEUS can quantitatively determine the level of microvasculature involvement with significant alteration in TIC parameters.[42]

Carotid Stenosis

Recent guidance has reaffirmed the role of duplex US in evaluation of carotid disease with further literature established in the vulnerability of the intravascular plaque, identified through neovascularity.[43] This modality may be particularly useful in a patient population whereby brittle renal function and susceptibility to iodinated contrast is common. In assessment of the macrovasculature CEUS can provide angiographic images of plaque morphology. This has led to poststenting evaluation with CEUS which was shown to be more sensitive than conventional Doppler.[44] Furthermore, the use interprocedural US in carotid stenting has already been shown to decrease contrast load and, although not yet studied, CEUS may also provide further intraprocedural confidence and information.[45]

Abdominal Aortic Aneurysm

Endovascular aortic repair (EVAR) is an alternative to open aortic aneurysm repair, which provides a minimally invasive apprach and similar initial outcomes.[46] Endoleaks are a known complication due to persistent aneurysmal filling outside the graft in EVAR. The dynamic nature of CEUS and ability to perform prolonged imaging allows great accuracy in assessment of endoleaks. In particular, the late nature can be assessed and so can cause reclassification of endotension on CT, where sac size increases but no source is seen often due to late filling.[47] Three-dimensional CEUS has further been shown to increase diagnostic accuracy for endoleaks with better performance than CT angiography.[48]

While still experimental, intraoperative CEUS-assisted EVAR in patients with infrarenal aortic aneurysms represents a new option for intraoperative visualization of aortoiliac segments and identification of type I endoleaks, especially in those patients with contraindications for usage of iodinated contrast agents.[49,50] Intraoperative CEUS has also demonstrated to detect a greater number of type II endoleaks compared with digital subtraction angiography. Limitations of CEUS use in EVAR include patient body habitus whereby it is often difficult to visualize the aneurysmal sac in the case of severe obesity. While no particular graft material has demonstrated superiority in EVAR, the use of expanded polytetrafluoroethylene is common and causes echo reflection which decreases the power of endoleak detection. There has been a small study of patients with reported iodinated contrast allergy using carbon dioxide angiography combined with intraprocedural CEUS to perform EVAR safely and effectively entirely free of iodinated contrast.[51]

Bleeding

CT angiography provides the mainstay for the emergency assessment of bleeding. However, inherent disadvantages associated with this modality involve the need to transfer a potentially unstable patient to scan department, (usually distant to dedicated resuscitation facilities), the contrast load needed, and duration of time involved. Furthermore, the increased spatial and temporal resolution of CEUS may mean it has the potential to identify hemorrhage not seen on CT, particularly if there is a single phase (►**Fig. 6**). In a mixed splenic and liver trauma population, Lv et al evaluated the performance of CEUS in comparison to CT angiography to identify bleeding. The authors observed a sensitivity of 76% for CEUS to detect active bleeding.[52] Limitations are due to the inability to screen the entire abdomen simultaneously, limiting features of general US such as body habitus and intervening gas. In cases of embolization of active bleeding, intraprocedural CEUS can be performed either through intravascular or catheter intra-arterial administration to ensure endpoint of embolization. This is of particular use when coil artifact may obscure detailed evaluation on CT or angiography, even in cases where B-mode US may seem insufficient.[53]

Pseudoaneurysms

Pseudoaneurysms are a common complication of procedures involving arterial puncture, but may also occur in the context

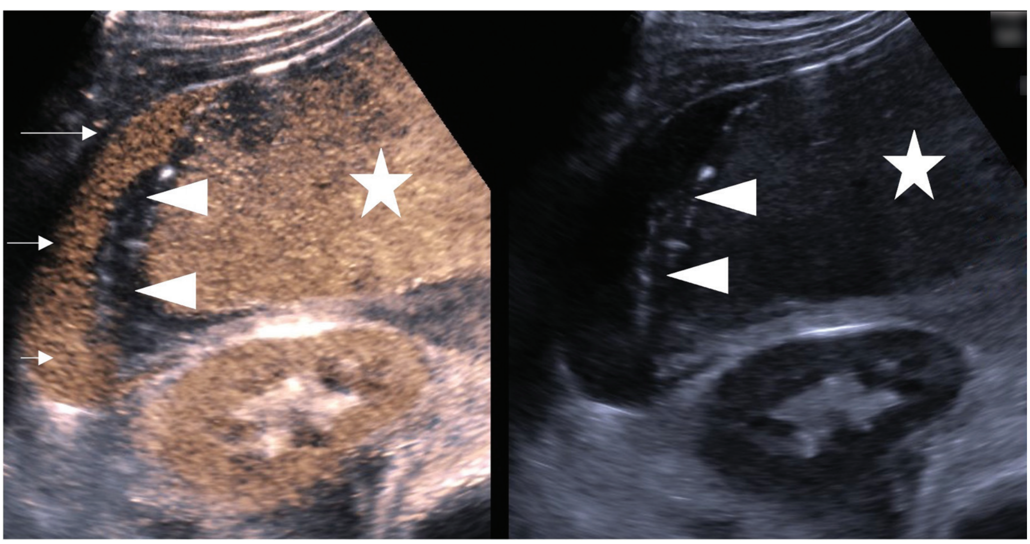

Fig. 6 Contrast-enhanced ultrasound (CEUS) image post-liver biopsy with split screen grayscale image. Pooling contrast (arrow) is seen in a pulsatile fashion into the perihepatic hematoma (arrowhead) adjacent to the liver (star) indicating active arterial hemorrhage.

of trauma or infection.[54] Partial loss of the arterial wall results in risk of spontaneous rupture and life-threatening hemorrhage. When superficial (particularly at femoral access sites), US-guided thrombin injection is usually performed if compression fails. Visceral pseudoaneurysms may be observed, embolized, or treated with thrombin injection.[55] When observation is undertaken focused CEUS can prevent the need for multiple CTs and is of particular use in pediatrics.[56] CEUS allows accurate definition of the viable pseudoaneurysm as well as anatomy such as the neck, which may be difficult to determine in the context of hematoma, edema, or artifact from color Doppler. UCA allows intraprocedural assessment of completeness of treatment and can assess distal vasculature for evidence of infarction or distal thrombus.[57]

Uterine Artery Embolization

Uterine artery embolization is an established technique. Currently, MRI is the reference standard for assessment of fibroids pre- and postintervention. However, the expense and relative inaccessibility of MRI for many mean a need for more ubiquitous imaging technology.[58] As well as providing information on the location, size, and number of tumors, CEUS provides additional detail on the fibroid pseudocapsule, central necrosis, and intralesion vascular pattern compared with other US modes.[59] CEUS can be used as an adjunct to determine vascularity in cases of equivocal enhancement in persistent symptoms.

Intraprocedural CEUS allows determination of complete devascularization and endpoint of embolization (►**Fig. 7**),

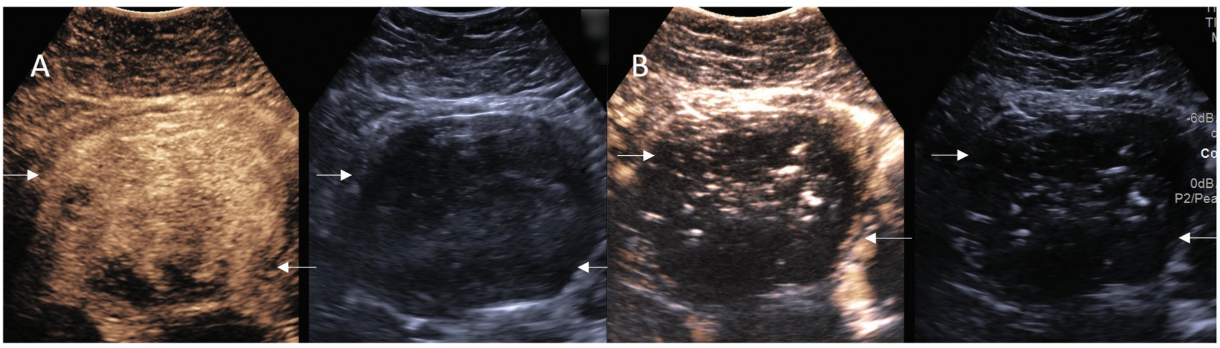

Fig. 7 Split screen contrast-enhanced ultrasound (CEUS) and simultaneous grayscale imaging (**A**) pre- and (**B**) post-embolization showing post-embolization devascularization of the uterus.

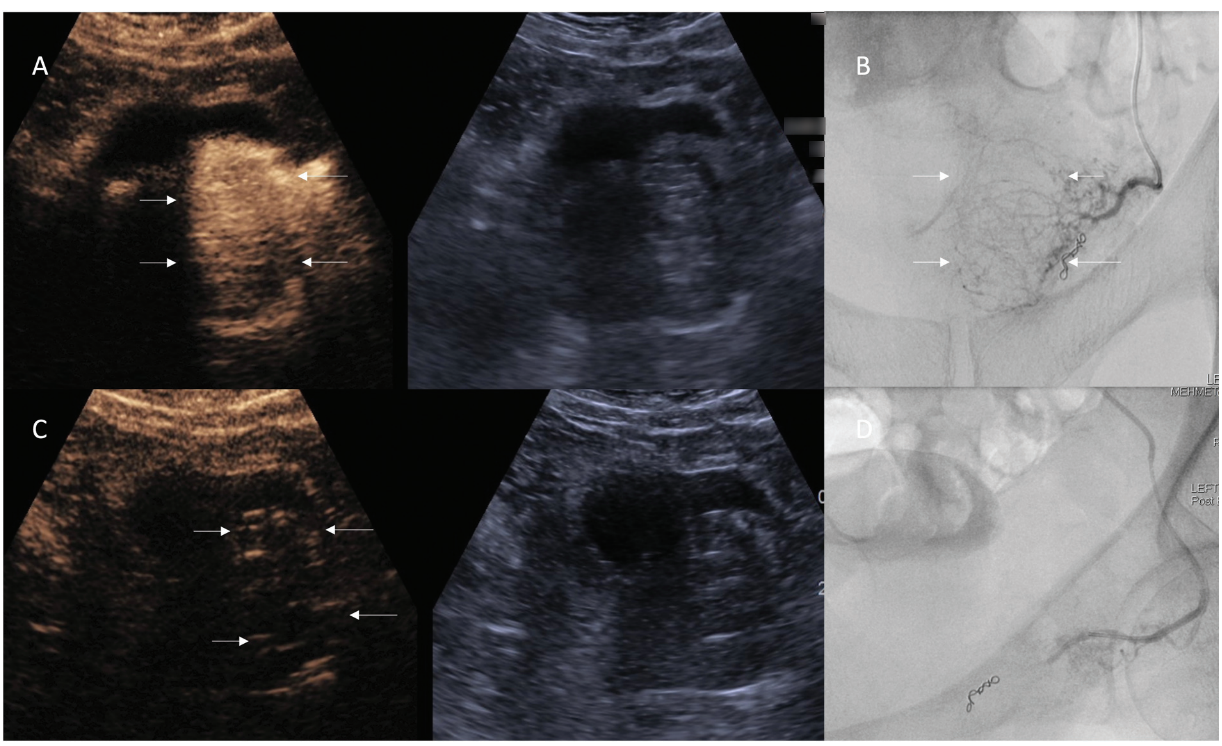

Fig. 8 Simultaneous grayscale and contrast-enhanced ultrasound (CEUS) image of the prostate (**A**) prior to embolization showing enhancement with (**B**) angiographic confirmation and (**C**) post-embolization showing no enhancement on CEUS or (**D**) angiography.

and may be of use when iodinated contrast taken up by the lesion obscures assessment.

In the follow-up period CEUS has been suggested to effectively demonstrate treatment failure on day 1 by evidencing enhancement. Beyond the immediate postoperative period, its role requires further evaluation but has been postulated in ensuring normal myometrial ischemia does not occur.[60]

Embolization endpoint assessment can also be performed for other viscera in a similar fashion including the prostate (►**Fig. 8**), kidneys, and chemoembolization of the liver.

Conclusion

Multiparametric US has challenged the conventional understanding of limitations of US in intervention. CEUS allows accurate depiction of the macrovasculature, microvasculature, and luminal integrity in real time. This can be done radiation free, at the bedside with the knowledge of a proven safety profile. The evolution of CEUS has meant it is an essential tool in intervention to guide procedures, identify complications, and evaluate postprocedure results. In the future the use of drug-loaded microbubbles and sonoporation open avenues of treatment for targeting focal tumors or thrombus disruption.[61,62] The skillset of interventionalists and development of these techniques cements the position of US in intervention.

Conflict of Interest
None declared.

Acknowledgment
The authors would like to acknowledge Dr. Aghiad Al-Kutoubi for is advice and guidance which has been invaluable. The authors would like to thank the editor for the kind invitation to write on this topic which we feel is of great importance in the ever-developing world of interventional radiology and we hope it can help progress innovation within the journal's community.

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