Color Doppler Ultrasound with Superb Microvascular Imaging Compared to Contrast-enhanced Ultrasound and Computed Tomography Angiography to Identify and Classify Endoleaks in Patients Undergoing EVAR

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Background: The aim of the study was to evaluate the diagnostic effectiveness of color Doppler ultrasound (CDUS) with superb microvascular imaging (SMI) compared to contrast-enhanced ultrasound (CEUS), computed tomography (CT) multislice angiography (64 slices), and angiography required for therapeutic reasons, for follow-up after endovascular aneurysm repair (EVAR).

Methods: From March 2014 to May 2015, 57 patients treated with EVAR were evaluated with CT, CEUS, CDUS, SMI, and angiography in cases requiring treatment. Evaluation included sac diameter, stent-graft integrity, identification, and classification of endoleaks. Sensitivity, specificity, accuracy, and negative and positive predictive values were evaluated for each modality of endoleak identification.

Results: Eight endoleaks (16.3%), all type II, were documented. Sensitivity of CT, CEUS, CDUS and SMI was 88%, 100%, 63%, and 75%, respectively. Specificity of CT, CEUS, CDUS, and SMI was 100%, 100%, 96%, and 98%, respectively With SMI, CDUS sensitivity significantly increased, whereas specificity did not register great differences.

Conclusions: SMI was more accurate than CDUS but less accurate than CEUS and CT to identify endoleaks after EVAR. SMI could be concretely used in the follow-up phase to increase CDUS accuracy especially in patients who cannot be studied with CEUS or CT.

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Ann Vasc Surg 2017; 40: 136–145
http://dx.doi.org/10.1016/j.avsg.2016.06.038

Manuscript received: March 12, 2016; manuscript accepted: June 22, 2016; published online: 23 September 2016

INTRODUCTION

Abdominal aortic aneurysm repair (endovascular aneurysm repair [EVAR]),[1] is complicated in about 30% of cases by persistent arterial communication between the aneurysm sac and systemic circulation, that is, endoleak.[2,3] In 10–45% of cases, endoleaks can be associated to a dilation of the aneurysm sac,[4] requiring a reintervention in 8.7% of cases over an average period of 12 ± 13 months.[5] As most post-EVAR complications, including endoleaks, are asymptomatic but potentially dangerous, patients must be kept under lifelong surveillance.

The ideal imaging modality should be inexpensive, repeatable, safe, and accurate.[5] Currently, the correct follow-up modality and timing are still controversial.[5] Computed tomography angiography (CTA) was initially the first choice and still today is the reference diagnostic method because of its wide availability, diagnostic value acquisition speed, resolution, and uniformity of protocols. However, it is expensive, and it uses ionizing radiation and potentially allergenic and nephrotoxic contrast agents.

Valid alternatives to CTA are contrast-enhanced ultrasound (CEUS) and magnetic resonance angiography (MRA).[6,7] The latter is quite expensive and often unavailable.

Currently, in several centers specialized in vascular imaging, including ours, CEUS is considered inexpensive and effective for long-term surveillance of EVAR because of its ability to correctly identify and classify endoleaks without exposing the patient to ionizing radiations.

An innovation in the ultrasound (US) field came up in January 2014 with the introduction of SMI (superb microvascular imaging [SMI]; Toshiba).[8] Such algorithm allows purification of the Doppler signal, by eliminating the noise and background artifacts, without reducing vascular signals. Conventional Doppler techniques have been developed with the main aim to visualize blood flow at a high resolution. SMI is able to identify even slower blood flow compared to traditional color Doppler, obtaining images similar to CEUS, but without using intravenous (iv) contrast agents.

The aim of this work was to evaluate the diagnostic effectiveness of color Doppler ultrasound (CDUS) with SMI compared to US with contrast agent and CT multislice angiography (64 slices). The results are also compared with angiography required for therapeutic reasons.

MATERIALS AND METHODS

In the period between March 2014 and May 2015, 57 patients, who had previously undergone EVAR, were recruited for this study. Indication for treatment was considered aneurysm diameter >5.5 cm for men and 5.0 cm for women, or evidence of rapid growth (>1 cm in 1 year). Thirty-four Medtronic, Endurant II; 9 Zenith, Cook; 9 GORE EXCLUDER; and 5 Bolton, Treovance devices were used. The population included 50 men and 7 women (mean age, 75 ± 8 years). Patients were studied within 30 days after EVAR and followed up at 3, 6, and 12 months through CDUS, SMI, and CEUS. CTA was performed within 30 days and 12 months if symptomless. Angiography and treatment were performed in patients with endoleak and increase of the aneurysm sac. In these cases, angiography was the gold standard, and in the remaining cases, the imaging follow-up.

Diagnostic accuracy of the different procedures was evaluated in terms of sensitivity, specificity, and positive and negative predictive values. The main parameters taken into consideration included sac diameter, stent-graft integrity, identification, and classification of endoleaks.

CTA Technique

Within 1 week postoperatively, all patients underwent CTA examination carried out with Somatom 64 (Siemens, Erlangen, Germany). A triphasic CT protocol was used with a precontrast phase, an arterial phase (started with bolus tracking), and a late phase at 120 sec, using 130 mL of nonionic contrast agent: Iomeron (Bracco, Milan, Italy) at 4 mL/s. The other scanning parameters were the following: 1.2-mm acquisition; reconstruction with a soft-margin kernel algorithm (B30) at 1.5 and 3 mm with a reconstruction increase of 1.5 mm; precontrast scans at a low-power tube (120 mAs); the other phases at 120 kV and 200 mAs. Images were analyzed on a dedicated workstation (Aquarius; TeraRecon, San Matteo, CA) using conventional post-processing techniques. CTAs were evaluated by 2 radiologists with more than 10 years of experience in the field. The size of the aneurysm sac, the integrity of the prosthesis, and the presence or absence and type of endoleak were evaluated.

Color Doppler Ultrasound

Patients were advised to follow a low residual diet the day before the examination and to fast in the morning of the day of the investigation. The color

Doppler examination was conducted with a high-end machine (Toshiba Aplio 500), equipped with a convex probe (1–6 Mhz), using real-time scanning.

The first part of the examination consisted of a complete study of the abdominal aorta in B-mode, from the diaphragm to the iliac arteries. The aneurysm sac was measured both in its longitudinal and transversal size in the segment with the largest dimension.

Later a color and power Doppler evaluation of the vessel, and most importantly of the aneurysm sac, was used, to identify suspect endoleak areas. Hemodynamics were documented through the measurement of speed with Doppler spectrum.

CEUS Technique

After the B-mode study and color–power Doppler, CEUS was performed on the same machine under low mechanical index between 0.06 and 0.10. A quick bolus injection with 1.2 mL of second-generation contrast agent (SonoVue; Bracco, Milan, Italy), in the antecubital vein, through a peripheral venous catheter 18–20 G, followed by 5 cc of saline was given. To avoid the rupture of the microbubbles during injections, the catheter and the vein were kept in longitudinal position, straight, and without any corners.

The whole abdominal aorta (up to the iliac arteries) was examined for 5 min after the injection of SonoVue, and the presence of contrast enhancement within the aneurysm sac was evaluated, by monitoring the time of appearance (if synchronous or delayed with respect to prosthesis enhancement) and persistence in inflow and outflow vessels.

The examinations were digitally recorded in the form of cine loops, and all cases were analyzed by 2 operators to characterize lesions in ''consensus reading.''

Color Doppler SMI Technique

Before and after CEUS, color Doppler with SMI was performed. Both color and grayscale images were used for the vascular system, and the presence of a low-flow signal was evaluated at the same time outside the stent graft and inside the aneurysm sac. The examinations were analyzed by 2 operators in ''consensus reading'' and digitally recorded in the form of cine loops. Real-time SMI algorithm enables the machine to increase the frame rate that allows to display signals coming from low flow normally disturbed by background noise and filtered by color and power Doppler. It is therefore able to thoroughly separate the real vascular signal from tissue motion artifacts keeping the whole Doppler spectrum including low-flow signals in real time.[8]

Both the blood flow and tissue motion produce Doppler signals, and the latter, if intense, overlaps the low-velocity blood components. Conventional Doppler systems use filters that, in order to eliminate motion artifacts, lose also low-velocity blood flow components. SMI uses a new algorithm on one hand to identify and remove the signals deriving from the motion of nearby structures (motion artifacts) and on the other hand to reveal the real components of low-velocity blood flow. This is possible because the software does not concentrate mainly on the Doppler effect or on the intensity of a specific signal but on the local distribution through the region of interest, and although motion indicated as background noise is present in the whole region, blood flow regards only a specific area.

This procedure should guarantee a significant reduction of pulsatility artifacts that invalidate the study with the color and power Doppler technique, increasing accuracy and reducing interobserver variability.

SMI presents in 2 modes: color SMI mode and Monochromatic SMI mode. The color SMI mode shows the anatomy of the district explored in B-mode with information about low flow on a color map, whereas monochromatic SMI mode cuts the background in the region of interest giving more focus on the flow structure which improves the sensitivity of the system and obtaining an image quite similar to CEUS but without using iv contrast agents (Fig. 1).

Digital Subtraction Angiography Technique

Patients who were positive to endoleaks or showed contrasting results underwent digital subtraction angiography (DSA). The procedure was carried out through a digital angiographer (Artis Zee; Siemens, Berlin, Germany). Aortography was carried out through transfemoral access with a 4F pigtail catheter (Cordis Endovascular, Miami Lakes, FL) positioned above the renal arteries by injecting 20 mL of iodinated contrast at a speed of 20 mL/sec, to evaluate the flow inside endoprostheses, the patency of the splanchnic arteries and of the iliofemoral runoff, and the presence of endoleaks. The following selective catheterizations were also carried out according to the diagnostic results and indications of US with CEUS and SMI and CTA: of the superior mesenteric artery, by means of a SIM 1 4F catheter (Cordis Endovascular) to

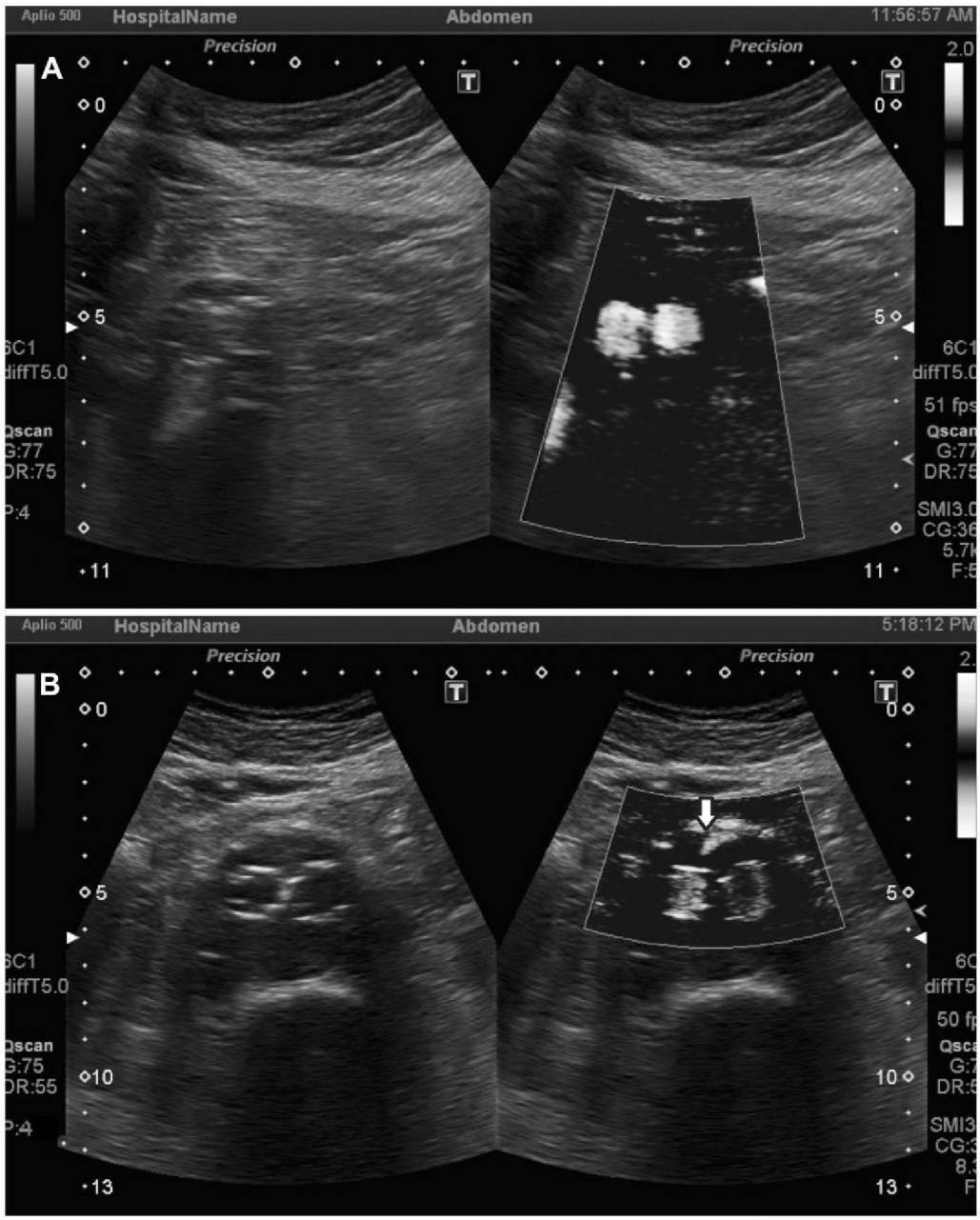

Fig. 1. SMI images. **(A)** Absence of endoleak. **(B)** Presence of Type II endoleak (*arrow*).

evaluate collateral flow of the arc of Riolan and the complete exclusion of the inferior mesenteric artery and of the internal iliac arteries bilaterally to evaluate revascularization through the iliolumbar arteries. In case of an endoleak with a progressive growth of the aneurysm sac, treatment with definitive embolic agents or prosthesis segments (aortic cuffs) was performed for type I endoleak and percutaneous embolization or intra-arterial embolization for type II.

Statistical Analysis

The maximum transversal diameter of the aneurysm sac was measured with all diagnostic procedures, and data were expressed as an average of values. The variables taken into account were sensitivity, specificity, and positive and negative predictive values. The paired *t*-test (Student *t*-distribution) was used to evaluate the correlation between the average size of the aneurysm sacs

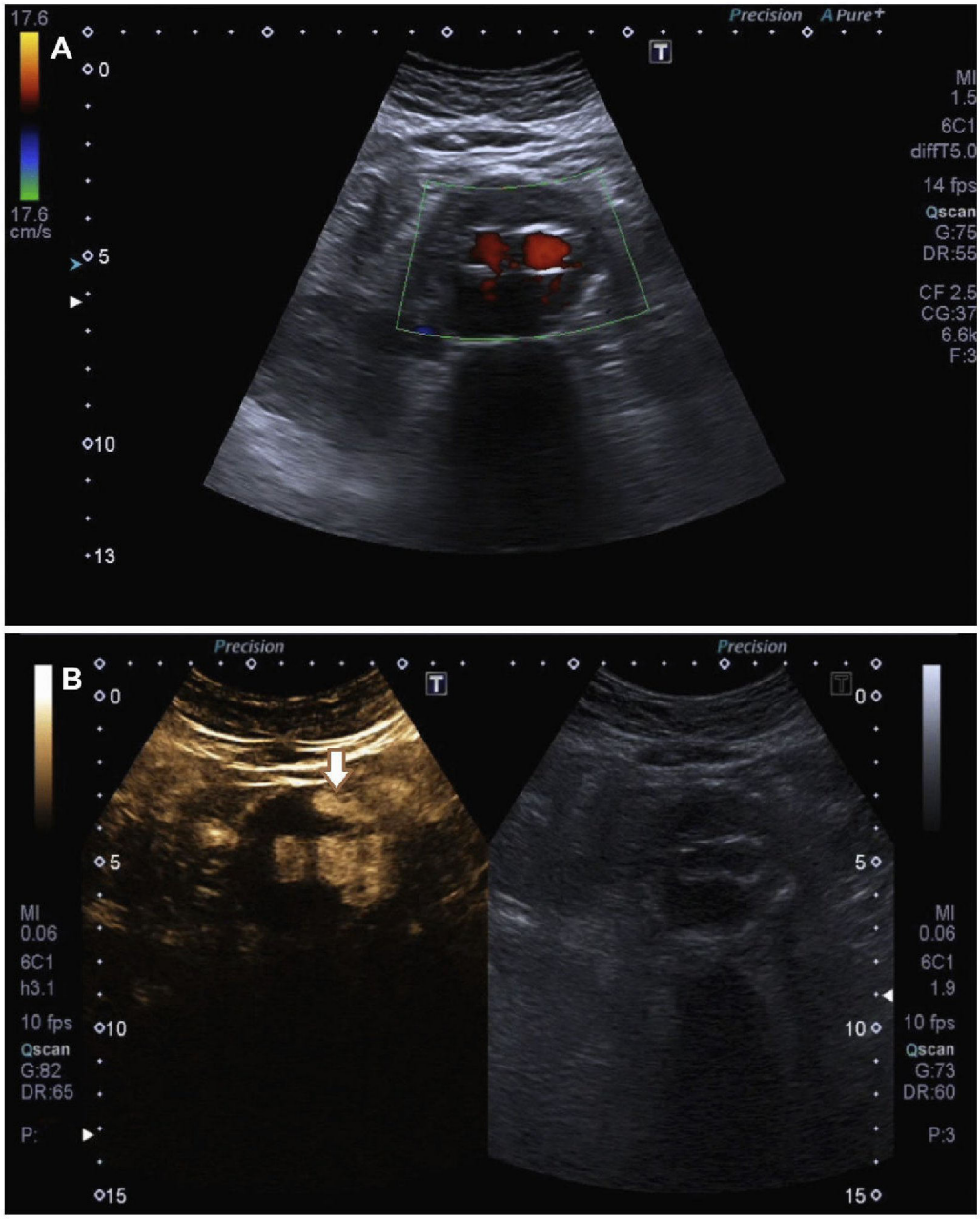

Fig. 2. **(A)** CDUS shows a normal stent-graft bifurcation. **(B)** Type II endoleak detected by CEUS (*arrow*).

observed with CT compared to US. This test was applied both to the 48 patients recruited and to the patients who were positive to endoleaks.

RESULTS

Of the 57 patients recruited, 8 endoleaks were detected (16.3%), all in male patients. Among the endoleaks documented, 6 were late endoleaks and 2 were early endoleaks. All 8 endoleaks were type II endoleaks (7 through lumbar arteries and 1 through the inferior mesenteric artery). In 2 cases, both with an increase of the sac >4 mm, reintervention was necessary. The remaining cases were only followed up.

The 2 endoleaks treated were confirmed by angiography. CT evidenced all endoleaks except 1 (7 true positives and 1 false negative) because of its small size. CEUS evidenced all endoleak

Table I. Endoleaks detected

Technique	False positives	False negatives	True positives	True negatives
CT	0	1	7	49
CEUS	0	0	8	49
CDUS	2	3	5	47
SMI	1	2	6	48

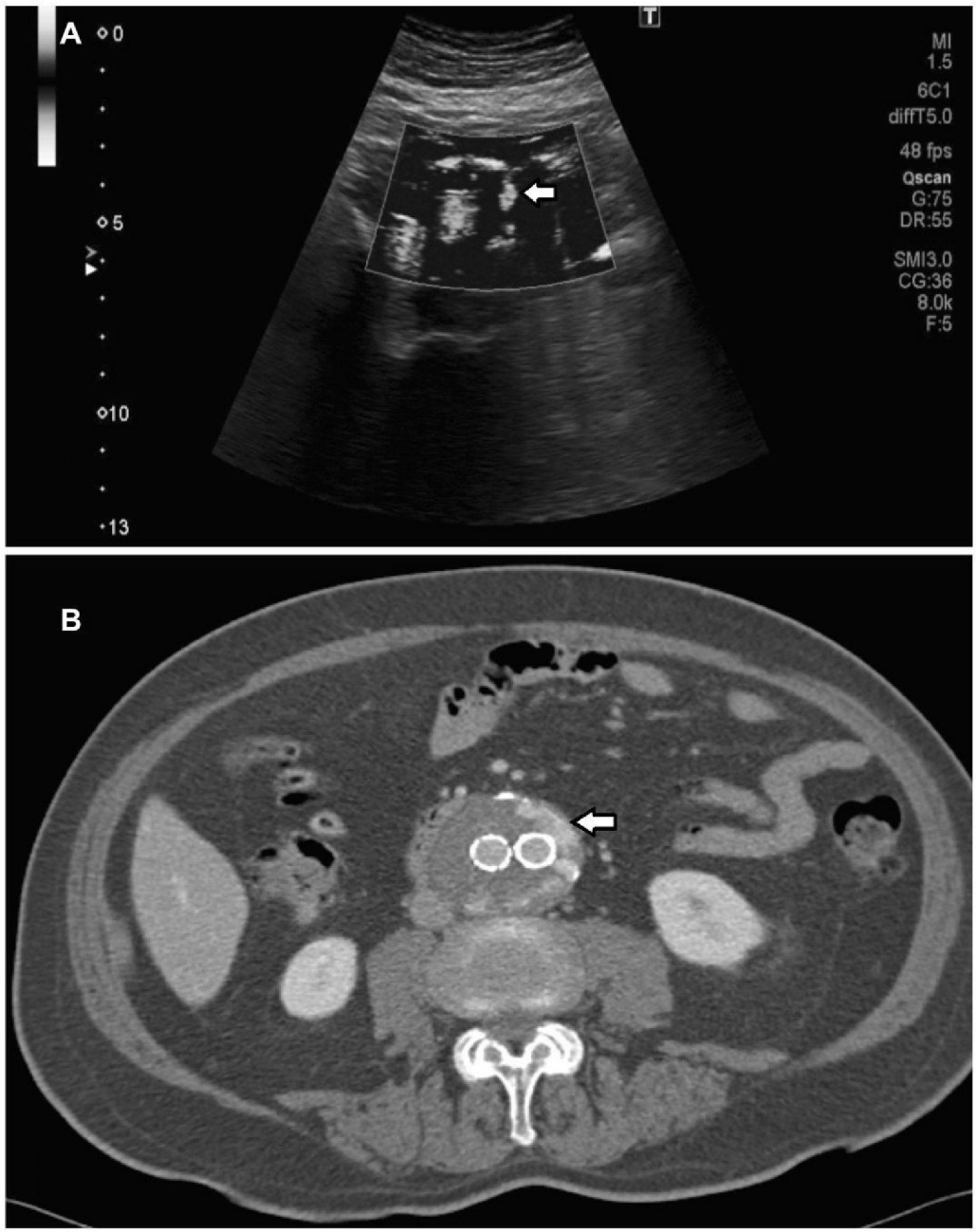

Fig. 3. **(A)** Type II endoleak detected by SMI. **(B)** CTA, venous phase: the endoleak (*arrow*) is supplied by a lumbar artery.

Table II. Accuracy in recognizing endoleak

Technique	Sensitivity %	Specificity %	Negative predictive value %
CT	88	100	98
CEUS	100	100	100
CDUS	63	96	94
SMI	75	98	96

cases (8 true positives and 0 false negative). The remaining part of the subjects studied gave negative results for both procedures (0 false positives). SMI evidenced 7 endoleaks instead, 6 of which were true positives, 1 false positive, and 2 false negatives. Finally, CDUS documented 3 false negatives and 7 endoleaks, 5 of which true positives and 2 false positives (Fig. 2).These results are summarized in Table I. CT was able to characterize appropriately 6 type II endoleaks, localizing the artery that perfused the aneurysm (Fig. 3) but misdiagnosed 1 case of type II endoleak as type I.

CEUS characterized appropriately all type II endoleaks, documenting in 7 cases lumbar arteries as origin of endoleak and in 1 case the inferior mesenteric artery. CDUS, despite its limited sensitivity and specificity, classified all endoleaks appropriately. Even SMI characterization was coherent with the other procedures. Sensitivity and specificity of CT, CEUS, CDUS, and SMI were respectively of 88%, 100%, 63%, and 75%, and 100%, 100%, 96%, and 98%.The negative predictive value was 98%, 100%, 94%, and 96%, respectively.

The analysis of the data in this study evidenced that CEUS sensitivity is similar to CT, which is much more sensitive than CDUS and SMI and has an excellent specificity, equivalent to the other procedures. As far as endoleak characterization is concerned, CEUS performed better than CT, managing to correctly classify a case as type II endoleak in which CT did classify it as type I. Confirmation of type II endoleak was therefore achieved by means of angiography. SMI showed high specificity, not statistically different from CEUS and CT. However, it was less sensitive than CEUS and CT. SMI was also reliable for endoleak classification. The accuracy of the different procedures has been summarized in Table II.

DSA was performed in 2 of 8 patients because in 2 type II cases (during the follow-up), the increase of the aneurysm sac was >4 mm, therefore requiring embolization.

DISCUSSION

Early identification and correct classification of endoleaks are the fundamental aims of the follow-up of patients treated with EVAR. CDUS is a safe, inexpensive, and repeatable examination; however, in our experience[9] and in literature,[10–13] it is not sensitive enough, unless it is performed by an expert in perfect "anatomic" conditions.[9] At the moment, CTA is the most used imaging procedure,[14,15] thanks to its wide availability, panoramic view, acquisition speed, resolution, and uniformity of protocols. CTA is usually performed using precontrast scans, although some authors suggest not to carry out the precontrast phase[16] and postcontrast scans, in the arterial and delayed phase, the latter particularly useful to identify low-flow endoleaks. CT is accurate for identifying endoleaks, with a sensitivity of 70% (53–82%) and a specificity of 98% (94–100%).[17] However, the unsuccessful directional identification of the flow makes the origin of the endoleak more difficult to detect.[18–20] CTA allows only multiphase imaging and not dynamic acquisitions of the flow inside the aneurysm sac; therefore, CEUS can identify some types of slow endoleaks, as reported by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) 2011 guidelines[21] and some authors in literature.[22,23] The emergent role of CEUS and its growing indications compared to CT are also shown by several studies,[24,25] which prove its applications in the body, for liver, kidney, testis, lymph nodes, thyroid, prostate, and small bowel. Moreover, the costs and the use of ionizing radiation and potentially allergenic and nephrotoxic contrast agents raise doubts about the repeated use of CT on patients at risk of endoleak. Nonetheless, CT, with all its limits regarding classification and identification of endoleaks, cannot be replaced because it gives a more precise evaluation of the aneurysm sac and provides information about anchorage, integrity, and morphology of the graft, which cannot be obtained with US.

CEUS, performed with harmonic B-mode imaging and second-generation contrast agents, has been evaluated for the follow-up of EVAR in some studies[6,26–28] and has given promising results both for the identification of endoleaks and their correct classification. The introduction of second-generation contrast agents and specific software has eliminated problems connected to artifacts and operator dependence, as well as the influence of obesity and intestinal gas.[4,6,29,30]

US contrast agents can be used also in patients with renal failure, and no laboratory tests are needed before administration. Elimination takes

place through the respiratory system, and it does not depend on gender or quantity injected.[31–34]The incidence of severe hypersensitivity or anaphylactic reactions is very low and can be compared to the one of contrast agents used in magnetic resonance (MR).[32] However, it is necessary to pay attention to patients suffering from severe congenital heart failure and significant lung, kidney, or liver disease,[31] and it is contraindicated in patients with unstable angina or with a recent episode of acute coronary syndrome.

To summarize, CEUS is a safe and repeatable procedure, even because it does not use ionizing radiation, it is inexpensive and pleasant for the patient. It allows a dynamic analysis of the flow with real-time acquisition of images over up to 10 min, therefore allowing the identification of late or low-flow endoleaks, usually not evidenced by spiral CT.[35] The EFSUMB 2011 guidelines recommend its use for surveillance after EVAR. However, CDUS with SMI and/or CEUS present the limits of B-mode US, as far as the patient's habitus, the presence of intestinal gas, ascites, extended calcifications, subcutaneous emphysema caused by surgery, and metal artifacts are concerned. Other limitations to its use are connected to some components of the endoprosthesis (such as the GORE EXCLUDER—Endoprosthesis) which limit explorability, producing artifacts the first 6 months after surgery.[28,36] Moreover, this procedure is highly operator dependent, it is not available in all institutes, it has a minimum extra cost because of the use of the contrast agent, and sometimes it can only be performed during hospitalization. These disadvantages do not allow CEUS to reach the ''gold standard'' level. On the other hand, new software, such as SMI, has opened new diagnostic possibilities, which are less invasive and easier to use.

The results of our study have shown that SMI is an effective and more accurate procedure than color Doppler to identify endoleaks, less sensitive compared to CEUS and CT but with high specificity, and not statistically different from CEUS and CT. As regards endoleak classification, SMI seems to be a reliable procedure. It could allow a better and more effective identification and characterization of endoleaks compared to traditional US with color—power Doppler, guaranteeing, in theory, results similar to CEUS and CT. At the same time, it solves the main limitations of such procedures such as invasiveness, costs, nephrotoxicity, and the use of ionizing radiation. SMI is also able to eliminate motion and respiratory artifacts, to identify low flow, but, unlike CEUS, it does not guarantee real-time evaluation of flow dynamics. Diameters of the aneurysm sac can be measured in a precise way by US, which is also able to effectively visualize the proximal and distal anchorage sites of the endoprosthesis.[1,37] In addition, type II endoleaks, which need constant monitoring, can be kept under observation with US, reducing the use of CT and therefore expenses and radiation exposure.

Some authors have reported a coefficient of variation of 10% between CEUS and CTA for measuring the residual diameter of the sac.[38] Such a high level of interindividual or intraindividual variability suggests that the 2 procedures are not interchangeable and have to be used with 2 separate protocols. A group of researchers, on the basis of a multicenter study lasted 5 years,[39] developed a surveillance protocol starting from 30 days with CT and X-rays with 4 projections. Later surveillance changes according to the presence or absence of endoleaks: if an endoleak is present, whether it is necessary or not, intensive surveillance is put in place every 6–12 months with CT. If no endoleaks are registered, a less intensive surveillance protocol is put in place, with a second CTA after 12 months and then a yearly CDUS. In the following checks, if an endoleak is documented or the aneurysm sizes have grown, the patient is transferred to the intense surveillance protocol and/or retreatment. Other authors support a less-expensive protocol, with a surveillance system based on CDUS and X-rays.[1,40–42] Others still use a protocol mainly based on CEUS and CDUS that includes a CTA after 3 and 12 months of EVAR, then periodical CDUS and CEUS to solve suspected problems.[43] Our research team instead, on the basis of our experience,[9] follows a protocol which emphasizes CEUS. After EVAR and the first discharge of the patients, on the second or third day, CEUS and CTA or MRA are performed, and surveillance with CEUS is continued after 3 and 6 months, and then 12 months after surgery, another CTA is performed. If type I or III endoleaks are documented, then it is necessary to intervene again and follow more intensely the patients with CT or MR, in addition to CEUS and then continue like after the first treatment. If a type II endoleak is documented instead, the patient is followed only with CEUS, every 2 or 3 months to register possible growths of the aneurysm sac. If no growth is showed, the patient is followed with CEUS until the endoleak disappears.

CONCLUSION

Our study shows that SMI is more accurate than CDUS but less accurate than CEUS and CT to identify endoleaks after EVAR. CEUS proved to be

effective in clarifying the diagnosis when doubts persisted after CT about endoleak classification, giving more information about their origin and extension. It could be suggested for those patients who have a growing aneurysm sac, but CT did not reveal a reperfusion of the aneurysm sac.

SMI could be concretely used in the follow-up phase to increase CDUS accuracy especially in patients who cannot be studied with CEUS or CT, reducing the time of the execution of the examination and the costs for the national health system. In fact SMI is installed in US software in the equipment we used; it is instantaneous and very comfortable for the patients, avoiding the administration of contrast medium, and therefore without risks. If further prospective studies will be carried out, the use of SMI could be concretely proposed for the follow-up after EVAR.

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