Title: General principles and overview of vascular contrast-enhanced ultrasound (CEUS)

Abbreviated title: Vascular CEUS

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**Type of manuscript:** review

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Acknowledgements / Conflict of interest statement:

VR has received a scholarship for his PhD studies on «Imaging of the carotid vulnerable plaque with contrast-enhanced ultrasound and multi-detector computed tomography angiography» from the Alexander S. Onassis Public Benefit Foundation.

VR has received honoraria from the Korean Society of Ultrasound in Medicine.
Author PS has received lecture fees from Bracco, Siemens, Samsung, Philips, and Hitachi.

The rest of the authors have no conflict of interest regarding the publication of this manuscript.
General principles and overview of vascular contrast-enhanced ultrasound (CEUS)
Abstract

Ultrasonography (US) is the first-line modality for the evaluation of vascular pathology. Although well-established in many diseases, US has inherent limitations which can occasionally hinder an accurate diagnosis. The technique’s value has been improved with the introduction of microbubbles as ultrasonographic contrast agents (UCA) and the emergence of contrast-enhanced ultrasound (CEUS), following the introduction of second generation UCA and the availability of modern contrast-specific techniques. CEUS offers valuable information about vascular disease both on a macro and a micro-vascular level, with well-established applications in carotid disease, post-interventional follow-up of abdominal aortic aneurysm and assessment of portal vein thrombosis. The purpose of this review is to discuss CEUS principles and present an overview of vascular applications.

Key words: Ultrasonography; carotid artery diseases; aorta; atherosclerosis; aneurysm

Introduction
Ultrasonography (US) is at the forefront of imaging of vascular disease, being an ubiquitous, cost-effective, well-tolerated and safe modality. One essential feature of US is its multifaceted nature, being able to provide anatomic information with B-mode and physiologic information with colour Doppler, power Doppler and pulsed-wave Doppler techniques; indispensable for assessment of vascular pathology. The multi-parametric nature of US is further advanced with the introduction of new technologies including elastography and contrast-enhanced ultrasound (CEUS), indicating the term multi-parametric ultrasound (MPUS) [1,2]. From the report of intravascular “bubble clouds” after intra-aortic catheter injection of saline by Gramiak and Shah in 1968, impressive advances have been made in the field of CEUS, both in terms of microbubbles structure and contrast-specific ultrasonographic techniques [3].

The added value of CEUS lies in compensating Doppler inherent limitations including lower signal-to noise ratio, lower sensitivity for slow flow particularly in deeper located vessels and technical artifacts such as Doppler angle dependence, aliasing and overwriting artifact. As a result, CEUS not only significantly improves blood flow visualization and wall delineation but also demonstrates microvascularity. Currently an increase of more than 30dB can be achieved in the blood’s echogenicity after administration of UCA, and even single microbubbles can be visualized circulating at the capillary level [4,5]. The introduction of second-generation ultrasound contrast agents (UCA) in 2001 and the emergence and widespread availability of low-MI contrast-specific techniques revolutionized CEUS and led to an increase of applications.

CEUS is already a well-established modality for a series of applications in adult patients, with official guidelines and recommendations available [5,6]. An explanation and guidance on how to perform CEUS was recently published by the European and World Federations for Ultrasound (EFSUMB and WFUMB) [7]. In this paper we will discuss the basic principles of CEUS and present an overview of vascular applications.
Microbubbles: structure and principles of interaction with ultrasound

UCA microbubbles consist of two parts: i) an internal gas encapsulated by ii) an outer shell consisting of phospholipids or albumin. Gases contained in first generation UCA like Levovist® (Bayer Schering Pharma, Berlin, Germany) consisted of small molecules readily traversing the microbubble’s shell and being diffused within the blood. Consequently, duration of enhancement was brief, leading to the use of more inert, hydrophobic and slowly diffusing gases such as sulfur hexafluoride or perfluorobutane in second generation UCA, including SonoVue® also marketed as Lumason® in the USA (Bracco), Definity® (Lantheus Medical Imaging), Optison® (GE Healthcare) and Sonazoid® (GE Healthcare). Each of these agents have different properties, with some being used exclusively for cardiac applications (Optison®) and some only for characterization of focal liver lesions (Sonazoid®). SonoVue® is the most frequently used UCA for vascular applications, being the only one licensed for use in macrovascular applications including cerebral arteries, extracranial carotid or peripheral arteries and the portal vein in adult patients, as well as microvascular applications in liver and breast.

SonoVue® consists of sulfur hexafluoride (SF₆) and a phospholipid monolayer shell, which is amphiphilic, with an outer side being hydrophilic and an inner being hydrophobic. With these properties, the shell can successfully contain the gas inside the microbubble. Also importantly, this shell is flexible, allowing for changes in microbubbles shape and size, a feature useful for generation of an US reflective signal [4]. Microbubbles contained in SonoVue® have a mean size of 2.5 μm (ranging from 1 to 10 μm). This is a crucial for three reasons: i) this size is large enough to prevent exit of the microbubble to the extravascular space, ii) it is small enough to permit passage from the lung micro-capillaries (having a mean diameter of 7 μm) and iii) allows for optimal oscillation in an US field. The resonance frequency of a microbubble is associated with the size of the microbubbles, and as a result, the resonance frequency of microbubbles ranges from 1 to 10 MHz, covering the frequencies used...
in diagnostic US. The mean diameter of SonoVue® (2.5 μm) has a resonance frequency of approximately 4 MHz, a frequency used for abdominal applications, explaining the excellent signal produced by microbubbles even with a small dose of UCA [4]. Ultrasound contrast agents dissolve some minutes after their intravenous administration, with the internal gas being exhaled by the lungs and the phospholipid shell metabolized by the liver. Since the kidneys are not involved in UCA metabolism, these agents are not nephrotoxic, offering a crucial advantage over CT and MR imaging contrast agents. Moreover, UCA have no effect on the thyroid, contributing to the safety profile [6]. One UCA’s property which is crucial for vascular CEUS is the strictly intravascular nature, never leaving the vascular bed (also termed blood-pool agents), in distinction to CT and MR imaging contrast agents, which typically gradually traverse the vascular wall into the extracellular space, reaching equilibrium in concentration between the intravascular and extravascular space. The property of being strictly intra-vascular is explained by the similar diameter of microbubbles to a red blood cell and therefore unable to pass through the vascular endothelium. An exception to this rule is Sonazoid® and Levovist® which are phagocytosed by Kupffer cells in the liver, a property which is not useful in vascular imaging [7,8].

The Mechanical Index (MI) is an important parameter in CEUS, representing the peak negative pressure divided by the square root of US frequency. In essence, the MI is an indicator of insonation power (amplitude of the US wave pressure) applied to the microbubbles and tissues within the examination field and is typically displayed on screen during an US examination. Typical MI values for conventional grayscale imaging are 1.6-2.0, and CEUS can be currently performed with much lower MI values [7-9].

Microbubbles tend to respond linearly at very low MI values, meaning that they reflect the same frequency with that emitted by the transducer (fundamental). When exposed to higher acoustic pressure, but still at a low MI, the microbubbles oscillate, which is a non-linear response and generate harmonic frequencies. In high MI values, microbubbles oscillate very
strong and are eventually disrupted, emitting strong signals detectable by the transducer. With the UCA shell flexibility, these agents can oscillate at MIs well below the breaking point, allowing for optimal visualization [4,8,9]. The non-linear oscillation, with the microbubbles periodically changing in size, expanding during the negative peak of US beam pressure wave and contracting during the positive peak can be usefully imaged. The microbubble expansion observed is greater than the contraction, explaining the non-linear nature of the response. This oscillation results in the generation of frequencies higher than the fundamental initially hitting the microbubble, termed “harmonic frequencies”. In the case of SonoVue® exposed at 3.5 MHz, frequencies generated include the sub-harmonic (half the fundamental), the ultra-harmonic (1.5 times the fundamental) and the 2nd harmonic (double the fundamental). Even the destruction of a microbubble exposed in high MI generates detectable signals of high intensity, which are only very transient and referred to as “stimulated acoustic emission”. These signals can be accurately visualized and with high sensitivity, even with conventional colour Doppler US, but this technique cannot be performed continuously due to the destruction of microbubbles [4].

Static tissues exposed to low-MI US beam generate linear signals. The opposite though happens when a higher MI is applied, with static tissues responding non-linearly and producing harmonic frequencies, similar to those originating from microbubbles and thus hampering UCA visualization, a further reason for using low-MI for CEUS examinations [8,9].

The safety profile of UCA is well established, with no evidence of cardiac, hepatic, thyroid or renal toxicity. Severe adverse reactions occur less frequently than with current CT contrast agents and at roughly the same rate with MR contrast agents. In a series of 23.188 patients undergoing abdominal CEUS, the rate of life-threatening allergic reactions was reported to be 0.001% with no death reported and only two patients complaining of serious adverse reactions [10]. Anaphylactoid reactions have been reported to affect 0.014% of patients undergoing CEUS, a rate lower than CT (0.035-0.095%) and comparable with MR imaging (0.001-0.01%) [10-14]. UCA were equally safe for echocardiographic applications
and for paediatric applications [17]. Albeit the favorable safety profile of UCA, departments where CEUS examinations are performed should be equipped with appropriate equipment and the personnel should be trained to treat allergic reactions [5-7].

**Principles of contrast-specific ultrasonographic techniques**

Based on the US wave-microbubbles interaction, there are two ways of visualizing the UCA signal, also corresponding to the type of UCA. First generation agents were basically imaged with high-mechanical index techniques (high-MI CEUS with values >0.7) and inevitably with intermittent scanning, and subsequent early destruction of microbubbles. These techniques deployed the conventional colour Doppler and power Doppler technique. In simple terms, the UCA were simply administrated in order to increase the signal deriving from blood flow and improve signal-to-noise ratio, enhancing Doppler signals [18].

Second generation agents are more stable, allowing continuous scanning, taking advantage of the emergence of low-MI CEUS techniques, evolving into the standard method for CEUS imaging. Current machines image adequately with MI as low as ≤0.1 (reaching 0.05) and maintain microbubble preservation [4,8]. Pulse-inversion technique is the latest advance in contrast-specific technologies and currently the most commonly used technique. This technique makes use of the different frequencies generated by microbubbles and static tissue to separate them and thus exclusively visualize microbubbles. The transducer initially emits a sequence of two pulses in rapid succession, identical in frequency and amplitude but the second pulse is 180° out of phase compared to the first, actually representing an inverted copy. Static tissue reflects the same frequencies with those received and thus the two pulses are cancelled and generate no detectable signal in the transducer. Microbubbles though generate harmonic frequencies, which are not opposite and thus added to produce strong signal [6] (Fig. 1). Amplitude modulation technique makes use of a series of pulses with different amplitude, whose reflected signals from microbubbles can be selectively detected and visualized. This
technique has better depth penetration than pulse-inversion techniques, although with poorer resolution and could thus be preferred for deep situated blood vessels [5,7,19-23].

In an attempt to minimize microbubbles disruption, a useful strategy is to continuously image for the first 60 seconds (complete arterial phase and part of venous) and thereafter scan intermittently with short loops at 30 seconds intervals to observe the wash-out. This technique is more useful for liver applications, as with vascular applications continuous scanning of 60 seconds is usually sufficient for establishing the diagnosis and collecting relevant clinical information [7].

In low-MI techniques, re-observation of arterial enhancement and microbubbles arrival is possible after destruction of microbubbles with a high-MI pulse, lasting for a couple of seconds. This pulse destroys every microbubble in the plane of insonation and allows the observation of the filling pattern of structures examined for a second or third time. This strategy can be usefully applied in vascular pathology, including: i) re-evaluation of the origin of an endoleak, ii) analysis of enhancement of a plaque and iii) evidence of contrast extravasation in vascular injury.

The injection of UCA is usually performed with a bolus intravenous injection, followed by 5 to 10 ml of normal saline as a flush. Antecubital fossa veins are usually used although central venous lines and ports may also be used if a peripheral vein cannot be accessed. According to the manufacturer, 2.4 ml of SonoVue® is the recommended dose for vascular applications. Nonetheless, the dose can be adjusted according to the patient characteristics and scanning device. For instance, if a high frequency transducer (>10 MHz) is to be used for superficial applications (e.g. scrotal), an increased dose of 4.8 ml should be considered. In order to avoid microbubble destruction during administration, a 20 gauge cannula should be used and the dose should be administered either directly to the cannula or via the straight line of a three-way stopcock [4,7]. A study has indicated that no difference in
enhancement is observed if catheters ranging from 18 to 21 gauge are used [24]. A continuous
and constant delivery of UCA (at about 1 ml/min) can be sometimes performed in order to
lengthen the duration of enhancement and time of examination, often used in oncologic
applications for assessment of response to therapy or in myocardial perfusion studies in
cardiology and in contrast-enhanced voiding urosonography for the diagnosis of vesicoureteral
reflux in children [4,7].

Temporal Maximum Intensity Projection (MIP) is another feature of CEUS, useful for
demonstration of vascular architecture. In this mode, the ultrasound device records bright
echoes for a defined time period and accumulates them in order to form detailed images of the
macro- and micro-vasculature. To achieve this, the physician should initially apply a high-MI
pulse in order to disrupt all microbubbles and erase every signal. After this point, every
microbubble entering the imaging plane adds its signal to the aggregated image, thus forming
the vascular architecture. In essence, the US transducer acts as an “open shutter camera” and
produces images similar to those produced with MIP in CT and MR imaging. Colour coding in
temporal maps has been recently introduced by some manufacturers to better and more
objectively evaluate microbubbles arrival with the MIP technique [25].

Useful tips regarding optimal application of vascular CEUS can be found in table 1
[7,9].

Quantitative CEUS

CEUS can be subjectively and qualitatively evaluated and interpreted by the physician
performing the examination. However, current technology also provides the possibility to
quantify enhancement and generate quantitative indexes. Quantitative analysis can be
performed either with a bolus injection or with the so called “burst-replenishment” technique,
where microbubbles are destroyed by a high-MI pulse after having reached an adequate
concentration in the vascular bed and then re-observed during refilling the field-of-view. The
fact that UCA remain strictly within the vascular bed means that calculation of tissue perfusion and microvasculartiy indices is much more straightforward, compared with agents of CT and MRI that diffuse in the extravascular space [4,7]. Quantitative CEUS is performed using Time-Intensity Curve analysis (TIC), where the signal intensity of a region-of-interest is plotted over time. The curve formed represents the pattern of enhancement, increasing with time during the arterial enhancement, reaching a plateau of variable degree and duration and then decreasing during wash-out. Quantitative parameters calculated include peak enhancement, time to peak and area under the curve. An example of how this analysis can help with vascular disease is the quantification of enhancement in carotid plaques, in order to quantify intraplaque neovascularization [26] and the TIC analysis of an abdominal aortic aneurysm sac post-EVAR for detection of endoleaks [27,28].

**CEUS artifacts**

Many artifacts affect CEUS, some of which are common with conventional US and some are exclusively encountered in contrast-specific techniques. In the former case, artifacts include increased through transmission, mirror artifact, acoustic shadowing and reverberation (Fig. 2). These artifacts may appear accentuated in CEUS images, since techniques like spatial compounding and frame averaging are inactive to reduce microbubble disruption. In the second category, there are artifacts caused by the inadvertent disruption of microbubbles such as the signal loss due to continuous scanning in one image plane or the near field signal loss caused by an inappropriately high MI [9,29]. In this section, we will focus on CEUS artifacts more related to vascular applications of CEUS.

Nonlinear propagation artifact is a form of pseudo-enhancement observed in tissues or the vascular wall situated deep to the vascular lumen. This artifact is caused by the non-linear propagation of US wave through a cloud of high concentration of microbubbles (situated within the vascular lumen) and is visualized as apparent bubble signals in areas with no true
enhancement. In vascular applications, this artifact may lead to false diagnosis of neovascularization in carotid plaques affecting the distal wall of the carotid. True microbubble signals can be differentiated based on comparison with grayscale image, showing only those signals artifactually produced and on observation of enhancement dynamics exhibited by true microbubble movements in all phases. This artifact can be avoided by avoiding an excessively high dose of UCA. Another artifact observed is the visualization of a hyperechoic structure on grayscale image, which is unsucessfully suppressed and thus appears on contrast-specific image as bright echoes. This can be misinterpreted as enhancement although discrimination is easy based on the fact that true microbubbles move but artifactual echoes are static. In vascular applications this artifact is frequently encountered due to wall calcifications which should not be mistaken for plaque ulcerations or neovascularization [7,29-31] (Fig. 2).

In colour Doppler US, microbubbles tend to significantly increase the signal intensity of blood vessels and adjacent perfused static tissue. This means that low intensity signals previously filtered now become visible, whilst the intensity of visualized flow signals is markedly enhanced, resulting in excessive colour blooming or overwriting artifact, demonstrating flow signals in areas with no flow (e.g. mural thrombus) and obscuring the surface of a plaque and vascular wall (Fig. 2). Moreover, this artifact may cause false interpretation of findings as turbulent flow, mimicking stenosis. In pulsed-wave Doppler technique, early reports showed that peak systolic velocity could be falsely measured, up to 45% greater than the real value, when the measurement was performed after UCA administration, attributed to the increase of signals by the UCA. Nevertheless, this observation was made with older systems and more recent studies have not been confirmatory [20,32,33]. Finally, pulsed-wave Doppler technique may record high-intensity transient signals superimposed on the Doppler waveform, appearing as sharp spikes. These spikes, also audible as crackling sounds, are caused by the disruption of microbubbles by the high-MI pulse used for Doppler technique (Fig. 2). Based on all these Doppler-related artifacts, it is recommended that Doppler
techniques including colour Doppler visualization of blood flow and pulsed-wave Doppler interrogation should be performed prior to the administration of microbubbles and CEUS should be performed with contrast-specific techniques [20].

**Overview of vascular CEUS**

The role of CEUS in vascular imaging is multifaceted, with the technique involved in initial diagnostic work-up, guiding of interventional treatment and follow-up. Moreover, there are various types of vascular applications which can be convened into four groups for educational purposes as follows, described in table 2 and illustrated in figure 3: i) luminal applications, ii) characterization of intraluminal pathology, iii) characterization of vascular wall, iv) investigation of potential extravascular leakage. The 2017 version of the EFSUMB guidelines and recommendations on vascular CEUS are presented in table 3 [6]. Similarly to unenhanced US, CEUS of the carotid and other superficial arteries can be performed with a linear-array transducer of 5-10 MHz, while the abdominal aorta, portal vein and other abdominal blood vessels can be examined with a convex transducer of 2.5-5 MHz [5].

**Carotid Artery**

In carotid artery disease, CEUS has the potential to provide information both on a macro-vascular level and a micro-vascular level. In the first case, CEUS offers improved blood flow visualization and vascular wall delineation, thus providing accurate grading of stenosis, with a strong correlation with conventional angiography for diametric stenosis of the internal carotid artery and with MR imaging for area stenosis [34-36]. Furthermore, CEUS is comparable to CTA and MRA for distinguishing occlusion from pre-occlusive stenosis and outperforms conventional Doppler US as it is more sensitive in detecting a thread-like lumen in pre-occlusive stenosis [37-39].

In terms of plaque delineation, the use of microbubbles improves delineation of endovascular border, including plaque, thrombus or vascular wall in the pre-, intra- and post-
stenotic part of the vessel [40]. In this respect, UCA can accurately diagnose superficial plaque ulcerations, which can be detected with improved sensitivity compared to colour Doppler US and represent an essential feature of plaque vulnerability [41-44] (Fig. 4). On a microvascular level, CEUS can accurately evaluate intraplaque neovascularization, both qualitatively and quantitatively using TIC analysis. CEUS findings of neovascularization correlate with histologic findings of neovascularity and inflammation and are predictors of cerebrovascular symptoms as plaques in symptomatic patients exhibit significantly higher enhancement [41,45-54]. In carotid inflammation including transient perivascular inflammation of the carotid artery (TIPIC) syndrome, CEUS not only better delineated vascular wall irregularities caused by inflammation but importantly highlights wall enhancement, consistent with inflammatory vascularization, a marker of disease activity [55,56] (Fig. 5).

Beyond these applications, CEUS is valuable in evaluating re-stenosis after stenting of the internal carotid artery, improving visualization of stent lumen [57], has the potential to identify carotid dissection [58] (Fig. 6), although MR imaging is still the reference method, able to demonstrate intramural haematoma and finally can better delineate fistulae and demonstrate flow within aneurysms or pseudoaneurysms occurring as a complication after intervention [40,59].

Aorta

Contrast-enhanced ultrasound can readily evaluate an aortic aneurysm, whilst also detecting aortic aneurysm rupture by demonstrating microbubbles extravasation, although CTA remains the standard method for this diagnosis [60]. In the setting of inflammatory abdominal aortic aneurysm, CEUS can depict the enhancement of aneurysm wall, caused by inflammatory vascularity [61]. As a result, CEUS can discriminate covered rupture of an aneurysm, showing mural thickening with no enhancement and inflammatory aortic aneurysm, exhibiting marked enhancement of the vascular wall [62]. Similarly to carotid arteries, dissection of the
abdominal aorta can be readily visualized with CEUS and with improved accuracy compared with colour Doppler US, particularly with the improved sensitivity for slow flow, commonly encountered in the false lumen. Microbubbles are also helpful in differentiating true from false lumen since the first enhances earlier than the second. Importantly, CEUS offers the opportunity to assess tissue perfusion during the same examination readily demonstrating parenchymal organ ischemia, as a complication of dissection [62,63].

After endovascular aortic repair (EVAR), an endoleak represents a common complication and is defined as the presence of blood flow outside the stented lumen, remaining within the borders of the aneurysmal sac and within the thrombotic material filling the latter. Based on the origin of the endoleak, five different types are documented. A Type I endoleak is a high flow endoleak originating from the proximal (Ia) or distal (Ib) end of the stent and into the aneurysmal sac. A Type II endoleak is the most common, may be a high or low flow leak originating from the inferior mesenteric artery or the lumbar arteries and is further classified in type IIa if a single vessel is involved or type IIb if two vessels are affected. A Type III endoleak is rare, being a high flow leak originating from a defect in the stent graft. A Type IV endoleak is associated with porosity of the stent graft material and is observed during stent implantation, requiring no further treatment. Type V endoleak is associated with an enlargement of the aneurysm sac with no detectable source (“endotension”) [62] (Fig. 7).

This is a clinically significant classification given the different treatment required for different types of endoleaks. Endoleaks type I and III require interventional treatment given their higher risk for rupture, whereas endoleaks type II can be followed up with imaging until spontaneously thrombosed. If spontaneous resolution is not achieved, but an enlargement of aneurysmal sac of more than 1 cm is documented, an intervention may be required [62]. CTA is the most commonly used modality for detection of endoleaks, although it entails the disadvantage of ionizing radiation and use of a nephrotoxic contrast agent, particularly harmful as there is a lifelong need for imaging of these patients. CEUS can be able to diagnose
endoleaks with improved accuracy compared to CTA and re-categorizes previously diagnosed type V endoleaks [27,64-69] (Fig. 8, 9). Detection of endoleaks with CEUS is typically performed with qualitative assessment of enhancement, although quantitative analysis with TIC has also been considered, with promising results [27,28]. CEUS could be potentially incorporated in imaging algorithms of endoleak detection as a second complementary step to colour Doppler US screening. Further imaging with CTA could be safely deferred if no evidence of endoleak is recorded on CEUS, whereas CTA could be performed in those cases with abnormal or equivocal findings.

Hepatic vessels

The portal vein can be affected by thrombosis, the deposition of thrombotic material in any part of the portal venous system, which may be completely or partially occluded. Portal vein thrombosis is encountered in cirrhotic livers with a prevalence of 0.6-11% [70]. The thrombus may be bland, usually being silent and having no clinical importance, but may be malignant, almost always associated with hepatocellular carcinoma of the liver. The latter finding carries great clinical significance with alteration of treatment options and upstages the disease. Portal vein thrombus is typically hyperechoic but may be anechoic, thus making the vessel appear normal on B-mode technique or hypoechoic. Grayscale imaging of the portal vein should be complemented with colour Doppler technique and pulsed-wave Doppler interrogation. No blood flow signals will be detected in case of complete occlusion by thrombus. If blood flow signals with arterial waveform on spectral examination are demonstrated inside the thrombus, this is a highly specific sign of malignancy although moderately sensitive. Continuity of thrombus with hepatic tumour is another feature in keeping with malignant nature of thrombus, evident on grayscale imaging.

CEUS is characterized by improved sensitivity for visualization of thrombus and neovascularity (suggesting malignancy) within the thrombotic material. Bland thrombus
appears as a filling defect within the portal vein, avascular in all phases, although most conspicuous in the portal venous phase. Malignant thrombus has the same enhancement pattern with the tumour of origin, including rapid arterial phase hyper-enhancement simultaneously with hepatic artery and rapid or late and mild portal venous wash out (Fig. 10).

The thrombus can be targeted for biopsy under US-guidance, attempting to take specimens from enhancing regions of the thrombus. CEUS has been found very useful also in complementing US-guided biopsy of the thrombus in order to establish the diagnosis of benign or malignant thrombus. The tumour causing the thrombus may not be visible with US, although sometimes it can be detected during scanning the liver in any phase after UCA administration. Washed-out areas detected in the portal venous phase can be observed in the arterial phase (for vascularization) after re-injection for confirmation of diagnosis. Compared with CT and MR imaging, CEUS offers the advantage of continuous and real-time scanning of thrombus vascularity for several minutes, whereas the former techniques typically record a few “snapshots” of thrombus enhancement [70-75].

Peripheral Arteries

When it comes to peripheral arteries, conventional Doppler US techniques are well-established and CEUS did not demonstrate significant superiority for detecting stenosis, although it can be used for detection of complications after interventional procedures such as in the case of femoral artery pseudoaneurysm (Fig. 11, 12). Vascular injury after trauma, along with other causes, may result to the formation of aneurysms or more commonly pseudoaneurysms, entities potentially requiring interventional treatment if becoming symptomatic and ruptured. CEUS not only can detect such a complication but can also potentially determine the anatomic location of ongoing hemorrhage origin [76] (Fig. 13, 14). In a paediatric population series, pseudoaneurysm were encountered in 17% of children
sustaining liver or splenic injuries and CEUS was 83% sensitive and 92% specific for this diagnosis, offering a valuable alternative to CT for diagnosis and follow-up of this entity [77].

Conclusion

CEUS is a well-suited modality for evaluation of vascular pathology given its favorable inherent characteristics such as the strictly intravascular nature of microbubbles used as UCA. Physicians performing this technique should be familiar with basic physical principles in order to recognize artifacts, avoid misdiagnosis and correct them by making adjustments to scanning parameters. CEUS has already been studied in many vascular applications such as carotid disease, post-EVAR aortic evaluation and portal vein thrombus characterization, providing promising results and thus being included in official recommendations, although there are many more potential applications not yet thoroughly studied.

References


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Tables

- Place the **Focus** just deep to the target vessel in order to achieve homogeneous energy distribution over the imaging plane.

- The **Gain** should be adjusted at the beginning of the examination so that no UCA signals are lost due to non-detection (too low gain) or obscuration by noise and erased because of signal saturation (too high gain). The image prior to UCA administration should be virtually black except for highly echogenic structures like the diaphragm, helpful for orientation.

- The **Dynamic Range** (range of signal intensities displayed) should be wide if fine differences of enhancement are sought for (as in lesion characterization) but can be kept low to make the blood vessels stand out brighter, with good contrast with background.

- A **Frame Rate** of ≥10 Hz (or frames per second) is useful for assessing wash-in patterns of focal liver lesions or fast-flowing blood as in some endoleaks, but at the expense of microbubble disruption.

- Carefully choose **UCA Dose** as too much will result to flare (signal saturation) and acoustic shadowing deep to microbubbles, while too little may cause inadequate enhancement.

- The **Mechanical Index (MI)** should be properly adjusted. Too high MI will cause microbubble disruption, particularly in the near field, whereas too low MI will lead to poor visualization of the far field (e.g. aortic applications).

- **Video Clips** should be recorded for re-evaluation of pathology, such as in the case of endoleak characterization.

- **Prolonged scanning** in the same plane should be avoided as it causes disruption of microbubbles in a specific location, a phenomenon observed more commonly in parenchymal organs applications.
CEUS imaging in **great depth** is always a challenge due to wave attenuation, limiting depth penetration of a low-MI wave. When possible lower insonation frequency can be used (with slightly lower spatial resolution) or different and suitable imaging windows should be chosen to bring the examined organ closer to the transducer (e.g. lateral decubitus position for evaluation of renal vascularity).

**Table 1.** Tips for performing vascular CEUS.

| UCA: Ultrasound Contrast Agents, MI: Mechanical Index, CEUS: contrast-enhanced Ultrasound | Table 1. Tips for performing vascular CEUS. |
### Table 2. Overview of various types of potential vascular CEUS applications grouped in four categories.

<table>
<thead>
<tr>
<th>Category</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>i) Luminal applications</td>
<td>• Grading stenosis (e.g. carotid)</td>
</tr>
<tr>
<td></td>
<td>• Occlusion vs pre-occlusive stenosis</td>
</tr>
<tr>
<td></td>
<td>• Detection of superficial plaque irregularities and ulceration</td>
</tr>
<tr>
<td>ii) Characterization of intraluminal pathology</td>
<td>• Evaluation of atherosclerotic intraplaque neovascularization</td>
</tr>
<tr>
<td></td>
<td>• Characterization of portal vein thrombus</td>
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<tr>
<td></td>
<td>• Characterization of venous thrombus in peripheral veins</td>
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<tr>
<td>iii) Evaluation of vascular wall</td>
<td>• Qualitative and quantitative evaluation of wall vascularity in inflammatory conditions (e.g. aortitis, TIPIC)</td>
</tr>
<tr>
<td>iv) Investigation of potential extravascular</td>
<td>• Endoleak detection after EVAR</td>
</tr>
<tr>
<td>leakage</td>
<td>• Pseudoaneurysm (e.g. peripheral arteries, parenchymal organs)</td>
</tr>
<tr>
<td></td>
<td>• Extravasation (e.g. aneurysm rupture, vascular injury)</td>
</tr>
</tbody>
</table>

TIPIC: TransIent Perivascular Inflammation of the Carotid artery

EVAR: EndoVascular Aortic Repair
<table>
<thead>
<tr>
<th>Vascular system</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid arteries</td>
<td>Differential diagnosis between carotid / vertebral artery occlusion and severe stenosis.</td>
</tr>
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<td>Evaluation of carotid plaque neovascularization, suggestive of plaque instability.</td>
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<tr>
<td>Abdominal aorta</td>
<td>Identification of dissection (also in carotid &amp; vertebral arteries)</td>
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<td>Characterization of inflammatory vascular disease</td>
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<td>Follow-up of endovascular aortic repair (EVAR) for detection and classification of endoleaks.</td>
</tr>
<tr>
<td>Cerebral vessels</td>
<td>Improved diagnostic capabilities of contrast-enhanced transcranial Doppler.</td>
</tr>
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*Table 3.* The 2017 version of the EFSUMB guidelines on vascular use of CEUS.
Figures legends

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Fig. 13E

Fig. 13 Hepatic artery pseudoaneurysm. B-mode image (A) showing an enlarged anechoic rounded structure with thickened wall, situated near the porta hepatis. Colour Doppler US (B) showing the filling of the structure with colour Doppler signals, establishing the diagnosis of pseudoaneurysm. Note that parts of the cavity are not filled with signals due to lack of sensitivity. CEUS image (C) showing the filling of the pseudoaneurysm with microbubbles except for the limited mural thrombus, which appears anechoic. CTA (D) confirming the diagnosis of a hepatic artery pseudoaneurysm, with mural thrombus and calcifications. After the placement of a stent (arrowhead), CEUS (E) confirms the exclusion of the aneurysmal sac from circulation by documenting lack of enhancement.
Fig. 14A

Fig. 14 Pseudoaneurysm formation after renal biopsy. B-mode image (A) shows a subcapsular renal haematoma (asterisk). Colour Doppler US (B) demonstrates blood flow signals in the renal hilum, with no clear evidence of further pathology. CEUS image (C) demonstrates a pseudoaneurysm (arrow), while the sub-capsular haematoma (asterisk) and an intra-parenchymal haematoma (arrowhead) became prominent due to lack of enhancement. Follow-up CEUS image (D) after embolization of the pseudoaneurysm showed absence of the pseudoaneurysm and normal perfusion of the renal parenchyma, confirming the success of the intervention.
Fig. 14B

Fig. 14 Pseudoaneurysm formation after renal biopsy. B-mode image (A) shows a subcapsular renal haematoma (asterisk). Colour Doppler US (B) demonstrates blood flow signals in the renal hilum, with no clear evidence of further pathology. CEUS image (C) demonstrates a pseudoaneurysm (arrow), while the sub-capsular haematoma (asterisk) and an intra-parenchymal haematoma (arrowhead) became prominent due to lack of enhancement. Follow-up CEUS image (D) after embolization of the pseudoaneurysm showed absence of the pseudoaneurysm and normal perfusion of the renal parenchyma, confirming the success of the intervention.
Fig. 14C

Fig. 14 Pseudoaneurysm formation after renal biopsy. B-mode image (A) shows a subcapsular renal haematoma (asterisk). Colour Doppler US (B) demonstrates blood flow signals in the renal hilum, with no clear evidence of further pathology. CEUS image (C) demonstrates a pseudoaneurysm (arrow), while the sub-capsular haematoma (asterisk) and an intra-parenchymal haematoma (arrowhead) became prominent due to lack of enhancement. Follow-up CEUS image (D) after embolization of the pseudoaneurysm showed absence of the pseudoaneurysm and normal perfusion of the renal parenchyma, confirming the success of the intervention.
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