3D Contrast Enhanced Ultrasound for Detecting Endoleak Following Endovascular Aneurysm Repair (EVAR)

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WHAT THIS PAPER ADDS

CT angiography (CTA) has been widely used to detect endoleak following endovascular aneurysm repair, but is expensive and there is a risk of kidney damage because of the X-ray contrast media. 3D contrast enhanced ultrasound (CEUS) is at least as sensitive to endoleak, is less expensive, and may detect endoleaks missed by CTA. As 3D CEUS has no known toxicity, we plan to replace CTA with 3D CEUS; a major clinical trial is indicated to determine whether 3D CEUS is more sensitive than CTA.

Objective: CT angiography (CTA) for endovascular aneurysm repair (EVAR) surveillance involves irradiation and nephrotoxic X-ray contrast agents. Three-dimensional contrast enhanced ultrasound (3D CEUS) is a novel imaging technique that may be more sensitive to blood flow detection than CTA or 2D CEUS. 3D CEUS utilises positional information from magnetic field emitters to assemble all ultrasound reflections into a high-definition image. We compared 3D CEUS with CTA for the detection of endoleak and aneurysm expansion following EVAR.
Methods: 3D CEUS (Curefab), 2D CEUS (Philips IU22), and CTA were compared in 30-paired images from 23 patients. Sensitivity, specificity, positive, and negative predictive value were calculated for 2D and 3D CEUS against CTA as the 'gold standard'. Pearson correlation was used to compare aneurysm sac diameter. Data were analysed using SPSS version 19.0.
Results: 30 paired 3D CEUS and CTA images were analysed from 23 patients. Endoleaks were detected in 17 images with CTA, 18 on 2D CEUS, and 18 on 3D CEUS. The sensitivity, specificity, positive, and negative predictive values of 3D CEUS to detect endoleak were 100%, 92%, 94%, and 100%, respectively. There was excellent correlation ($r = 0.935$; $p \leq .0001$) between CTA and 3D CEUS for AAA sac diameter. Only 3D CEUS detected the inflow and outflow arteries in all 18 scans with endoleak. 2D CEUS detected the inflow in 16 (88.8%) and CTA on 12 (66.6%) of the images.
Conclusion: 3D CEUS may be more sensitive to endoleak following EVAR than either 2D CEUS or CTA.

Article history: Received 2 September 2013, Accepted 3 February 2014, Available online 4 March 2014
Keywords: 3D ultrasound, Abdominal aortic aneurysm, Endoleak, Endovascular aneurysm repair, Surveillance

INTRODUCTION

Endovascular aneurysm repair (EVAR) has a lower operative mortality for elective abdominal aortic aneurysm (AAA) repair than open surgery.[1–3] This has become increasingly accepted, accounting for over 70% of AAA repairs currently performed.[4] The disadvantage of EVAR is the need for life-long surveillance to monitor stent-graft related complications.[5] Surveillance is traditionally by computed tomographic angiography (CTA), which requires irradiation and nephrotoxic X-ray contrast media.[6] More recently, duplex ultrasound has been proposed as a safe and inexpensive alternative.[7]

Conventional duplex ultrasound has been reported to be effective at detecting endoleaks after EVAR that were not identified by intraoperative completion angiography.[8] Contrast enhanced ultrasound (CEUS), using sulphur hexafluoride microbubbles, is reported to detect endoleaks missed by CTA and is safe with minimal side effects.[9–11] Three-dimensional contrast enhanced ultrasound (3D CEUS) is a novel technology that utilises positional information from magnetic field emitters to assemble all ultrasound reflections into a high-definition 3D image. This technology is used in the same way as standard duplex imaging, but produces higher quality images. Unlike standard CEUS, angiography, or CTA, 3D CEUS detects the source (Type I, III or II) of any endoleak with confidence.

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1078-5884/$ — see front matter
http://dx.doi.org/10.1016/j.ejvs.2014.02.002

Aims

The aim of this prospective pilot study was to assess the clinical utility and accuracy of 3D CEUS compared with standard 2D CEUS and CTA in post EVAR-surveillance, and its influence on patient management. The primary outcome measure was the detection of endoleak and its source.

METHODS

This pilot study was conducted at a single tertiary referral vascular centre and was approved by the local research ethics committee (REC number 13/NW/0485). Consecutive subjects attending for CTA and 3D CEUS imaging who were thought to possibly have an endoleak following an EVAR were included in this study ($n = 23$). The subjects were recruited from the South Manchester EVAR surveillance programme between May 2012 and May 2013. Subjects who did not have paired CTA imaging were excluded. Demographic data were collected and all images were reviewed by a research fellow and these were reported by either an accredited vascular laboratory technologist (2D or 3D CEUS) or consultant interventional radiologist (CTA).

Our institution has a novel 3D ultrasound system (Curefab, Munich, Germany) available for clinical use. 3D CEUS and 2D CEUS were compared with CTA, which was considered to be the 'gold standard'.

3D contrast enhanced ultrasound technology

The Curefab 3D system comprises tracking sensors installed in the transducer of a high-definition duplex Doppler ultrasound system (IU22- C5) and an electromagnetic box. This technology uses a motion tracking mini-GPS (global positioning system) with a magnetic field emitter and two tracking sensors that transform standard 2D CEUS images into high-definition 3D format.[12] These instruments utilise positional information from magnetic field emitters to place and orientate the transducer probe precisely in time and space. Unlike conventional ultrasound, where a small number of representative 2D images taken from the many thousand generated during an average 10 minute scan are used for diagnosis, all the acquired 2D information is utilised to construct a high-definition 3D image. The system's pattern recognition software and algorithms compare each frame to a multitude of others to construct a single 3D volume image within seconds (Figs. 1 and 2b). These are dynamic images that may be manipulated by the operator to interrogate any area of interest. The colour coding of the stent-graft is added manually, by scrolling through the images in transverse and drawing around the graft at 3—5 mm sections. The colour is based on a segmentation that the user has to add manually by drawing planimetry contours. Basically, the opacity of all voxels outside the segmentation of the aneurysm sac will be reduced, whereas all voxels inside the segmentation of the stent will be coloured. In practice, it is only necessary to add the colour coding in complex cases. Importantly, the 3D modality adds no extra time to image acquisition and neither the mechanical nor thermal index on the ultrasound machine are increased.

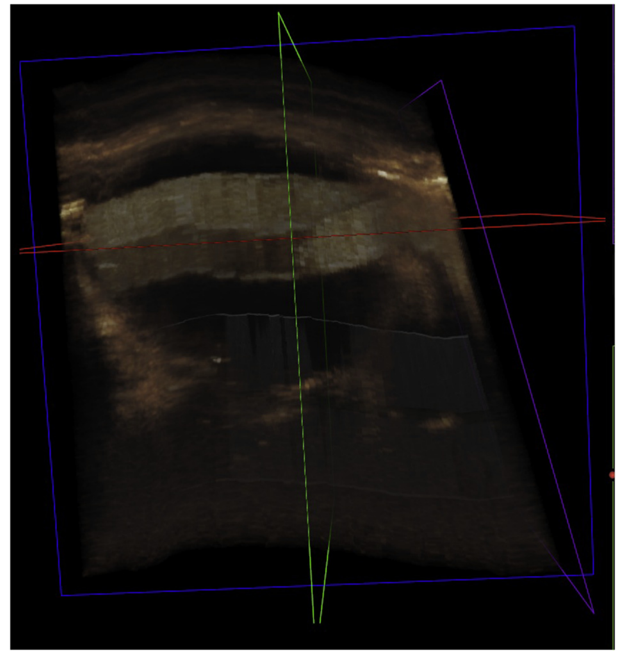

Figure 1. 3D contrast enhanced ultrasound (3D CEUS) showing an EVAR at 2 years with no endoleak.

2D and 3D CEUS images are acquired simultaneously by the same vascular laboratory technologist without requiring additional ultrasound contrast administration. The acquired 3D images can be interrogated subsequently and allow slow playback enabling detailed interrogation of the vessels, blood flow, and the source of any endoleak.

The 3D system augments the 2D CEUS images, with the 2D CEUS identifying the direction of the flow shown in a cineloop displayed by the 3D system. The 3D reconstruction enables the operator to view the path of the endoleak. The ability to manoeuvre the 3D reconstruction and view the images in sagittal, coronal, and transverse planes simultaneously without moving the probe, enables the operator to accurately identify if flow is within or outside the aneurysm sac. Blood vessels lying adjacent to the aorta would not be misidentified as inflow or outflow vessels.

2D contrast enhanced ultrasound

2D CEUS images were obtained using a duplex ultrasound instrument (Philips IU22) with the C5-1 curved array transducer.

2D and 3D CEUS image acquisition

With patients supine, the AAA and stent-graft were visualised and traced to the proximal neck, which was measured in cross-section and interrogated for potential endoleak using low colour flow velocity or power Doppler colour flow settings. The AAA diameter was measured using calipers placed on the inner reflection of the anterior and posterior walls; multiple transverse and antero-posterior (AP) measurements were obtained and the maximum recorded. After administration of sulphur hexafluoride contrast (SonoVue, Bracco, Milan, Italy; cost £48/-) into a peripheral

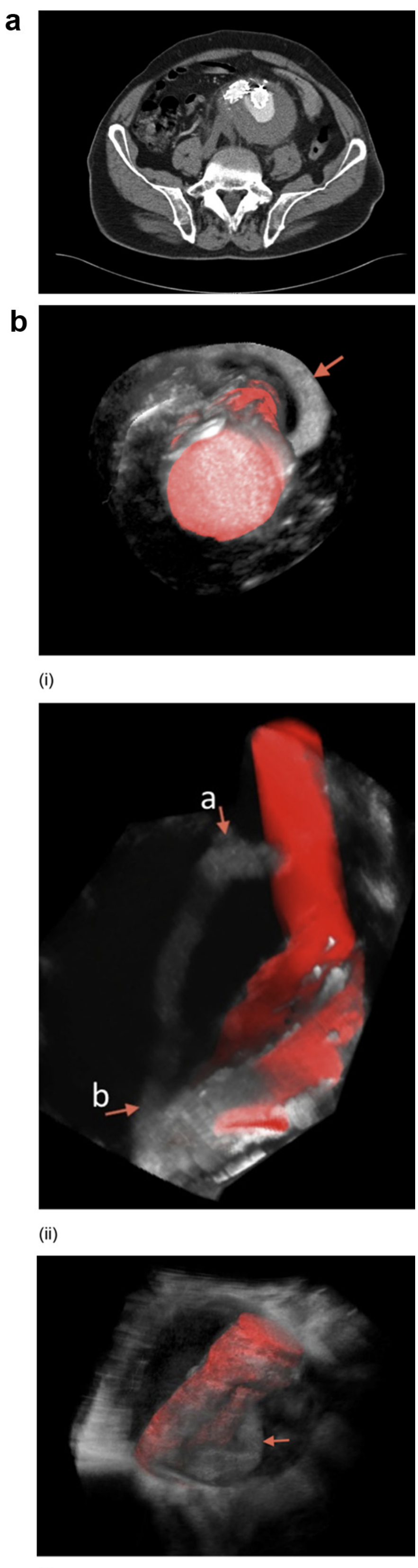

Figure 2. (A) CTA showing Type II endoleak. (B) 3D CEUS of same subject showing a Type II endoleak (red arrows) flowing from the (a) inferior mesenteric artery (b) to a lumbar artery. The stent-graft is coloured red by the 3D ultrasound software to distinguish flow within the stent-graft from flow outside (i) cross section (ii) longitudinal section (iii) oblique.

vein (2—5 mL), the aorta was scanned methodically in transverse section from the neck of the graft to the distal stent-graft in the iliac arteries. If an endoleak was identified, the inflow and outflow vessels were identified if possible. The image acquisition for 2D and 3D CEUS is simultaneous and takes 10—15 minutes, with subsequent analysis of the 3D images taking a further 5—10 minutes. AAA diameter measurement was AP inner to inner. The images were analysed independently by two fully trained vascular laboratory technologists.

CTA imaging

All patients had paired CTA images as a part of their routine EVAR surveillance protocol. These contrast enhanced images were obtained on a 16-slice helical scanner with a 1 mm slice thickness (Siemens Sensation, Siemens Medical, Germany). CTA from the diaphragm to femoral heads was performed with the patient supine. A dose of 100 mL of the iodinated contrast medium Omnipaque 240 (iohexol, 240 mg/mL) was administered at a flow rate of 3 mL/s. The duration of imaging was 15—20 minutes. The diameter was measured AP inner to inner. The estimated radiation dose was 5.4 mSv or 300 dose length product.[13]

Statistics

Measures of accuracy relating to endoleak detection (categorical variable) including sensitivity, specificity, positive, and negative predictive values were calculated using contingency tables.[14,15] Pearson's correlation was used to compare AAA diameter measured by 2D and 3D CEUS with CTA. An interobserver reliability analysis using the Kappa statistic was performed to determine consistency between two observers to detect endoleak on 3D CEUS. A p-value less than .05 (two sided) was considered significant.

The data were analysed using SPSS version 19.0 statistical software (SPSS Inc., Chicago, IL, USA). This pilot study will provide guidance for the power calculations required to perform future definitive studies.

RESULTS

Thirty paired 2D and 3D CEUS and CTA images were analysed from 23 patients. Paired images at different time intervals were included in seven patients. Patient demographics are shown in Table 1. The interval between paired images was 3.9 $\pm$ 2.7 (mean $\pm$ SD) weeks. Endoleaks were detected in 17 images with CTA, 18 on 2D CEUS, and 18 on 3D CEUS (Table 3). Assuming CTA to be a gold standard, the sensitivity, specificity, positive, and negative predictive values of 2D and 3D CEUS to detect endoleak were 100%, 92%, 94%, and 100%, respectively (Table 2). 2D and 3D CEUS had the same accuracy for the simple detection of an endoleak. There was an excellent correlation ($r = .935$; $p \leq .0001$; Fig. 3) between 3D CEUS and CTA for

Table 1. Demographic characteristics.

Characteristics	$n = 23$
Age (years; mean ± SD)	77.4 ± 6
Gender	
Female	12% (3)
Male	88% (22)
BMI (kg/m^2; mean ± SD)	29 ± 4
Stent-graft	
Bifurcated	80% (20)
Uniliac	20% (5)
EVAR	
Elective	96% (24)
Emergency	4% (1)
Creatinine (mmol/L; mean ± SD)	101 ± 35

AAA diameter, but CTA (6.6 ± 1.1) measured AAA diameter greater than ultrasound (6.0 ± 0.97). The interobserver reliability of 3D CEUS was an almost perfect agreement between two observers (Kappa = 0.88; 95% CI 0.718 to 1.0; $p \leq .0001$).

3D CEUS classified all endoleaks accurately; one patient had both Type Ib and Type II endoleaks. 3D CEUS detected the inflow artery in all 18 patients with endoleak. 2D CEUS detected the inflow site in 16 (88.8%) and CTA on 12 (66.6%) images. CTA could not differentiate between Type II and Type III in four cases, and in one case between Types Ib and II. 2D CEUS failed to classify two endoleaks between Type Ib, Type II, or Type III (Table 3).

One patient had an expanding 9 cm AAA with oscillating thrombus but no colour flow in the aneurysm detected on 2D ultrasound, which would be indicative of an intermittent endoleak. CTA also failed to identify an endoleak. 3D CEUS showed a Type Ib endoleak, tracking along the postero-lateral edge of the aneurysm with the outflow into a lumbar artery. Following multidisciplinary team (MDT) discussion, this was treated by relining the left iliac limb and bilateral iliac limb extensions. Postoperative angiography and 3D CEUS confirmed that the endoleak had been excluded.

DISCUSSION

Our pilot study was the first to investigate 3D CEUS for the detection of an endoleak following EVAR. 3D CEUS was superior to both 2D CEUS and CTA in the identification of the inflow source. The results of this study also show that 3D CEUS had similar sensitivity and specificity to 2D CEUS for detection of endoleaks, and may be more sensitive than CTA. This pilot study provides valuable information to advise the design of a definitive study to determine the clinical place of 3D CEUS in EVAR surveillance. 3D CEUS was performed initially when there was clinical suspicion of an endoleak; therefore data relating to '3D CEUS specificity' were based on only 10 subjects with no endoleak. A larger study is required to explore specificity. The interval between paired images was an average of 3.9 weeks (range: same day to 8 weeks). This study is based on paired images rather than individual patients.[16] Therefore, 30 paired images from 23 patients were analysed.

Conventional imaging failed to identify an endoleak in a patient with an expanding AAA 6 years following EVAR; CTA did not detect any endoleak during arterial or late phase acquisition and 2D CEUS did not identify colourflow outside the endograft. Non-contrast greyscale duplex identified thrombus movement adjacent to an iliac limb, extending from the flow divider to the aortic bifurcation, raising the suspicion of an intermittent endoleak because of thrombus movement being the only clue. Finally, 3D CEUS showed a Type Ib endoleak, which was discussed at the MDT and subsequently treated successfully.

Our results on the accuracy of CEUS were consistent with the recently published meta-analysis reporting the accuracy of the duplex ultrasound, 2D CEUS, and CTA for surveillance following EVAR.[7] 2D CEUS may be superior to both duplex ultrasound without contrast and CTA for this purpose.[17] CTA

Table 2a. Contingency table showing accuracy of 3D CEUS vs CTA.

3D CEUS	CTA Endoleak (yes)	Endoleak (no)	
Endoleak (yes)	17	1	Positive Predictive Value (94%)
Endoleak (no)	0	12	Negative Predictive Value (100%)
	Sensitivity (100%)	Specificity (92%)	

Table 2b. Contingency table showing accuracy of 2D CEUS vs CTA.

2D CEUS	CTA Endoleak (yes)	Endoleak (no)	
Endoleak (yes)	17	1	Positive predictive value (94%)
Endoleak (no)	0	12	Negative predictive value (100%)
	Sensitivity (100%)	Specificity (92%)	

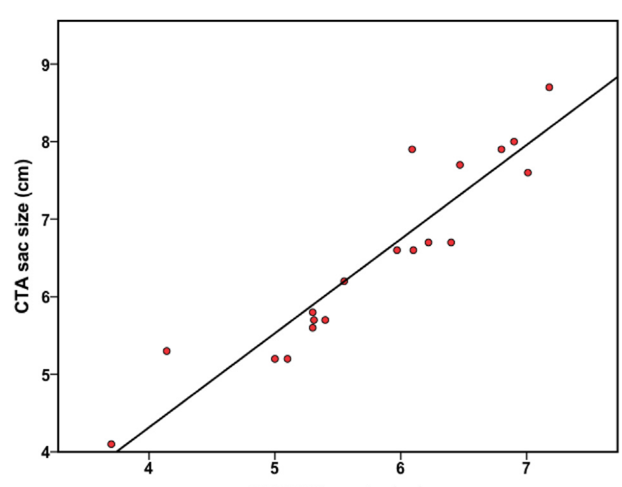

Figure 3. Correlation in post-EVAR sac size measured by CT and 3D CEUS (Pearson's $r = .935$; $p \leq .0001$).

Table 3. 3D CEUS classified all endoleaks accurately.

Type of endoleak	CTA	2D CEUS	3D CEUS
All endoleaks	17	18	18
Type 1	1?[a]	1	1
Type 2	12	15	17
Type 3	4?[a]	2[a]	None
Type 4	None	None	None
Type 5	None	None	None

[a] CTA could not differentiate in four cases between Type 2 or Type 3 and in one case between Type 1 and 2. 2D CEUS failed to classify endoleak accurately in two patients.

has low sensitivity (70%) but high specificity (98%) to detect endoleaks when compared with 2D CEUS (sensitivity 96%; specificity 85%).[7] In our pilot study, there was an excellent correlation between post-EVAR AAA diameter measured by CTA and ultrasound, but diameter measured by CTA was greater than ultrasound and this is in keeping with published literature.[16]

CEUS has the advantage that dynamic imaging may classify endoleaks with more certainty than CTA, the direction of flow can often be seen. Duplex ultrasound helps in visualising the flow within renal arteries and also identifies blood flow disturbance caused by stent-graft deformation. 3D CEUS allows a reconstruction of these images that is easier to interpret than CTA or 2D CEUS. Moreover, 3D CEUS can be performed within a vascular clinic setting and results are available immediately for review. An operator experienced with vascular ultrasound and CEUS, can learn to use and interpret the 3D images during a 1 day training session. The limitation of CEUS is that it does not visualise stent-graft migration or fracture, although this is resolved by adding a plain X-ray to detect graft migration in a CEUS-based EVAR surveillance programme.

Although CTA is non-invasive, the cumulative nephrotoxicity of contrast media and radiation exposure are major side effects.[18] Conversely, ultrasound is entirely safe and non-invasive; ultrasound contrast can be used repeatedly for surveillance, although caution is advised in subjects with coronary artery disease and heart failure because of risk of pre-mature ventricular contractions.[9,19,20] It is eliminated from the body by the lungs.[9] The disadvantage of ultrasound is that the aorta may be difficult to visualise because of obesity or bowel gas.

EVAR surveillance is time-consuming and costly; a comparison of the clinical and cost effectiveness of 3D CEUS-based surveillance with CTA-based surveillance will have a major impact on the management of patients following EVAR. Duplex ultrasound-based surveillance has been reported to be less expensive than CTA-based surveillance after EVAR.[10,21,22] In our institution, the EVAR surveillance programme entails CTA at 3 months and 1 year post-EVAR and annual 2D duplex thereafter. 3D CEUS is performed if an endoleak is suspected. In comparison with CTA only annual surveillance, this has afforded a 67% reduction in surveillance cost (CTA = £250; 3D CEUS including contrast = £108).

CONCLUSION

3D CEUS was more sensitive than CTA for the detection of the source and outflow in endoleak following EVAR. Intervention and treatment of endoleak depends on this information. A definitive study is required to explore the role and cost effectiveness of 3D CEUS in EVAR surveillance.

FUNDING

Manchester Surgical Research Trust (MSRT) as the source of funding with (Registered Charity Number 2415906).

CONFLICT OF INTEREST

Professor Charles McCollum has shares in Curefab EIG.

ACKNOWLEDGEMENTS

Helen O'Donnell (EVAR surveillance nurse practitioner). Curefab supplied the 3D CEUS instrument.

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