Single-centre Prospective Comparison Between Contrast-Enhanced Ultrasound and Computed Tomography Angiography after EVAR


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Contrast-enhanced ultrasound; Computed tomography; Endoleak; Endovascular aneurysm repair

Abstract
Aim: To evaluate contrast-enhanced ultrasound (CEUS) as an effective alternative to CT-angiography (CTA) for endoleak detection and aneurismal sac diameter measurement in the follow-up after endovascular abdominal aortic aneurysm repair (EVAR).

Methods: From January 2006 to December 2010, 395 patients underwent EVAR follow-up with both CTA and CEUS. The diameter of the aneurismal sac and the presence of endoleaks were evaluated in all the 395 paired examinations.

Results: Bland–Altman plots showed a good agreement in aneurismal sac diameter evaluation between the two imaging modalities. The mean diameter was 54.93 mm (standard deviation (SD) ± 12.57) with CEUS and 56.01 mm (SD ± 13.23) with CTA. The mean difference in aneurismal sac diameter was −1.08 mm ± 3.3543 (95% confidence interval (CI), −0.75 to −1.41), in favour of CTA. The number of observed agreement in endoleak detection was 359/395 (90.89%). The two modalities detected the same type I and type III endoleaks. McNemar’s $\chi^2$ test confirmed that CTA and CEUS are equivalent in endoleak detection.

Conclusions: CEUS demonstrated to be as accurate as CTA in endoleak detection and abdominal aortic aneurysm diameter measurements during EVAR follow-up, without carrying the risks of radiation exposure or nephrotoxicity. Even if it cannot be proposed as the sole imaging modality during follow-up, our analysis suggests that it should have a major role.

Endovascular repair of abdominal aortic aneurysm (AAA) was introduced more than 20 years ago as a minimally invasive option to treat infrarenal AAAs. Since then, endovascular abdominal aortic aneurysm repair (EVAR) has gained widespread acceptance. Although conceived and initially used to treat patients deemed to be at high risk for conventional open surgery, recent randomised controlled trials have shown at least a short-term advantage for EVAR.
in fit patients. On the other hand, EVAR has been associated with a higher incidence of secondary interventions due to endoleak, migration or kinking. A strict follow-up is therefore mandatory for early detection — and correction — of these issues to avoid more severe complications.

Computed tomography angiography (CTA) is considered, at present, the gold standard for EVAR follow-up, but has several important drawbacks such as cumulative radiation dose and subsequent risk of malignancies, nephrotoxic contrast agent load and high costs that can limit its use as a lifelong surveillance tool. Some authors indicated that colour duplex ultrasound (US) can be used for post-EVAR follow-up, but a systematic review by Ashoke et al. highlighted that US alone is insufficient in endoleak detection. Contrast-enhanced ultrasound (CEUS) seems to be a highly sensitive modality for endoleak detection and EVAR surveillance, but the available literature is, at present, still scant.

In our present single-centre study, we prospectively collected and analysed 395 patients who underwent EVAR and were subsequently followed up with both CTA and CEUS. The efficacy of the two techniques in endoleak detection and aneurysmal sac diameter measurement was compared.

Materials and Methods

Patients and study design

The study enrolled all patients who underwent EVAR for abdominal aortic aneurysms at our institution and for whom a follow-up with CTA and CEUS was undertaken, during the period from January 2006 to December 2010. The time interval between the two examinations was <15 days. If a patient had repeated follow-up with both CEUS and CTA, we only included the first CEUS that was performed and compared it to the corresponding CTA.

EVAR was performed with Zenith (Cook Medical, Bloomington, IA, USA), Talent (Medtronic, Santa Rosa, CA, USA), Anaconda (Vascutek, Terumo, Inchinnan, Scotland) or Fenestrated endografts (Cook Medical). All cases were performed in a dedicated operating theatre with an OEC 9900 Elite MD Imaging System (GE Healthcare, Salt Lake City, UT, USA).

This study was approved by the Ethical Review Board of our institution, and written informed consent was obtained from all patients.

CTA

All the CTAs were performed in our institution with a 64-slice CT scanner (Philips Brilliance 64 CT scanner, Philips Healthcare, Amsterdam, Netherlands). Triple-phase acquisition with unenhanced and contrast-enhanced in arterial (with bolus tracking) and delayed phases (at 70 s) was carried out from the thorax to the femoral bifurcations. Contrast medium (100 ml of Iomeron 350 Bracco SA, Milano, Italy or Omnipaque 350, Amersham Health, Princeton, NJ, USA) was injected through a 18-gauge cannula in an antecubital vein with the use of a power injector (Envision, Medrad, Pittsburgh, PA, USA) at a rate of 4.5 ml s⁻¹, followed by 40 ml of saline solution injected at a rate of 4.5 ml s⁻¹. A region of interest in the proximal abdominal aorta was used to monitor the bolus; the scan started 6 s after the enhancement of this region had crossed the threshold trigger of 200HU. Further data acquisition parameters were 0.625 mm detector width, 120 kVp and 250 mA, reconstructed at 1-mm thickness every 0.7 mm. Patients with renal insufficiency were prepared for CTA with intravenous hydration before and after the examination. Patients with a history of iodinated contrast media allergy were pre-medicated with oral corticosteroids and antihistamines before the examination.

The CTAs were analysed on an independent dedicated workstation (Aquarius, TeraRecon, San Matteo, CA, USA) by both vascular surgeons and vascular radiologists (who were blinded to the results of CEUS, if already performed) to determine the maximal aortic diameter by centreline measurements and to depict and characterise endoleaks. Both diagnostic techniques (CTA and CEUS) were also used to identify patency and proper graft placement (features not analysed in this study).

CEUS

All US scans were performed by three angiologists experienced in vascular ultrasonography and in the use of ultrasound contrast material who were blinded to CTA findings at the time of examination. These scans were performed with three instruments: a Philips iE33 (Philips Healthcare, Amsterdam, Netherlands), a Vivid 7 and a Vivid 9 (GE Healthcare, Salt Lake City, UT, USA) equipped with a convex 3.5-MHz probe. A typical US examination started with standard B-mode investigation to measure the aneurysm sac diameter (outer wall to outer wall, dimensions recorded as the mean of three measurements). Then, the blood flows from the main body of the endograft to the femoral arteries were analysed with pulse wave modality. In the setting of a fenestrated or multibranched endograft, the visceral arteries were also evaluated (a feature not analysed in this study). CEUS was then performed after the administration of a bolus of ½ bottle (2.5 ml) of SonoVue (Bracco, Milan, Italy — the only second-generation contrast agent approved in France), flushed with an injection of a 5-ml bolus of isotonic saline solution through an intravenous cannula. Endoleak detection was performed at a low mechanical index (0.2—0.3) and with the focus positioned behind the aorta to delay bubble destruction. If the 6-min time frame allowed by this bolus was insufficient to properly detect or characterise the endoleak, the rest of the bottle of contrast media was injected with the same modalities in order to complete the examination.

We have classified the endoleaks according to the ‘Reporting standards for endovascular aortic aneurysm repair’ published in 2002.

Statistics

The maximal external aneurysm sac diameter was measured with both diagnostic techniques, and data were expressed as mean ± standard deviation (SD). Comparison of size measurements between CTA and CEUS was...
performed by Bland–Altman plots. A McNemar’s $\chi^2$ test was performed to identify differential endoleak detection by the two imaging modalities.

Results

In the period from January 2006 to December 2010, 614 patients underwent EVAR in our centre. The following patients were excluded from this study: 61 patients who underwent thoracic endografting, 17 with severe contrast media allergy and 22 with severe renal insufficiency. In addition, 83 refused enrolment in the current study.

We enrolled in this prospective study 431 patients who underwent subsequent follow-up with both CEUS and CTA in our institution. Thirty-six potential paired examinations were excluded from this comparative analysis for one of the following reasons: time interval between CEUS and CTA >15 days as a consequence of logistic problems ($n = 35$) and failure to perform CEUS because of intervening bowel gas ($n = 1$). Overall, 395 patients and as many paired examinations were available for comparative analysis. The paired imaging was performed less than 1 month after the procedure (typically before discharge) in 274 patients (69.4%), and during follow-up (median 18.55 months, range 35 days to 9 years after the procedure) in 121 patients (30.6%). EVAR was performed with 308 bifurcated endografts (77.97%), 31 aorto-uni-iliac (7.85%) and 56 fenestrated endografts (14.18%). Endografts were manufactured by Cook (386/395 grafts, 97.72%), Medtronic (7/395, 1.77%) or Vascutek (2/395, 0.51%). All patients completed the follow-up, and no adverse events were recorded during these examinations.

AAA diameter

The mean diameters of the abdominal aortic aneurysm sac at follow-up were 54.93 mm (SD ± 12.57) with CEUS and 56.01 mm (SD ± 13.23) with CTA. The mean difference in aneurysm sac diameter was $-1.08$ mm ± 3.3543 (95% confidence interval (CI), $-0.75$ to $-1.41$), in favour of CTA. The agreement between maximal external aneurysm sac diameter measurements by CTA and CEUS was represented in Bland–Altman plots (Fig. 1), which showed a good agreement between the two imaging modalities (only 4.81% of data points were outside the limits of agreement). The regression line of differences confirmed this agreement (correlation coefficient: $0.1968$, $p < 0.001$) showing a minimal slope of the trendline ($slope = -0.0516$, $p < 0.001$).

Agreement between measurements obtained from the two methods was confirmed by the correlation coefficient $R = 0.967$, $p < 0.001$; slope of the trendline $= 1.0179$, $p < 0.001$; intercept – the point where the trendline intersects the y-axis $= 0.0989$) (Fig. 2).

Endoleaks

Endoleaks were detected by CTA in 25.06% (99/395 patients) and by CEUS in 26.08% (103/395). Endoleaks were detected by both imaging modalities in 83 patients (Table 1). The number of observed agreements was 359/395 (90.89%) (Figs. 3 and 4). McNemar’s $\chi^2$ test confirmed that the two methods are equivalent. In fact, with a $\chi^2$ value of 0.25 the null hypothesis cannot be rejected ($p > 0.5$).

Analysing more in detail the ability of the two techniques in detecting the endoleaks according to their type, we noticed that the majority of detected endoleaks were type II endoleaks (Table 2), and were found in 20.76% of the patients with CEUS, and in 19.75% of the patients with CTA. CEUS detected 21 type II endoleaks that were not shown by CTA and CTA showed 17 type II endoleaks that were not detected with CEUS (McNemar’s $\chi^2$ value $= 0.2368$, $p > 0.5$, the two imaging modalities have to be considered as equivalent). The two modalities detected the same type I and type III endoleaks. No type IV endoleaks were detected in this study.

Discussion

CTA is considered, at present, the gold standard for radiologic follow-up after EVAR. Unfortunately, CT scan presents several important disadvantages that are exacerbated by the lifelong surveillance needed for these patients. The radiation dose of a thoraco-abdominal CT scan is more than 20 mGy, and a standard follow-up performed only with this modality equates to a total effective radiation dose of around 145–205 mSv over 5 years with a subsequent, significant, higher risk of cancer. Nephrotoxic contrast agent load causes an important renal
function decline during long-term follow-up (significantly greater if compared to open repair);\(^{17}\) preservation of renal function is vital to obtain favourable long-term outcomes\(^{18}\) and must be pursued. Moreover, high costs represent an additional limitation for its widespread use in lifelong surveillance.\(^{6}\)

For these reasons, a safer and more cost-effective alternative to CTA is an issue that must be addressed. This alternative tool, to be effective, should be able to provide information about the maximal diameter of the aneurysm, occurrence of endoleaks, migration of the endograft, component separation, kinking and thrombosis of graft limbs with a high sensitivity and specificity.

Colour duplex ultrasound is less expensive and does not carry the risks associated with ionising radiations or contrast-induced renal insufficiency. For these reasons, it has been investigated as an alternative to CTA for EVAR follow-up. Even if this modality proved to be highly accurate during EVAR follow-up in diameter measurements\(^{20}\) (an element that is suggestive of endoleak), an initial systematic review by Ashoke \textit{et al.}\(^{10}\) and a recent systematic review and bivariate meta-analysis by Mirza \textit{et al.}\(^{11}\) highlighted that non-CEUS lacks sufficient diagnostic accuracy for sole use in endoleak detection. Moreover, US performance could be poorer in the presence of unfavourable body habitus such as obesity, coexistent pathology like ascites or excessive intervening bowel gas, endoprosthesis factors such as echo reflection from the stent graft and slow endoleak flow.

![Figure 3](image1.png) **Figure 3** Visualization of a type 2 endoleak with CEUS (a, transverse scan, harmonic) and CTA (b, axial MPR view).

![Figure 4](image2.png) **Figure 4** A type II endoleak perfused by the Inferior Mesenteric Artery. a) Power-Doppler image of the endoleak, longitudinal scan. b) MIP view of the same endoleak on post-operative CTA.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Endoleaks detected with CTA and CEUS.</th>
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<tbody>
<tr>
<td></td>
<td>CTA+</td>
</tr>
<tr>
<td>CEUS+</td>
<td>83</td>
</tr>
<tr>
<td>CEUS−</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>99</td>
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<table>
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<tr>
<th>Table 2</th>
<th>Classification of the endoleaks detected with CEUS and CTA.</th>
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<tbody>
<tr>
<td>Endoleak</td>
<td>CEUS</td>
</tr>
<tr>
<td>No endoleak</td>
<td>292</td>
</tr>
<tr>
<td>Type I</td>
<td>18</td>
</tr>
<tr>
<td>Type II</td>
<td>82</td>
</tr>
<tr>
<td>Type III</td>
<td>3</td>
</tr>
<tr>
<td>Type IV</td>
<td>0</td>
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</table>
All these drawbacks can be minimised by the use of contrast media.\textsuperscript{11,21} These stabilised microbubbles of sulphur hexafluoride gas (that is eliminated through the respiratory system) surrounded by a phospholipid shell improve blood flow echogenicity by resonating with low-intensity US, which enhances backscatter and thereby increases the detected signal. Second-generation ultrasonographic contrast agents are safe agents for which no adverse events such as nephrotoxicity have been described.\textsuperscript{11}

Literature evaluating CEUS in EVAR follow-up is still scant, especially if compared to the data available on unenhanced ultrasound. In fact, the largest amount of data is provided by the systematic review and bivariate meta-analysis by Mirza et al.,\textsuperscript{11} published in 2010, which suggests that CEUS has superior sensitivity compared to unenhanced ultrasound for the detection of endoleaks after EVAR. Mirza et al.,\textsuperscript{11} analysed 21 studies with a total of 2601 patients for the unenhanced US group, and only seven studies and 288 patients in the CEUS group. Considering also the two studies published after this review by Ten Bosch et al.,\textsuperscript{22,23} and by Cantisani et al.,\textsuperscript{19} which present 83 and 108 patients, respectively, the total number of paired examinations comparing CEUS to CTA is, at present, 479 in nine different studies. Moreover, these studies present a high degree of heterogeneity in the existing evidence, and Mirza et al.,\textsuperscript{11} concluded that further research is required.

So far, our study provides the largest case series of patients followed up with both CTA and CEUS, showing that the two techniques have the same efficacy in endoleak detection, with a number of observed agreements of 359/395 (90.89%). The equivalence of the two imaging modalities was confirmed by the McNemar’s $\chi^2$ test ($\chi^2 = 0.25$, $p > 0.5$, the null hypothesis of ‘marginal homogeneity’ cannot be rejected).

There are limitations in CEUS examinations that cannot be — apparently — minimised by the use of contrast media. First of all, the well-known operator dependency of US examinations might limit the reproducibility of the results. However, as demonstrated by the interobserver analysis in the study by Ten Bosch et al.,\textsuperscript{22} variability in AAA sac diameter measurements was low if performed by well-trained operators. Second, factors such as obesity, ascites or intervening bowel gas might interfere with US imaging. However, in the present study, only one CEUS was unsuccessful (and therefore the patient was excluded), indicating that fasting associated to a new-generation ultrasonic imaging device can overcome this issue and obtain an adequate visualisation of the AAA. Another potential drawback of CEUS might be the inability to detect stent-strut failure, kinking of the limbs or migration of the endoprosthesis. Plain abdominal X-ray, in two to four projections, provides all of this information; the radiation dose is about 1 mSv and the subsequent risk of cancer therefore negligible.\textsuperscript{15} The higher rate of endoleak detection (especially type II endoleaks) with CEUS compared to CTA is not to be considered as a ‘false positive’, but represents its higher sensitivity in the detection of true low-flow endoleaks (this may be explained by the continuous real-time scanning opposed to the two static temporal angiographic images in CTA).\textsuperscript{22,23} Also in our study, CEUS detected a higher number of endoleaks compared to CTA. However, this difference did not reach statistical significance, and our statistical analysis indicated that the two methods are equivalent.

Finally, CEUS allows better classification of endoleaks\textsuperscript{19} since it has the advantage to provide haemodynamic information on blood-flow direction in addition to the possibility to compare, in real-time and on the same screen, the baseline and the contrastographic images. Defining inflow and outflow vessels perfusing the endoleak is of potential interest in preinterventional planning of transarterial embolisation.

The shrinkage or the growth of the aneurismal sac refers to elements that are suggestive of successful aneurysm exclusion. Thus, AAA sac diameter measurement during EVAR follow-up is mandatory. In our experience, US and CEUS demonstrated to be as accurate as the CT for AAA sac measurements: Bland–Altman analysis of aneurism sac diameter demonstrated good agreement between the two imaging modalities.

The role of post-EVAR surveillance is also to guide re-intervention. CT provides superior information related to graft anchoring, kinking and integrity or aneurysm morphologic changes including aneurismal degeneration of the iliac arteries. It is thus mandatory to perform a new CT for proper planning in case of re-intervention.

In accordance with the recent literature,\textsuperscript{11,19,22} providing a significantly larger number of patients, this study indicates that CEUS has demonstrated to be at least as accurate as CTA in post-EVAR follow-up, especially if associated to plain X-ray. CEUS cannot be proposed for the sole imaging modality during EVAR surveillance, particularly if a re-intervention is needed, but it can surely replace most of the CTA reducing the ionising radiation load and the risk of renal insufficiency. In our centre, CEUS has already replaced the 6-month and 24-month (and yearly thereafter) CTA scheduled in the standard post-EVAR surveillance protocol, and we are planning to further reduce the number of CTA in the future.

Conclusions

An ideal surveillance protocol is supposed to have an optimal sensitivity and specificity for the detection of possible complications without posing an extra health risk to the patient, and finally has to be cost-effective. CEUS has demonstrated to be as accurate as CTA in endoleak detection and AAA sac diameter measurements during EVAR follow-up, and does not carry the risks associated to radiation exposure and nephrotoxicity. Furthermore, it is cheap, fast, and can be repeated frequently. CEUS, in association with plain abdominal X-ray, should replace most CTAs performed during post-EVAR surveillance. CTA is still necessary for proper endovascular planning in case of re-intervention.

Conflict of Interest/Funding

None.
References