Contrast-enhanced Duplex surveillance after endovascular abdominal aortic aneurysm repair: Improved efficacy using a continuous infusion technique

Esteban A. Henao, MD,a Megan D. Hodge, RN, RVT,b Deborah D. Felkai, RN, RVT,c Charles H. McCollum, MD,a George P. Noon, MD,a Peter H. Lin, MD,a Alan B. Lumsden, MD, RVT,a and Ruth L. Bush, MD, RVT,a Houston, Texas

Introduction: Currently, postoperative endoleak surveillance after endovascular aortic aneurysm repair (EVAR) is primarily done by computed tomography (CT). The purpose of this study was to determine the efficacy of contrast-enhanced ultrasonography scans to detect endoleaks by using a novel infusion method and compare these findings with those of CT angiography (CTA).

Methods: Twenty male patients (mean age, 70.4 years) underwent surveillance utilizing both CTA and contrast-enhanced color Duplex imaging. One 3-mL vial of Optison (Perfluten Protein A microspheres for injection) and 57 mL normal saline, for a total of 60 mL, were administered to each patient as a continuous infusion at 4 mL/min via a peripheral vein. Each study was optimized with harmonic imaging, and a reduced mechanical index of 0.4 to 0.5, compression of 1 to 3, and a focal zone below the aorta to minimize microsphere rupture. One minute was allowed from the time of infusion to the appearance of contrast in the endograft. Flow was evaluated within the lumen of the graft and its components, as was the presence or absence of endoleaks. Findings were compared with standard color-flow Duplex imaging and CT utilizing CTA reconstruction protocols.

Results: All patients evaluated had modular endografts implanted for elective aneurysm repair. Contrast-enhanced duplex scans identified nine endoleaks: one type I and eight type II. No additional endoleaks were seen on CTA. However, CTA failed to recognize three type II endoleaks seen by contrast-enhanced ultrasound. The continuous infusion method allowed for longer and more detailed imaging. An average of 46.8 mL of the contrast infusion solution was used per patient.

Conclusions: Contrast enhanced Duplex ultrasonography accurately demonstrates endoleaks after EVAR and may be considered as a primary surveillance modality. Continuous infusion permits longer imaging time. (J Vasc Surg 2006;43:259-64.)

Although the benefits of less invasive surgery and shorter length of stay are triumphs of endovascular aneurysm repair (EVAR), long-term surveillance is necessary to monitor for persistent endoleaks, aneurysm growth, and potentially, rupture.4 Computed tomography (CT) is currently the standard modality used for following patients after EVAR,2 but the exposure to ionizing radiation and nephrotoxic contrast agents is also of concern. Financial issues of surveillance have also been noted, with a recent study showing about 65% of postoperative EVAR costs are due to CT scanning.3 For these reasons, alternative surveillance methods such as duplex ultrasound scans have been explored.

Color duplex ultrasound has been previously reported as having lower sensitivity and positive predictive value in detecting endoleaks after EVAR compared with CT.4 However, the ultrasound contrast agents that have shown marked benefit in echocardiography5-8 seem to increase sensitivity in ultrasound surveillance after EVAR by allowing improved blood flow echogenicity for better evaluation.9,10 For example, a recent study of patients with abdominal aortic aneurysm enlargement and no evidence of complications were evaluated with contrast-enhanced ultrasonography (CEUS), which identified endoleaks, challenging the existence of what has been defined as endotension.10 Similarly, another recent study characterized several endoleaks found on CEUS not identified on CT as hypodynamic, or slow leaks.9

Our study prospectively evaluated the use of a continuous infusion method of ultrasound contrast in the surveillance of abdominal aortic endografts in detecting endoleaks compared with CT. Our hypothesis was that CEUS was more sensitive than CT for endoleak detection.

METHODS

From July 2004 to May 2005, a prospective study, approved by the Institutional Review Board of Baylor College of Medicine, was conducted to evaluate the effective-
ness of CEUS imaging to detect endoleaks in patients who underwent endovascular treatment for an infrarenal abdominal aortic aneurysm. The standard for endoleak detection in this study was CT with contrast. We defined endoleak as the presence of persistent intrasac flow outside the stent-graft. The endoleaks were characterized in relation to the endograft, aneurysm wall, and aortic side branches, and recorded in accordance to the White-May classification as previously described.13,14

At our institution, patients are typically followed after a successful endovascular aneurysm repair at 1, 6, 12, and 24 months, and annually thereafter. All men and postmenopausal women seen at these follow-up intervals were asked to participate unless there was a documented contraindication to the use of ultrasound contrast, blood products, or albumin. Participants received an information sheet explaining the study and gave written informed consent on the day of the scan. Exclusion criteria included patients with a known endoleak from previous examinations, severe iodinated contrast allergy, or evidence of renal insufficiency marked by a serum creatinine level > 1.5 mg/dL. Patients were also excluded if there was evidence of a right-to-left cardiac shunt or severe pulmonary or hepatic disease.

Optison (Perflutren Protein Type A Microspheres for Injection, Amersham Health, Princeton, NJ) is a Food and Drug Administration-approved injectable, sterile suspension of human serum albumin and octafluoropropane gas microspheres used for contrast enhancement during echocardiography. It has a half-life reported by the manufacturer of 1.3 ± 0.69 minutes, and a benign toxicity profile shown to be free of nephrotoxicity.15 Contrast was prepared by using a single, 3-mL vial of Optison and 57 mL normal saline combined in a sterile 60-mL syringe. The solution was placed on a syringe pump set to deliver a continuous infusion at 4 mL/min, typically delivered via a right upper-extremity peripheral access (20-gauge angiocatheter). An assistant was available at each study to manually agitate the contrast to minimize microsphere precipitation during the examination.

Four experienced vascular sonographers (M. H., D. P., D. F., M. E.) performed all the ultrasound studies using a 3.5-MHz probe on a Phillips iU22 unit (Phillips Medical Systems, Bothell, Wash.). Ultrasonographers were blinded to the results of previous angiographic or CT angiographic (CTA) results. Fasting patients were scanned with grey scale and color Duplex before the intravenous Optison administration. Measurements of the aneurysm were recorded in all patients, as well as the entire duration of the study, and the amount of contrast. Time from the beginning of contrast infusion to appearance in the endograft was recorded in all patients, as well as the entire duration of the study, and the amount of solution used. The infrarenal aorta and native aneurysm sac was scanned after Optison injection in a longitudinal and transverse perspective from the renal to distal iliac arteries. Flow was evaluated within the lumen of the graft and its components, as well as the presence or absence of endoleaks. All procedures were recorded on standard VHS media for later evaluation and archiving purposes.

Computed tomography angiography was performed on the same day (Lightspeed Ultra, GE Healthcare, Waukesha, Wisc) before CEUS. The protocol called for the intravenous injection of 150 mL of a contrast agent at a rate of 2.5 mL/s. SmartPrep computer-automated scan technology (GE Healthcare) was used to optimize the injection phase. The standard scan delay for the arterial phase was 10 to 28 seconds; the delayed phase was timed to commence 70 seconds after the completion of the first scan, which took 20 seconds on average. Tomograms were reconstructed by using a 1.5-mm algorithm from celiac to iliac arteries.

RESULTS

Twenty men (mean age, 70.4 years) participated in our study from July 2004 to May 2005. The mean height and weight of the group was 179 cm (range, 162 to 200 cm) and 91 kg (range, 61 to 137 kg). Patients had a mean body mass index (BMI), calculated as kg/m², of 28.2. Mean aneurysm size was 5.27 cm at the time of follow-up. Average follow-up time was 8.7 months (range, 1 to 36 months). The endografts had varying modular designs and had been electively placed.

The average volume of ultrasound contrast solution administered to each study patient was 46.8 mL (range, 32 to 60 mL). The mean time necessary to perform the contrast enhanced portion of each exam was 11.8 minutes (range, 8 to 28 minutes). BMI was then compared with CEUS time, and a direct relationship was noted, with a Pearson correlation coefficient of 0.47 (Fig 1). None of the CEUS scans done after all of the CTA studies appeared to have been affected by the use of the standard iodinated contrast agents used in the CT scans. There were no adverse events secondary to CEUS.

Contrast-enhanced ultrasound detected nine endoleaks (Table). Eight of the endoleaks were classified as type II (Fig 2). Seven of the type II endoleaks were classified as lumbar in origin, and one was identified and confirmed on CTA as an inferior mesenteric arterial type II leak. A single type I endoleak was noted on all modalities. This patient also...
demonstrated a significant increase in aneurysm diameter that led to a therapeutic intervention in which an endoluminal extender cuff was successfully placed. Color Duplex ultrasound scans identified four (44%) endoleaks, including the type I endoleak. Six (67%) endoleaks were also identified with CTA. Three type II endoleaks found on CEUS were not confirmed on CTA (Fig 3). No endoleaks were seen on CTA that had not been found on CEUS.

DISCUSSION

Our study confirms previous observations that suggested the efficacy of CEUS vs CTA. Using a continuous infusion technique, we were able to clearly visualize eight type II endoleaks and one type I after EVAR, whereas CTA identified five type II and one type I. The amount of time

Fig 1. Relationship of contrast-enhanced ultrasound (CEUS) time with body mass index (BMI).

Table. Patient demographic data with endoleak type identified on contrast-enhanced ultrasound, color duplex, and computed tomography

<table>
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US, Ultrasound; CT, computed tomography.

Fig 2. A, Cross-sectional contrast-enhanced ultrasound image of main body of aortic endograft with a small type II endoleak (arrow). B, A cross-sectional color duplex ultrasound scan of same patient shows no evidence of endoleak. C, Computed tomography angiography of the same patient demonstrates no endoleak.
available to search for endoleaks was substantially greater with a continuous infusion. Thus, our continuous infusion modality may have contributed to improved detection compared with previous reports of bolus contrast.

Reports concerning CEUS as a surveillance tool after EVAR have all described the administration of contrast agents in the form of a bolus.9-12,16-18 The required or optimal dosage for administration of contrast agents after EVAR is not known, which has been the source of reported difficulties when using CEUS. Napoli et al10 were required to infuse multiple boluses in two patients because they could not show any clear endoleak with the first dose. Bargellini et al9 found the need to increase the bolus amount from 1.5 mL to 2.4 mL for similar reasons. After the administration of a contrast bolus, the time available to complete an enhanced scan was 3 to 11 minutes in previous reports.9-12,16

In our preliminary experience, the average learning curve for using CEUS in those experienced with abdominal vascular screening was 10 to 15 studies. The initial difficulty was thought to be attributed to the pump setup and the need for continuous agitation, as explained above. The continuous infusion allowed for a longer study window, lasting as long as 28 minutes, and allowed for a more deliberate search for small or slow endoleaks, potentially increasing the sensitivity and ease of the study. It also facilitated scanning of the challenging patient with excessive bowel gas or large body habitus, using even unorthodox views (ie, placing the patient in decubitus position) when necessary, without the worry of missing an endoleak because of limited contrast duration.

A weak correlation between BMI and the amount of time it took to perform CEUS was noted. The true significance of this is unknown because of the small sample size.

Ultrasound contrast may minimize scanning hindrances, such as body habitus, while optimizing those features of vascular blood flow.19 Enhanced ultrasound with harmonic imaging appears to diminish these effects, as there were more endoleaks identified than with color duplex imaging. In our comparison of color duplex and CEUS, it was noted that there was a tendency for more artifactual disturbances with color flow. This was despite the use of harmonics, compression, and adjustments in focal zone in both transverse and longitudinal views. Thus, there was a clear benefit in using contrast in that minimal-to-no change in ultrasonic gain was required to discriminate subtle type II endoleaks with contrast, whereas adjustments in the color modality may have led to artifacts. More CEUS observations are needed to clarify this preliminary data trend.

In general, the cost of an ultrasound study may range from $350 to $1000, and a vial of the Optison contrast agent is $140.40, according to the manufacturer. Several patients in our series required scanning periods well past the maximum duration reported in previous studies concerning bolus administration of contrast. If continuous infusion had not been used, this may have led to additional contrast administration as well as to increased cost.

Our study is limited by its small sample size. More patients are needed to accurately calculate the sensitivity and specificity of the technique. It could also benefit from a true cost analysis20 to justify the relatively expensive purchase of contrast, syringe pump setup, and maintenance, as well as the need for ancillary staff to monitor the contrast and provide continuous syringe agitation.

CONCLUSION

The potential for malignancy secondary to radiation exposure21 and the well-known complication of nephrotoxicity secondary to iodinated contrast agents drives the search for a better surveillance modality. While newer technologies such as intrasac pressure sensors22 are currently in development, a “perfect” surveillance tool does not yet exist. The need to characterize the dynamic flow of endoleaks may be useful in the decision for therapy, and CEUS may be an excellent tool for this use. However, CT scanning remains the gold standard in the periodic monitoring of aneurysm size, migration, and other physical factors such as changes in limb position and partial limb separation and should continue to be a part of the standard follow-up regimen in EVAR patients.

AUTHOR CONTRIBUTIONS

Conception and design: EAH, MDH, DDF, CHM, GPN, PHL, ABL, RLB
Analysis and interpretation: EAH, MDH, DDF, RLB
Data collection: EAH, MDH, DDF, RLB
Writing the article: EAH, RLB
Critical revision of the article: EAH, MDH, DDF, CHM, GPN, PHL, ABL, RLB
Final approval of the article: EAH, MDH, DDF, CHM, GPN, PHL, ABL, RLB
Statistical analysis: EAH, RLB
 Obtained funding: CHM, GPN, PHL, ABL, RLB
Overall responsibility: EAH
REFERENCES

DISCUSSION
Dr K. Craig Kent (New York, NY). You said that there is potential for decreased cost. Do you have any idea of what the cost of the agent is? Can you compare this to the cost of a CT scan?

Dr Esteban A. Henao. There was a study in 2003 by Bendick, which used a different contrast agent, demonstrating the cost effectiveness of CEUS. A figure that I can give you is $140 over US contrast vial used in our study. And the average cost for a follow-up US scan is anywhere from $150 to $400, depending on the area and the hospital.

Dr Ali AbuRahma (Charleston, WV). Did you follow your patients who had CT scans by delayed imaging, which may have shown leaks that were missed?

Second question, for patients who had duplex ultrasound without contrast, were the leaks type I or type II, which may have clinical significance?

When do you see this agent becoming commercially available, since we still don’t have it here in the United States?

Dr Henao. To answer your first question, this study used a biphasic CT scan, so there was an arterial phase and a delayed phase.

In terms of duplex without contrast, the grey scale view was done as part of our general evaluation, but it wasn’t used to look for endoleaks.

Lastly, the contrast used in our study is currently FDA-approved for echocardiography only.

Dr Munier Nazzal (Toledo, Ohio). What is the gold standard here? How do you know that what you are diagnosing is not an artifact leading to overdiagnosis of endoleak?

Dr Henao. That is a good question. And I don’t know if there are any hard data that says what is the gold standard. Right now CT is what we use.

Yesterday Dr Ohki gave an excellent presentation on pressure monitoring of the sac. That may actually be the new gold standard, depending on how that comes out.

The truth of the matter is that there is no one perfect study. I think even if we do implement a device that evaluates pressure measurements, we are still going to want to look at the integrity of the device, we are still going to want to see blood flow around the endograft. So inevitably, we are going to integrate all these different modalities and come up with a unified way to follow these grafts.

Dr Kent (New York, NY). You may have told us the answer to this question, but what are the next steps? How long until we have this available in clinical practice, and what other evaluations have to be conducted before we get to that stage?

Dr Henao. I am not sure what the answer is. I think we are making headway. This is going to be the sixth preliminary study. I think if we have more patients, we can present that to the FDA and get this thing underway, because the proof is in the pudding. One can see endoleaks and there is definitely evidence of ruptures despite negative CT findings. So if we are missing potential disas-
ters with computed tomography, it is imperative that we find a better modality.

Dr Kent. One last question. Do you sense that there has to be any special expertise in your ultrasound lab to use this technique, or does this diminish the need for special expertise?

Dr Henao. I think one of the criticisms of ultrasound in the follow-up of EVAR is that it is operator-dependent. But with the use of the contrast agent, there were many times that I felt that I could probably do the scan myself, and I am by no means a certified technologist. The clarity of blood flow makes the scan substantially easier. However, it is still a very labor-intensive scan. I don’t know if any of you have ever seen an ultrasound of an EVAR follow-up, but it is very hard on the technician, and I think using the contrast helps to speed up the process significantly.

Dr Julie Ann Freischlag (Baltimore, Md). Have you used this technique in other arteries besides the aorta looking for endoleaks, such as the carotid?

Dr. Henao. We have, but it is anecdotal at this stage, looking at SFA, a string sign of the carotid, but we don’t really have a hard-and-fast experience to comment on at this point, but it seems to be very useful.

INVITED COMMENTARY

Thomas L. Forbes, MD, London, Ontario, Canada

After endovascular repair of an aortic aneurysm, the infrarenal aorta continues to demonstrate characteristic changes during follow-up. Even in the successfully excluded aorta, there remains a remodeling process reflected in changes in aortic neck, aneurysm, and iliac artery geometry. With aneurysm sac pressurization these changes are exacerbated and unpredictable, reinforcing the need for long-term surveillance. Until fairly recently, many centers have used static computed tomography (CT) images as their surveillance modality of this dynamic remodeling. Although quite capable of identifying significant endograft migration, contrast-enhanced CT scans are less than perfect in identifying the source of some endoleaks, predicting their physiologic ramifications, and in planning endoleak directed therapies.

In the present study, the Baylor group is to be commended for further refining a contrast-enhanced ultrasound protocol for endograft follow-up. They used a continuous infusion technique of an albumin and microsphere suspension-based agent previously used with contrast echocardiography. It proved more accurate than CT imaging in the identification and classification of endoleaks and allowed for longer periods of monitoring compared with ultrasound scans using boluses of contrast. The findings of this 20-patient study certainly suggest further examination of this technique is warranted. This may also prove to be a more cost-effective method of surveillance.

Although static (CT) and dynamic (ultrasound) imaging modalities offer extensive detail about endograft integrity, aneurysm geometry, and endoleak identification and classification, they are incapable of predicting the ramifications of these changes. This requires a measure of aneurysm pressurization, of which aneurysm diameter, volume, and endoleak identification are but a surrogate. A noninvasive method of sac pressure measurement has recently been developed that offers the possibility of determining which aneurysms required reintervention based on physiologic parameters.

As the authors suggest, the perfect surveillance tool after endovascular repair undoubtedly involves an algorithm rather than a single imaging modality. This includes static imaging techniques (plain radiographs, CT, magnetic resonance) to monitor endograft integrity and aneurysm remodeling, dynamic imaging (ultrasound) to accurately identify and classify endoleaks, and physiologic monitoring (intrasc pressure transducer) to determine the need for reintervention. As this surveillance algorithm is elucidated further, it is likely that follow-up regimens will become patient specific, as all aneurysms will not require all surveillance modalities. This continues to be an important and evolving area of endovascular surgery that all vascular surgeons are encouraged to follow closely.

REFERENCE