Ultrasound in Med. & Biol., Vol. 00, No. 00, pp. 1−11, 2020

0301-5629/$ - see front matter

https://doi.org/10.1016/j.ultrasmedbio.2020.11.032

● *Original Contribution*

ARTIFACTS IN CONTRAST-ENHANCED ULTRASOUND DURING FOLLOW-UP AFTER ENDOVASCULAR AORTIC REPAIR: IMPACT ON ENDOLEAK DETECTION IN COMPARISON WITH COMPUTED TOMOGRAPHY ANGIOGRAPHY

Felix Frenzel,* Reinhard Kubale,* Alexander Massmann,* Paul Raczeck,* Philippe Jagoda,* Christian Schlueter,† Jonas Stroeder,* Arno Buecker,* and Peter Minko*

* Clinic for Diagnostic and Interventional Radiology, Saarland University Medical Centre, Homburg/Saar, Germany; and † Clinic for General, Abdominal and Vascular Surgery, Saarland University Medical Centre, Homburg/Saar, Germany

(*Received* 19 *August* 2020; *revised* 21 *November* 2020; *in final from* 25 *November* 2020)

Abstract—The study described here systematically analyzed how specific artifacts in contrast-enhanced ultrasound (CEUS) can affect the detection of endoleaks during follow-up after endovascular aortic repair (EVAR). Patients undergoing EVAR of atherosclerotic or mycotic abdominal aortic aneurysms using various standard and branched stent-graft material for visceral and iliac preservation were enrolled over 5 y and followed up with computed tomography angiography (CTA) and CEUS simultaneously. CEUS artifacts were frequently identified after EVAR procedures (59% of examinations) and were caused mainly by contrast agent, different prosthesis or embolization material and postinterventional changes in the aneurysm sac. This article describes how to identify important artifacts and how to avoid false-negative or false-positive interpretations of endoleaks. Despite artifacts, CEUS had higher sensitivity for endoleak detection after EVAR than CTA. CEUS was superior to CTA in the identification of late endoleaks type II and in follow-up examinations after embolization procedures, where beam-hardening artifacts limited CTA. (E-mail: Felix.Frenzel@uks.eu) © 2020 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: **Artifact, Endoleak, Contrast Agent, Sulfur hexafluoride, Endovascular aortic repair, Abdominal aortic aneurysm.**

INTRODUCTION

Endovascular aortic repair (EVAR) is a well-established treatment option for abdominal aortic aneurysms (AAAs) (Greenhalgh et al. 2004; Prinssen et al. 2004; Schermerhorn et al. 2008), with a spectrum of different endografts that allow for adaptation to the individual patient's anatomy (Massmann et al. 2018). Lifelong post-interventional surveillance is routinely needed (Cuypers et al. 1999; White 2000) to monitor aneurysm sac size, perfusion and stent position.

Endoleak, which is defined as persistent blood flow into the aneurysmal sac, is the most frequent reason for re-interventions after EVAR (Hiatt and Rubin 2004; Franks et al. 2007). Secondary interventions are necessary in an average of 8.7% of cases after 12 mo (Hobo and Buth 2006).

Address correspondence to: Felix Frenzel, Saarland University Medical Centre, Clinic for Diagnostic and Interventional Radiology, Kirrberger Strasse, Geb. 50.1, 66421 Homburg, Germany. E-mail: Felix.Frenzel@uks.eu

Diagnosis and stratification of endoleaks can be difficult, and there is wide heterogeneity in follow-up strategies used among EVAR centers (Tse et al. 2014). CT angiography (CTA) is considered the reference standard imaging modality (Mirza et al. 2010; Tse et al. 2014; Faccioli et al. 2018). Contrast-enhanced ultrasound (CEUS) has been established as a viable and tolerable (Chisci et al. 2018), as well as time- and cost-effective (Faccioli et al. 2018), imaging modality for the detection of endoleaks after EVAR. Furthermore, CEUS allows radiation-free, real-time dynamic examinations that offers comparable or even superior diagnostic performance in endoleak detection and classification versus CTA, if used by experienced sonographers (Bargellini et al. 2005; Clevert et al. 2008; Pfister et al. 2009; Cantisani et al. 2015; Rubenthaler et al. 2017). CEUS uses a contrast agent, composed of biologically inert microbubbles with no nephrotoxicity and an extremely low rate of adverse events with one large multicenter trial quoting an incidence in less than 0.01% of examinations (Piscaglia and

Bolondi 2006). Thus, it is recommended as a follow-up examination in EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) guidelines (Piscaglia et al. 2012). According to meta-analyses, CEUS reaches a pooled sensitivity of 98% and a pooled specificity of 88% for detection of endoleaks (Karthikesalingam et al. 2012).

The diagnostic accuracy of CEUS may, however, be reduced by misinterpretation of artifacts (Dietrich et al. 2014; Fetzer et al. 2018). Therefore, our study's purpose was to classify artifacts in CEUS in follow-up after EVAR with various standard and branched stent grafts and evaluate the artifacts' relevance for endoleak detection in comparison to corresponding CTA examinations.

METHODS

Patients

All patients undergoing EVAR between November 2012 and June 2017 were evaluated for inclusion and followed up prospectively using a standardized protocol. The local ethics committee provided approval for this study (Medical Chamber No. 13707). Written informed consent was obtained from all patients.

Patients underwent CTA and CEUS the first week after EVAR and at 3, 6 and 12 mo and yearly post-EVAR implantation. To assess the clinical significance of CEUS artifacts in endoleak detection, corresponding pairs of CTA and CEUS examinations were performed no more than 3 d apart in each eligible patient. Patients with good assessability of stent grafts on CEUS had their long-term examinations carried out with CEUS and CTA in alternating fashion to decrease radiation and CT contrast agent dose. All CTA and CEUS examinations were performed more than 3 d apart, and patients followed-up with CTA alone were excluded from the study.

Endoleaks were categorized into five types, as proposed by Baum et al. (2003). Two senior radiologists (with 12 y of experience in radiology/5 y of experience in CEUS and 40 y of experience in radiology/7 y of experience in CEUS, respectively) reviewed all paired examinations retrospectively on a consensus basis, beginning with CEUS before correlating CTA scans.

The radiologists' consensus decision based on both imaging modalities and the follow-up images was defined as the gold standard. Mainly late occurring endoleaks, which were not detected on CTA, were accepted as true-positive CEUS results despite negative CTA.

CEUS examination

Contrast-enhanced ultrasound was performed using an Acuson S2000/S2000 HELX Evolution ultrasound unit (Siemens Healthineers, Erlangen, Germany; software versions VB21 B through VE10 B) with SonoVue contrast agent (Bracco Imaging, Milan, Italy). A mean dose of 1.51 ± 0.23 mL of contrast agent (range: 1.2−2.0 mL), followed by a normal saline flush (10 mL), was used per series. In all patients a standardized protocol was performed using a 4 C1 (1−4.5 MHz, curved vector; Siemens Healthineers) or 6 C1 HD transducer (1.5-6 MHz, curved vector; Siemens Healthineers), with two consecutive series of CEUS images (two-bolus principle) acquired in real-time imaging Cadence mode at a low mechanical index <0.2 (Emanuel et al. 2020).

Siemens' Cadence contrast pulse sequencing (CPS) is a multipulse sequencing technique that combines amplitude modulation and pulse inversion. It utilizes sequences of two equal pulses and a third pulse with twice the amplitude and a 180° inverted phase. When reflections of all three pulses returning to the transducer are summed, waves at linear frequencies cancel each other, while non-linear components of the reflected waves are preserved, providing a strong contrast of microbubbles' non-linear harmonic oscillation (Quaia 2007; Emanuel et al. 2020).

Contrast-enhanced ultrasound was performed in longitudinal and cross sections, scanning from the level of the inferior mesenteric artery (IMA) over the entire aortic graft, including the iliac arteries, to identify leakage. by use of FLASH mode (Metoki et al. 2006), a high mechanical index "burst" was applied to destroy remaining contrast bubbles, and a second contrast bolus was administered to depict the time course and extent of previously detected endoleaks at the corresponding leakage site. In cases of complex stenting including chimneys (Supplementary Table S1, online only), a third series with contrast agent was run to document renal perfusion and chimney patency.

All ultrasound measurements were performed unaware of CTA results. Sonographic assessability of each ultrasound examination was categorized on a 3-point Likert scale (1 = limited, 2 = good, 3 = excellent) by consent of both radiologists.

CT angiography

Multislice CTA was performed with a commercially available CT scanner (SOMATOM Definition AS 64, SOMATOM Edge or Force; Siemens Healthineers) during a single breath-hold in inspiration for each of the three phases (native, arterial and venous) acquired. All patients were scanned with a kilovoltage of 120 kV and an automated dose-optimized selection of tube current levels (CARE dose 4 D).

Computed tomography angiography was performed *via* a peripheral arm vein by use of an automated intravenous injection with a commercially available injector

(Accutron CT-D, Medtron AG, Saarbrücken, Germany), using body weight-adapted doses (1 mL/kg), approximately 70−100 mL of iomeprol (Imeron 400, Bracco Imaging) at high flow rates (3.0−5.0 mL/s), to ensure optimal vessel contrast. Each contrast medium bolus was followed by a normal saline flush of 30−50 mL. Every examination was performed in accordance with ESUR's Contrast Agent Guidelines, using the lowest dose of contrast medium consistent with adequate diagnostic image quality (Van der Molen et al. 2018). Automated bolus tracking was achieved using a region of interest set in the descending abdominal aorta at the level of the celiac trunk with a trigger threshold of 120 Hounsfield units.

Iterative reconstruction protocols (Force: ADMIRE; Edge, AS 64: SAFIRE) were applied and routine post-processing was performed using thin-section reconstructions with a section thickness of 0.75 mm, an increment of 0.5 mm and a smooth reconstruction kernel (QR40). Image analysis was performed using axial sections and sagittal and coronal multiplanar reformations, as well as axial, sagittal and coronal maximum intensity projections with a section thickness of 10 mm.

Table 1. Numbers and kinds of different artifacts observed in 97 individual contrast-enhanced ultrasound examinations as well as correlation to their point in the study's time course

Artifacts observed in 97 examinations	n (total)	Point 1	Point 2	Point 3
1. Contrast agent related				
Saturation	12	5 (42%)	5 (42%)	2 (17%)
Glare/reverberation	7	2 (29%)	4 (57%)	1 (14%)
Attenuation by contrast agent	3	2 (66%)	1 (33%)	0
2. Intervention related				
Gas bubbles	7	4 (57%)	2 (29%)	1 (14%)
Fibrin strings/ inhomogeneous thrombosis	4	2 (50%)	2 (50%)	0
Interventional material (coils, acrylic resin)	10	6 (60%)	2 (20%)	2 (20%)
3. Stent graft specific				
Acoustic shadowing of graft material	6	2 (40%)	4 (60%)	0
Ring artifact (Ovation)	3	2 (67%)	1 (33%)	0
Reverberation of graft material	2	1 (50%)	1 (50%)	0
4. Transducer specific				
Side lobes/focal banding (4 C1 transducer)	3	3 (100%)	0	0

Statistical analysis

Descriptive statistics were used to evaluate demographic data, depicting categorical variables as counts (percentage). For continuous variables, values are expressed as the mean ± standard deviation (SD). Statistical measures for accuracy of both diagnostic modalities were derived from a 2 × 2 contingency table. Classification functions are given as percentages [95% confidence interval (CI)]. Statistical analysis was performed using SPSS (Version 24, IBM, Armonk, NY, USA).

RESULTS

Of 76 consecutive patients undergoing EVAR, 21 patients were excluded because of they lacked CEUS examinations or CTA and CEUS examinations with a longer than 3-d difference. Thus, our study included 55 patients (46 males, 9 females) with a mean age of 72.5 ± 8.4 y at the time of intervention (range: 51–85 y), which were followed up with CTA and CEUS (Supplementary Table S1, online only). Two hundred fifty-seven post-interventional CTAs (3.2 ± 2.3 per patient, range: 1−10) and 135 CEUS scans (2.2 ± 1.8 per patient, range: 1−9) were obtained over a mean follow-up period of 417 d (range: 5−2328 d). Every enrolled patient had at least one simultaneous control with CEUS and CTA before admission. Ninety-seven corresponding CTA/CEUS pairs were recorded, which served as the basis for further analysis.

Artifacts

A total number of 57 artifacts were observed in 97 individual CEUS examinations and classified into four categories, as determined by their cause of occurrence (Table 1).

Subsequently, the clinically most relevant artifacts were differentiated with respect to their possible impact on endoleak detection, whether reducing the diagnostic conclusiveness or leading to false-negative or false-positive reports.

Saturation artifacts feature loss of differentiation of contrast enhancement within stent lumina reaching maximum image brightness. They can be associated with glare and reverberation artifacts (Supplementary Video S1, online only). Diagnostic conclusiveness is diminished, and perfusion quantification is skewed or impossible.

False-negative interpretation of endoleaks was due mainly to attenuation artifacts. Assessment of the aneurysm sac in the far field is limited because of distal acoustic shadowing, which can be caused by contrast agent in stent grafts (Supplementary Video S2, online only). This was observed often in the case of contrast saturation and presented in varying degrees.

Likewise, acoustic shadowing was observed to various extents with different stent grafts. The circumferential polymer-filled O-rings of the Ovation system (Endologix Inc., Irvine, CA, USA) are prone to creating

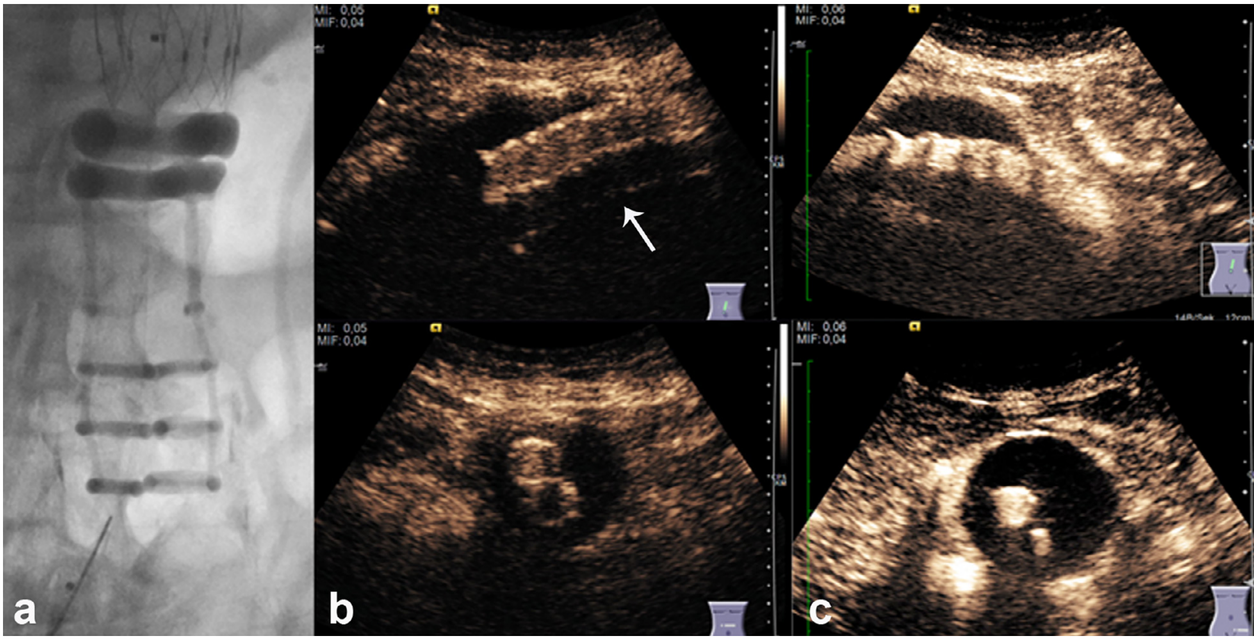

Fig. 1. Attenuation by prosthesis material (Ovation, Endologix Inc., Irvine, CA, USA). (a) Digital fluoroscopy reveals the polymer-filled O-rings of the Ovation system. (b, c) Longitudinal and cross-sectional assessment of the Ovation system in two patients. The assessment of the stent lumen and distal aneurysm sac is extremely diminished because of strong attenuation and minuscule reverberation artifacts as consequence of the stent graft design. The combination of acoustic shadowing due to prosthesis material and contrast agent in the proximal stentgraft prevents evaluation of the distal stentgraft completely (arrow).

strong attenuation artifacts and may almost completely limit evaluation of stent perfusion with CEUS (Fig. 1).

Potential reasons for false-positive assumptions of endoleaks were generally more diverse but due mostly to interaction with tissue or foreign material in the context of EVAR or additional interventional procedures.

In the short term after EVAR, residual gas presented as a usually rather sharply delineated local hyperechoic signal inside the aneurysm sac (Fig. 2). Gas bubbles tended to be located proximally to the transducer, in contrast to fibrin strings or inhomogeneous thrombosis of the aneurysm sac. Artifacts caused by the latter were more likely to appear areal, patchy and comparatively low in contrast (Fig. 3).

Glare artifacts impede the assessment of aneurysm sac areas close to stent bodies as result of excessive local

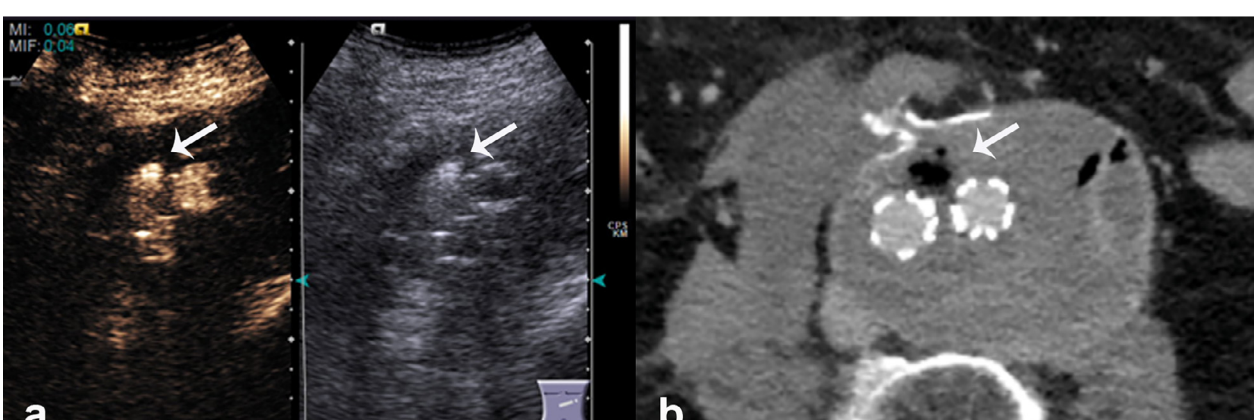

Fig. 2. False positive: Post-interventional gas. (a) Cross-section of an aneurysm sac in a contrast-enhanced ultrasound image revealing a hyperechoic lesion (*arrow*) located ventrally between two stent branches. The lesion is also visible as a hyperechoic structure in corresponding B-mode sonography or contrast mode before intravenous contrast agent injection. (b) Computed tomography angiography confirms post-interventional gas bubbles (*arrow*) and inhomogeneous thrombosis of the aneurysm sac in a corresponding location.

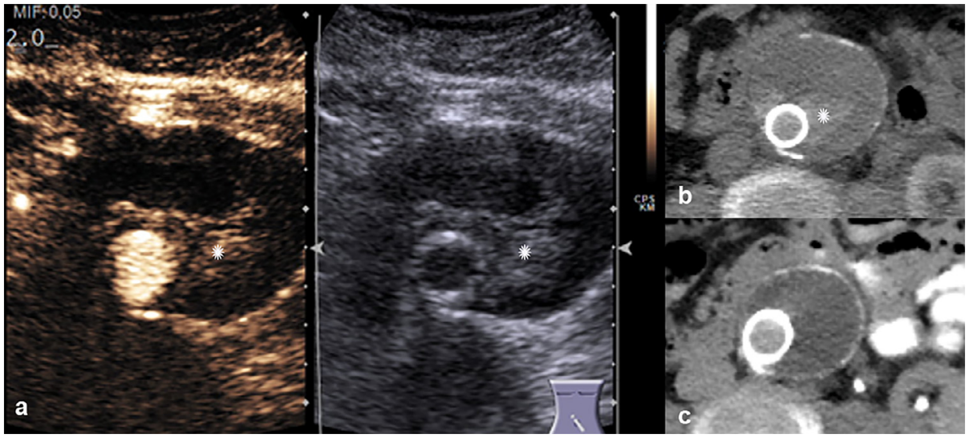

Fig. 3. False positive: Inhomogeneous thrombosis. (a) Extensive inhomogeneous hyperechoic structure (*asterisk*) inside the aneurysm sac surrounding the aortic tube graft (Aorfix Extender, Lombard Medical Limited, Didcot Oxfordshire, UK). The structure is identically seen in B-mode sonography before and after intravenous contrast agent injection. (b) Verification of inhomogeneous hyperdense thrombus material (*asterisk*) surrounding the stent graft in computed tomography. (c) Follow-up computed tomography after 6 mo reveals a regressive thrombus and aneurysm sac shrinkage.

contrast agent concentrations. In three particular cases of mycotic aneurysms, a hypervascular inflammatory margin persisting after stent implantation posed a risk for misinterpretation as reperfusion.

Artifacts caused by acoustic interaction with embolization material presented as clearly delineated hyperechoic lesions (Figs. 4 and 5). Correlating CTA revealed excessive beam-hardening artifacts, especially in cases where coils were combined with acrylic resin (Fig. 5).

The diagnostic conclusiveness of CEUS was reduced in cases of transducer-specific side lobe artifacts, which appeared as hyperechoic curvilinear extensions of insonated stent walls across the image plane in cross sections, observed only with a 4 C1 transducer.

All artifacts were correlated to software version, transducer and examiner experience. The latter was defined by the study's time course (Table 1), which we divided in three parts (point 1 = 2012/2013, n = 22; point 2 = 2014/2015, n = 42; point 3 = 2016/2017, n = 33) to assess our own "learning curve" with CEUS in follow-up after EVAR and artifacts.

Endoleaks

On first appraisal of 97 paired CTA/CEUS examinations, endoleaks were identified with CTA in 47 cases, whereas CEUS detected endoleaks in 53 examinations (Supplementary Table S2, online only).

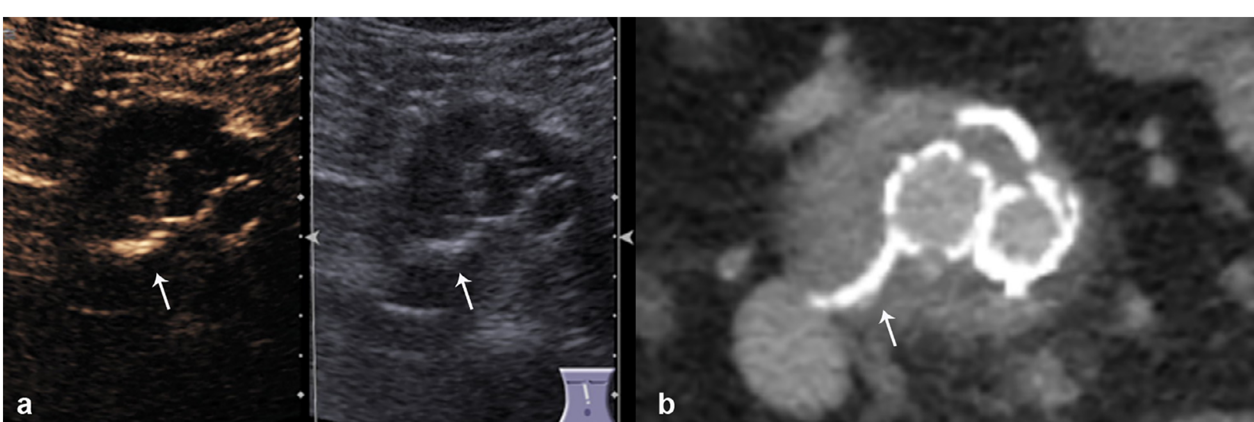

Fig. 4. False positive: Insonation of embolization material. (a) Interaction of contrast mode imaging with embolization material (coils and tissue adhesive, arrow), creating hyperechoic artifacts on contrast-enhanced ultrasound after occlusion of lumbar arteries bilaterally and inferior mesenteric artery for treatment of endoleak II. The artifact in the figure's lower left region is more easily visible because of the greater discontinuity in acoustic impedance. (b) Correlation with computed tomography angiography validates the absence of endoleaks.

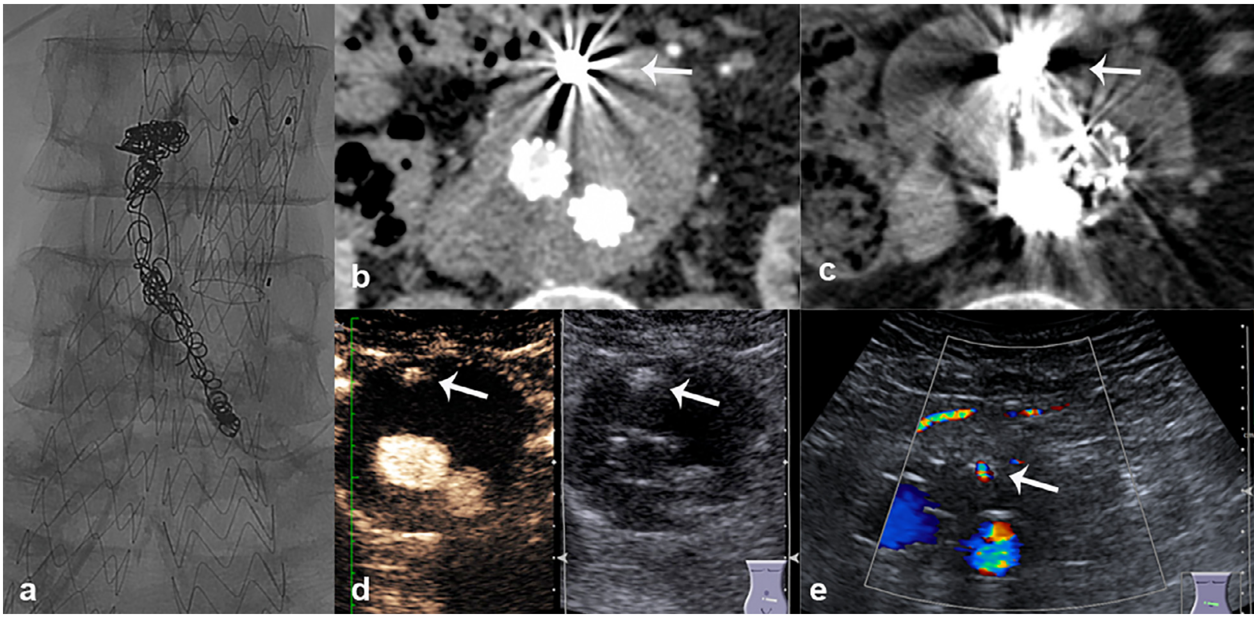

Fig. 5. Artifacts caused by embolization material (*arrow*) in contrast-enhanced ultrasound (CEUS) in comparison with computed tomography angiography (CTA). (a) Fluoroscopy after embolization of the inferior mesenteric artery for treatment of endoleak II after endovascular aortic repair. (b,c) Postinterventional assessment of an abdominal aortic aneurysm with CTA is greatly reduced because of the beam-hardening artifacts by coils and Onyx, potentially obscuring persisting endoleaks. (d) The impact of embolization material on CEUS is less marked, allowing better assessment of the aneurysm sac and stent grafts. Embolization material presents as a local hyperechoic artifact in CEUS, occasionally correlating with reverberation in B-mode sonography. (e) Twinkling artifacts (*arrow*) on embolization material in color-coded duplex sonography.

Agreement between the two methods in general detection of endoleaks, independently analyzed unaware of the other method's reports, were obtained in 89 cases (92%). Two of eight cases of general disagreement were due to misinterpretation of artifacts in CEUS. One false-negative result was reasoned in a faulty examination with non-recognition of an attenuation artifact by the proximal stent branch. The negative predictive value of CEUS was 97.73% [87.98%−99.94%]. One false-positive CEUS result was caused by interaction of CEUS with embolization material (coils). The positive predictive value of CEUS was 98.11% [89.93%−99.95%].

Contrast-enhanced ultrasound proved advantageous compared with CTA in recognition of late enhancing endoleaks in four cases, appearing later than at least 45 s after intravenous contrast agent injection that were not evident in CTA. In 2 cases, CTA lacked assessability because of the beam-hardening artifacts of embolization material (Onyx, Medtronic, Dublin, Ireland) after occlusion of IMA or lumbar arteries. While Onyx caused rather low contrast artifacts in CEUS, those were differentiated from simultaneously present endoleaks by comparison with B-mode sonography.

Contrast-enhanced ultrasound reached a sensitivity of 98.11% [89.93%−99.95%] and specificity of 97.73% [87.98%−99.94%], whereas CTA reached a sensitivity of 88.68% [76.97%−95.73%] and specificity of 100% [91.96%−100%].

Table 2. 10 cases of endoleaks diagnosed in CEUS and CTA simultaneously, with disagreement with respect to types and feeding arteries

n	CEUS	CTA	Advantage
4	IIb (IMA and lumbar)	IIa (IM)	CEUS
2	IIa (lumbar)	Ib	CEUS
1	IIa (IMA)	IIb (lumbar)	CEUS
1	IIb (lumbar and MSA)	IIa (lumbar)	CEUS
1	Ia, Ib, IIb (lumbar)	Ib	CEUS
1	Ic	Ic, IIb (IMA, SGA)	CTA

CEUS = contrast-enhanced ultrasound; CTA = computed tomography angiography; IMA = inferior mesenteric artery; MSA = median sacral artery; SGA = superior gluteal artery.

Of 46 endoleaks diagnosed with CEUS and CTA, identified feeding vessels were identical in 36 cases. In 9 of 10 cases of mismatching feeders, CEUS proved to be superior by giving additional information (Table 2).

Contrast-enhanced ultrasound revealed more feeding vessels in comparison with CTA, in 4 cases depicting endoleak type IIb instead of IIa or verifying an additional leak from the median sacral artery in an endoleak IIb in 1 case.

One patient's follow-up featured a sudden change in reperfusion from the lumbar artery to the IMA that was recognized only on CEUS. In 2 cases, CEUS distinctly diagnosed endoleak type IIb instead of Ib, which allowed continuation of the conservative concept of treatment. In another case in which CTA revealed an endoleak type Ib, CEUS was able to detect a combination of types Ia, Ib and IIb.

On the other hand, in one case with post-interventional gas artifacts, CEUS was only able to detect endoleak Ic while CTA diagnosed endoleaks Ic and IIb.

DISCUSSION

Artifacts in CEUS are common and have several causes. We observed artifacts of any kind in 59% of examinations and 80% of all patients, respectively. Thus, experience with CEUS and knowledge of technical aspects and related artifacts are crucial. The examiner needs to be experienced with the ultrasound device and all transducers used because some artifacts are device specific. After EVAR, information on additional procedures (stenting, coiling) is vital to handle material-related artifacts.

Technical principles

Contrast enhancement in CEUS, resulting from harmonic reflections of oscillating microbubbles induced by a transducer signal (Emanuel et al. 2020) is subject to three factors:

1. Local concentration of resonating microbubbles. Bubble sizes of $2-10$ μm create an enormous number of small interfaces resulting in high echogenicity, while allowing free passage of the capillary system and assessment of blood flow in real time.
2. Sufficient energy to allow bubble oscillation, while examination with low acoustic power is essential to prevent microbubble destruction.
3. Interaction of contrast mode imaging with tissues or foreign materials, creating potential false-positive or false-negative interpretations.

For endoleak detection, clinically most relevant artifacts can be differentiated as follows:

- False negative: attenuation artifacts (contrast agent, stent graft material).
- False positive: post-interventional gas or inhomogeneous thrombosis of aneurysm sac and tissue inflammation in mycotic aneurysms versus embolization material.

Saturation artifacts

An overdose of contrast agent leads to *saturation artifacts*, where the linear relationship between contrast agent dose and signal intensity is lost and any signal above a saturation threshold is displayed with maximum brightness (Dietrich et al. 2011). Comparable to superelevated gain settings, this results in loss of differentiation of contrast enhancement and increases risk of acoustic shadowing (Supplementary Video S1, online only). Saturation artifacts were the most common artifacts at the beginning of our study (12% of examinations) and a good example for our internal learning curve. Optimal device settings and a standardized examination protocol were crucial to reduce contrast saturation (Supplementary Video S3, online only). A dose of 1.4 mL of SonoVue per bolus, followed by injection of 10 mL of sodium chloride, was sufficient for most patients, whereas up to 1.6 mL proved helpful in obese patients.

Saturation artifacts will gain more importance in the context of perfusion quantification (Pfister et al. 2009; Jung et al. 2010), where enhancement kinetics of endoleaks are becoming important prognostic parameters that may help to predict spontaneous closure or need for treatment. In 2010, Jung et al. differentiated between endoleaks with high perfusion requiring further intervention and those with low perfusion that could be treated conservatively. However, endoleak quantification is only feasible with non-saturated ultrasound images. Otherwise, parameters such as time to peak and peak enhancement may be underestimated (Tranquart et al. 2012; Fetzer et al. 2018).

Commonly associated with saturation were glare, slice thickness and reverberation artifacts. *Glare artifacts* describe noise artifacts obscuring areas of weak enhancement and low echogenicity by nearby strong signal intensities because of high local contrast agent concentrations (Stiegler et al. 2015). Evident in 7% of cases, this artifact may be identified by distinct kinetics. It is not yet visible in the phase of arterial invasion and diminishes with washout of contrast. Glare artifacts can feign endoleaks by pseudo-enhancement or hinder their detection by interference. Strong enhancement of persistent inflammatory margins in mycotic aneurysms, as seen in 3 cases, causes glare artifacts and can pretend retrograde perfusion of arteries outside the aneurysm sac, not to be confused with an endoleak.

Reverberation artifacts present as multiple equidistantly spaced linear reflections at different depths of the acoustic field that can be observed when echoes generated from the ultrasound beam are repeatedly reflected back and forth between two parallel, highly reflective surfaces before returning to the transducer. Increasing travel times of sequential echoes, growing with each reflection, are interpreted as originating from deeper within the body by the ultrasound processor and thus placed an increased distance from the transducer. These artifacts are a common and nonspecific finding, which can also be caused by several stent grafts. Improved travel time calculation and suppression techniques in modern ultrasound units and probes help to diminish those artifacts (Dietrich et al. 2014).

Attenuation artifacts

Attenuation artifacts can be induced by prosthesis material, interventional material or the highly acoustic absorbing contrast agent itself.

Above a distinct threshold, strong echo signals close to the transducer caused by high local microbubble concentrations will lead to acoustic shadowing. The effect is comparable to shadowing behind structures of high echogenicity in B-mode, where the reduced response by loss of ultrasound energy in deeper regions cannot be adequately counterbalanced by time-gain compensation (Dietrich et al. 2011). Distal acoustic shadowing of **contrast agent** in the proximal stent occurred in 3% of cases, reducing assessment of the second stent in the far field.

A weaker insonation response occurs in deeper regions with another overlying perfused structure. Not to confuse this with stent obstruction, it is important to change the angle of insonation and thereby eliminate the cause of attenuation by removing the proximal stent branch from the ultrasound window, comparing cross-section with longitudinal section images or correlating color-coded duplex sonography (CDS). Low insonation response in one or both stent branches, independent of their positional relation, may be reasoned in the **prosthesis material** itself, as seen in 6% of cases (*e.g.,* Aorfix, Lombard Medical Limited, Didcot Oxfordshire, UK). Attenuation artifacts may obscure endoleaks dorsally of stent grafts, especially delayed and weak enhancing lumbar artery reperfusions.

Interaction with embolization material

Acoustic interaction with coils or acrylic resin after additional interventions was the second most common artifact in 10% of examinations and resulted in one false-positive report of an endoleak because of misinterpretation of hyperechoic signals of coils in CEUS. In B-mode sonography, metallic embolization material will create reverberation artifacts, whereas CDS will reveal twinkling artifacts, such as those usually seen on concrements. Correlation of CEUS with those modalities helps in artifact identification. In some instances, metallic graft or embolization material can also lead to *slice thickness artifacts.*

In two other cases, Onyx caused rather low contrast hyperechoic artifacts, which were recognized later during the study after learning from errors by comparison with B-mode sonography. In CTA, *beam-hardening artifacts* caused by embolization materials can render evaluation of endoleaks impossible (Lehti et al. 2020), which led to two cases of disagreement between CTA and CEUS in our study.

Stent graft-specific artifacts

Attenuation artifacts caused by the circumferential polymer-filled O-rings of the *Ovation* system (Endologix Inc.) were stent graft specific. A strong acoustic shadow heavily limited assessability of the stent lumina's perfusion and aneurysm sac areas, which were located strictly distal to transducer and O-rings. To a lesser extent, acoustic shadowing was observable with nearly all stent grafts in our study.

After completion of study recruitment, we noticed another non-artificial stent graft-specific characteristic of the *Altura* endograft system (Lombard Medical Limited, Didcot Oxfordshire, UK). CEUS revealed a rim of contrast agent outside the clearly discernible metal parts that appeared simultaneously with aortic enhancement. CTA confirmed perfusion of the gap between the braided nitinol stent and the surrounding woven polyester graft, as well as absence of an actual endoleak (Supplementary Video S4, online only). Because the sheathing is fixed to the supporting stent at a few points distant from each other, lifting off the graft material is allowed by Altura's design to a certain extent. However, this should not be confused with a broad material defect or endoleak type I/III.

Post-interventional artifacts

Post-interventional gas is a common finding, usually present within 5 d post-EVAR and not related to infection or endoleak (Saleptsis et al. 2018). Insonation of gas bubbles creates a bright echo artifact, comparable to the harmonic oscillation of contrast microbubbles in perfused vessels (Emanuel et al. 2020). Simple correlation with B-mode sonography, displaying gas as a hyperechoic structure even before contrast agent administration, will help in correctly recognizing this kind of artifact.

Learning curve assessment

In this trial's "learning phase" some artifacts remained unrecognized at first. On a second analysis of all video data throughout the follow-up and in correlation with CTA, the examination protocol was modified. Most importantly, an obligatory native B-mode scan was added as first step to identify or rule out potential gas bubbles. Second, a CDS scan was added to prevent false reports of graft obstruction. Learning curve analysis revealed that most avoidable artifacts (*e.g.,* acoustic shadowing by contrast agent) were only troublesome in the study's early phases and were averted later on because of sonographer experience, improved software and usage of the high-density 6 C1 probe. Artifacts caused by gas bubbles or fibrin strings were seen once at most in each patient, during control before discharge, as gases were resorbed later (Saleptsis et al. 2018). Being the reason for false-positive reports of an endoleak in one of our very first examinations, gas bubbles were adequately recognized as artifacts in CEUS thereafter. Saturation artifacts were mostly evident at time points 1 and 2, barely seen twice per patient and eliminated during follow-up after learning the correct individual contrast agent dose from errors.

Endoleak detection

Pfister et al. (2009) postulated that perfusion imaging with CEUS seemed to be superior in characterization of the exact types of endoleaks, which is in concordance with our findings. Apart from one false-negative result caused by non-recognition of an attenuation artifact by the proximal stent branch and one false-positive result caused by interaction of CEUS with embolization material (coils), CEUS performed better than CTA in the detection and classification of endoleaks in our study.

Most importantly, CEUS revealed additional information on endoleaks' feeding of arteries in several cases, either revealing a greater number of feeders, differentiating them more accurately or both. This finding's importance is supported by the study of Müller-Wille et al. (2015), who found that patients with early type II endoleaks and aneurysm enlargement had a significantly larger number of feeding and/or draining arteries. Furthermore, complex type II endoleaks, which the authors defined as blood flow from both the inferior mesenteric and lumbar arteries, remained associated with a high risk for aneurysm enlargement. CEUS provides functional hemodynamic information because of its ability to visualize blood flow within the aneurysm sac in a real-time pattern. Dynamic CT angiography is a recent approach aiming to partially compensate for this advantage (Lehmkuhl et al. 2013).

Apart from this, CEUS proved advantageous over CTA in recognition of late enhancing endoleaks and in patients who had undergone embolization procedures with consecutive beam-hardening artifacts in CTA in our study. Iterative Metal Artifact Reduction Algorithms (iMAR) might be able to overcome these artifacts in CTA imaging (Lehti et al. 2020); however, this software feature was not available to our institution at that time.

Lastly, CEUS allowed the evaluation of endoleaks without concern for nephrotoxicity and without the use of ionizing radiation. On the other hand, modern protocols for CTA imaging have been developed to reduce radiation and contrast agent exposure (Partovi et al. 2018).

Limitations

The eligible patient cohort for this specialized aneurysm treatment was rather small and several patients did not meet the inclusion criteria as they lacked comparable CTA/CEUS examinations, either because the time between the examinations was too long (> 3d) or CEUS could not be performed because of morbid obesity or excessive intestinal gas. With respect to radiation hygiene, patients with good sonographic assessability of stent grafts underwent CEUS and CTA examinations in an alternating fashion during follow-ups. Exclusion of those examinations further reduced our sample size.

Owing to these limitations, our study's enrollment phase lasted 5 y. Devices that were up-to-date at the beginning were further modernized during the course of our study. For instance, the early 4 C1 transducer's device-specific side lobe artifacts were not reproducible in the same patients after changing to a high-density 6 C1 probe. Travel time calculations and suppression of lateral echoes help diminishing side lobe artifacts in modern ultrasound systems, but it remains to be seen which artifacts will be affecting the latest high-resolution probes.

A few initial interpretations were not accurate because of the aforementioned ''learning curve.'' After sufficient experience, all examinations were re-assessed and a final judgment regarding the occurrence of artifacts and classification of endoleaks was made.

CONCLUSIONS

Contrast-enhanced ultrasound has high sensitivity and specificity in the detection of endoleaks after EVAR, albeit sonographer experience is unsubstitutable, and this also extends to artifacts. Although CTA may display the entire aortic vascularization in a panoramic representation, CEUS has better dynamic resolution. We identified advantages of CEUS in the dynamic assessment and ability to detect feeding arteries more often or more accurate; follow-up after embolization where beam-hardening artifacts hinder evaluation with CTA and detection of late endoleaks.

New methods, for example, FLASH-replenishment kinetics, allow quantification of endoleak perfusion with potential prognostic significance at no risk of contrast-induced nephropathy. However, optimal device settings and avoidance of saturation artifacts are strict prerequisites.

Knowledge of patients' history, including information on index and additional procedures (*e.g.,* embolization), is essential for anticipation and evaluation of potential artifacts involved. Artifacts in CEUS are frequent and can result in false-negative and false-positive reports of endoleaks.

Correct contrast agent dosage, comparison of CEUS examinations with standard B-mode sonography and CDS and repeated changes in the angle of insonation help to avoid most common artifacts. Experience with customarily used stent grafts and typical artifacts reduces the risk of misdiagnosis. Lastly, there is an individual learning curve to be considered when establishing CEUS as a follow-up modality after EVAR in a center.

Acknowledgments—This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Conflict of interest disclosure—The authors have no conflicts of interest to declare.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ultrasmedbio.2020.11.032.

REFERENCES

Bargellini I, Napoli V, Petruzzi P, Cioni R, Vignali C, Sardella SG, Ferrari M, Bartolozzi C. Type II lumbar endoleaks: Hemodynamic differentiation by contrast-enhanced ultrasound scanning and influence on aneurysm enlargement after endovascular aneurysm repair. J Vasc Surg 2005;41:10–18.

Baum RA, Stavropoulos SW, Fairman RM, Carpenter JP. Endoleaks after endovascular repair of abdominal aortic aneurysms. J Vasc Interv Radiol 2003;14:1111–1117.

Cantisani V, Grazhdani H, Clevert DA, Iezzi R, Aiani L, Martegani A, Fanelli F, Di Marzo L, Wlderk A, Cirelli C, Catalano C, Di Leo N, Di Segni M, Malpassini F, D'Ambrosio F. EVAR: Benefits of CEUS for monitoring stent-graft status. Eur J Radiol 2015;84: 1658–1665.

Chisci E, Harris L, Guidotti A, Pecchioli A, Pigozzi C, Barbanti E, Ercolini L, Michelagnoli S. Endovascular aortic repair follow up protocol based on contrast enhanced ultrasound is safe and effective. Eur J Vasc Endovasc Surg 2018;56:40–47.

Clevert DA, Minaifar N, Weckbach S, Kopp R, Meimarakis G, Clevert DA, Reiser M. Color duplex ultrasound and contrast-enhanced ultrasound in comparison to MS-CT in the detection of endoleak following endovascular aneurysm repair. Clin Hemorheol Microcirc 2008;39:121–132.

Cuypers P, Buth J, Harris PL, Gevers E, Lahey R. Realistic expectations for patients with stent-graft treatment of abdominal aortic aneurysms: Results of a European multicentre registry. Eur J Vasc Endovasc Surg 1999;17:507–516.

Dietrich CF, Ignee A, Hocke M, Schreiber-Dietrich D, Greis C. Pitfalls and artefacts using contrast enhanced ultrasound. Z Gastroenterol 2011;49:350–356.

Dietrich CF, Ignee A, Greis C, Cui XW, Schreiber-Dietrich DG, Hocke M. Artifacts and pitfalls in contrast-enhanced ultrasound of the liver. Ultraschall Med 2014;35:108–125 quiz 26−27.

Emanuel AL, Meijer RI, van Poelgeest E, Spoor P, Serné EH, Eringa EC. Contrast-enhanced ultrasound for quantification of tissue perfusion in humans. Microcirculation 2020;27:e12588.

Faccioli N, Foti G, Casagranda G, Santi E, D'Onofrio M. CEUS versus CT angiography in the follow-up of abdominal aortic endoprostheses: Diagnostic accuracy and activity-based cost analysis. Radiol Med 2018;123:904–909.

Fetzer DT, Rafailidis V, Peterson C, Grant EG, Sidhu P, Barr RG. Artifacts in contrast-enhanced ultrasound: A pictorial essay. Abdom Radiol 2018;43:977–997.

Franks SC, Sutton AJ, Bown MJ, Sayers RD. Systematic review and meta-analysis of 12 years of endovascular abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 2007;33:154–171.

Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: Randomised controlled trial. Lancet 2004;364:843–848.

Hiatt MD, Rubin GD. Surveillance for endoleaks: How to detect all of them. Semin Vasc Surg 2004;17:268–278.

Hobo R, Buth J. Secondary interventions following endovascular abdominal aortic aneurysm repair using current endografts: A EUROSTAR report. J Vasc Surg 2006;43:896–902.

Jung EM, Rennert J, Fellner C, Uller W, Jung W, Schreyer A, Heiss P, Hoffstetter P, Feuerbach S, Kasparzk P, Zorger N, Pfister K. Detection and characterization of endoleaks following endovascular treatment of abdominal aortic aneurysms using contrast harmonic imaging (CHI) with quantitative perfusion analysis (TIC) compared to CT angiography (CTA). Ultraschall Med 2010;31:564–570.

Karthikesalingam A, Al-Jundi W, Jackson D, Boyle JR, Beard JD, Holt PJ, Thompson MM. Systematic review and meta-analysis of duplex ultrasonography, contrast-enhanced ultrasonography or computed tomography for surveillance after endovascular aneurysm repair. Br J Surg 2012;99:1514–1523.

Lehmkuhl L, Andres C, Lücke C, Hoffmann J, Foldyna B, Grothoff M, Nitzsche S, Schmidt A, Ulrich M, Scheinert D, Gutberlet M. Dynamic CT angiography after abdominal aortic endovascular aneurysm repair: Influence of enhancement patterns and optimal bolus timing on endoleak detection. Radiology 2013;268: 890–899.

Lehti L, Söderberg M, Mellander H, Wassélius J. Iterative metal artifact reduction in aortic CTA after Onyx®-embolization. Eur J Radiol Open 2020;7 100255.

Massmann A, Shayesteh-Kheslat R, Frenzel F, Fries P, Bucker A. [New developements in endovascular infrarenal aortic aneurysm treatment]. Radiologe 2018;58:804–813.

Metoki R, Moriyasu F, Kamiyama N, Sugimoto K, Iijima H, Xu HX, Aoki T, Miyata Y, Yamamoto K, Kudo K, Shimizu M, Yamada M. Quantification of hepatic parenchymal blood flow by contrast ultrasonography with flash-replenishment imaging. Ultrasound Med Biol 2006;32:1459–1466.

Mirza TA, Karthikesalingam A, Jackson D, Walsh SR, Holt PJ, Hayes PD, Boyle JR. Duplex ultrasound and contrast-enhanced ultrasound versus computed tomography for the detection of endoleak after EVAR: Systematic review and bivariate meta-analysis. Eur J Vasc Endovasc Surg 2010;39:418–428.

Müller-Wille R, Schötz S, Zeman F, Uller W, Güntner O, Pfister K, Kasprzak P, Stroszczynski C, Wohlgemuth WA. CT features of early type II endoleaks after endovascular repair of abdominal aortic aneurysms help predict aneurysm sac enlargement. Radiology 2015;274:906–916.

Partovi S, Trischman T, Rafailidis V, Ganguli S, Rengier F, Goerne H, Rajiah P, Staub D, Patel IJ, Oliveira G, Ghoshhajra B. Multimodality imaging assessment of endoleaks postendovascular aortic repair. Br J Radiol 2018;91 20180013.

Pfister K, Rennert J, Uller W, Schnitzbauer AA, Stehr A, Jung W, Hofstetter P, Zorger N, Kasprzak PM, Jung EM. Contrast harmonic imaging ultrasound and perfusion imaging for surveillance after endovascular abdominal aneurysm repair regarding detection and characterization of suspected endoleaks. Clin Hemorheol Microcirc 2009;43:119–128.

Piscaglia F, Bolondi L. The safety of Sonovue in abdominal applications: Retrospective analysis of 23188 investigations. Ultrasound Med Biol 2006;32:1369–1375.

Piscaglia F, Nolsoe C, Dietrich CF, Cosgrove DO, Gilja OH, Bachmann Nielsen M, Albrecht T, Barozzi L, Bertolotto M, Catalano O, Claudon M, Clevert DA, Correas JM, D'Onofrio M, Drudi FM, Eyding J, Giovannini M, Hocke M, Ignee A, Jung EM, Klauser AS, Lassau N, Leen E, Mathis G, Saftoiu A, Seidel G, Sidhu PS, ter Haar G, Timmerman D, Weskott HP. The EFSUMB guidelines and recommendations on the clinical practice of contrast enhanced ultrasound (CEUS): Update 2011 on non-hepatic applications. Ultraschall Med 2012;33:33–59.

Prinssen M, Verhoeven EL, Buth J, Cuypers PW, van Sambeek MR, Balm R, Buskens E, Grobbee DE, Blankensteijn JD. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med 2004;351:1607–1618.

Quaia E. Microbubble ultrasound contrast agents: An update. Eur Radiol 2007;17:1995–2008.

Rubenthaler J, Reiser M, Cantisani V, Rjosk-Dendorfer D, Clevert DA. The value of contrast-enhanced ultrasound (CEUS) using a high-end ultrasound system in the characterization of endoleaks after endovascular aortic repair (EVAR). Clin Hemorheol Microcirc 2017;66:283–292.

Saleptsis V, Spanos K, Tsilimparis N, Rohlffs F, Debus SE, Kölbel T. The presence of gas in aneurysm sac during early postoperative period is associated to the type of endograft and perfused lumen's size. Ann Vasc Surg 2018;50:173–178.

Schermerhorn ML, O'Malley AJ, Jhaveri A, Cotterill P, Pomposelli F, Landon BE. Endovascular vs. open repair of abdominal aortic aneurysms in the Medicare population. N Engl J Med 2008;358:464–474.

Stiegler H, Kubale R, Weskott HP. Farbkodierte Duplexsonografie Interdisziplinärer vaskulärer Ultraschall. Stuttgart: Thieme; 2015.

Tranquart F, Mercier L, Frinking P, Gaud E, Arditi M. Perfusion quantification in contrast-enhanced ultrasound (CEUS)—Ready for research projects and routine clinical use. Ultraschall Med 2012;33 (Suppl 1):S31–S38.

Tse DM, Tapping CR, Patel R, Morgan R, Bratby MJ, Anthony S, Uberoi R. Surveillance after endovascular abdominal aortic aneurysm repair. Cardiovasc Intervent Radiol 2014;37:875–888.

White RA. Endograft surveillance: A priority for long-term device performance. J Endovasc Ther 2000;7:522.

Van der Molen AJ, Reimer P, Dekkers IA, Bongartz G, Bellin MF, Bertolotto M, Clement O, Heinz-Peer G, Stacul F, Webb JAW, Thomsen HS. Post-contrast acute kidney injury: Part 1. Definition, clinical features, incidence, role of contrast medium and risk factors: Recommendations for updated ESUR Contrast Medium Safety Committee guidelines. Eur Radiol 2018;28:2845–2855.